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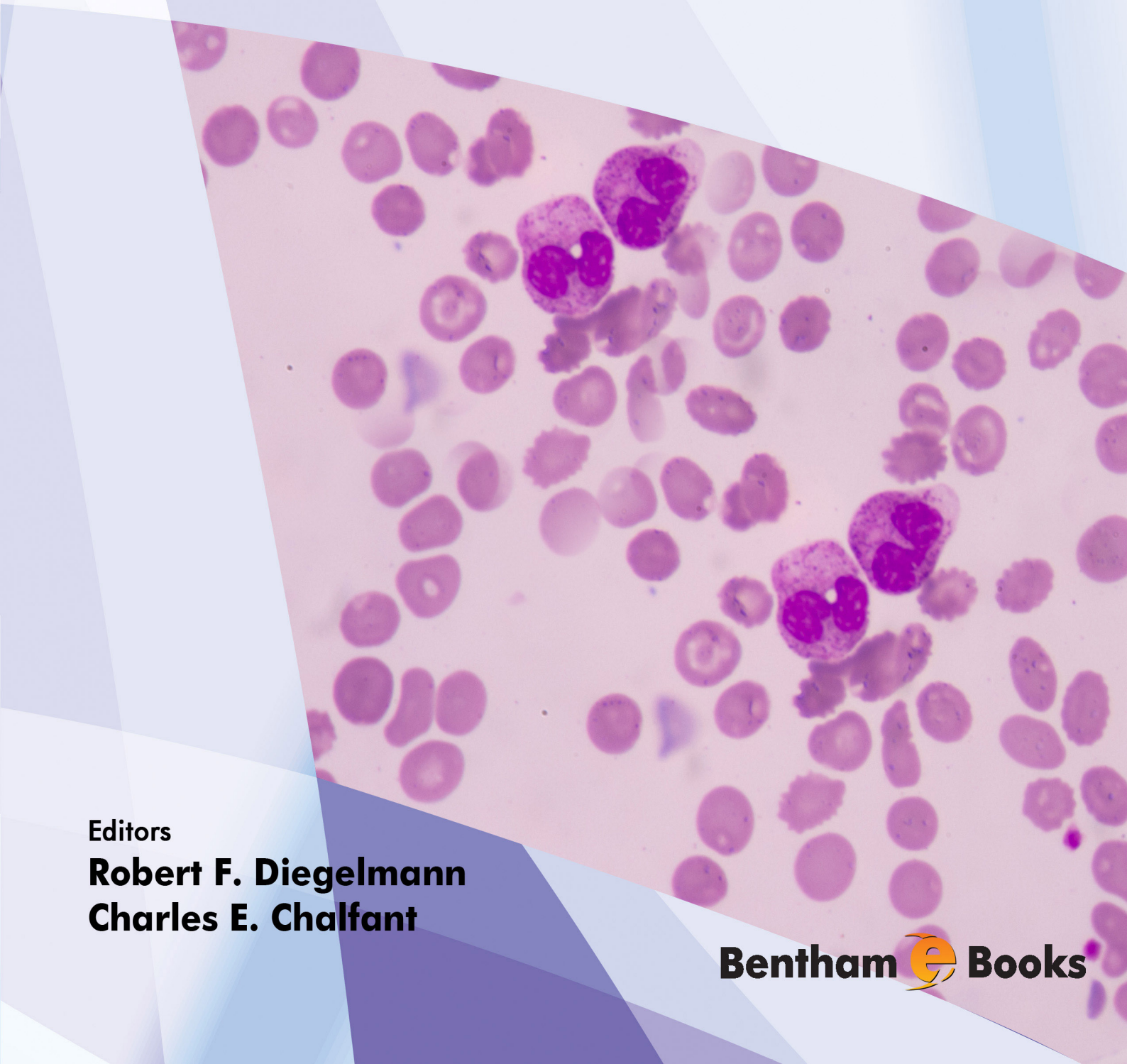
Frontiers in Inflammation Volume 1

Basic Biology and Clinical Aspects of Inflammation



Editors
Robert F. Diegelmann
Charles E. Chalfant

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Frontiers in Inflammation
(Volume 1)

Basic Biology and Clinical Aspects of Inflammation

Edited By

Robert F. Diegelmann & Charles E. Chalfant
Department of Biochemistry and Molecular Biology
Virginia Commonwealth University Medical Center
1101 East Marshall Street
Sanger Hall, Room 2-007
Richmond Virginia, 23298-0614
USA

Frontiers in Inflammation:

Basic Biology and Clinical Aspects of Inflammation

Volume # 1

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FOREWORD

In the post-genomic era, understanding inflammation and its intricate mechanisms is the final frontier. While ancient physicians recognized inflammation's cardinal signs as heat, redness, swelling and pain centuries ago,the cellular and molecular players in this vital inflammatory host response have only been elucidated for the most part in the last century. Today, it's now well appreciated that uncontrolled inflammation and excessive tissue levels of inflammatory mediators play central roles in the pathogenesis of many widely occurring diseases throughout the body and all its organs. At one time, the study of inflammation and inflammatory diseases was confined to chronic inflammatory diseases such as rheumatoid arthritis, periodontal disease and the like, while today it is commonly appreciated that neurodegenerative diseases, cognitive decline, vascular diseases, asthma, obesity and many other widely occurring diseases involve uncontrolled, recurrent bouts of inflammation. In order for us to gain and harness new approaches to treat these diseases and appreciate the complexity of the inflammatory response, it is essential for students, scientists and health care practitioners to command a detailed appreciation of the cellular and molecular language of the inflammatory response, the mediators and governance of this body defense system.

The acute inflammatory response is protective, many of the cell types, mediators and mechanisms are known today, and the control of self-limited responses and the progression to natural resolution and tissue homeostasis are beginning to be unraveled. As a major defense mechanism, the innate immune response protects from bacterial invasion and is centered on containment and killing of microbes for their elimination from the body. Hence, the interrelationship between infection and inflammation is a battleground with language that needs to be fully decoded and appreciated in order for us to gain advantage in treatment of diseases where inflammation plays a critical component and hopefully translate into protective practices in personalized medicine.

Inflammation and the controlled inflammatory response, namely its resolution, is thus linked to many of life's processes such as wound healing and aging, while an uncontrolled inflammatory response is viewed today as the instigating mechanism underlying diabetes, neurodegenerative diseases and neuroinflammation and likely many diseases, both sterile injury from within and yet-to-be-described invaders, emphasizing the importance of the inflammatory response and ongoinginflammation as maybe relevant in obesity, metabolic syndrome and aging. The microbiome's relationship to containment, infection and local tissue inflammation in organs throughout the body remains to be fully decoded, and it is well recognized that the stress of surgery and the local scalpel cut of the surgeon initiate inflammatory responses and potentially (*via* occlusion of blood vessels with blood reflow),

injury from within.

It is within the spirit of widely appreciating these cellular events, processes and mechanisms that the editors, Drs. Diegelmann and Chalfant, have assembled this eBook containing major contributions from an international distinguished panel of experts to present a didactic experience of the basic cell biology as well as clinical aspects of inflammation. The chapters are by authorities and leading investigators and systematically introduce the cellular and molecular initiators and defenders in the acute inflammatory response and go on to include chapters on inflammation in metabolism, aging, allergy, diabetes, cardiovascular, arthritis, oral disease, gastrointestinal and neural inflammation in well-illustrated and clearly presented didactic chapters.

Inflammation when presented in medical school is usually a component of general pathology, or immunology, and in some cases microbiology as well as each of the medical specialties in small bites. Thus, in many respects, the presentation of the innate immune response and its communication to acquired immunity is fragmented in the traditional medical curriculum. This ebook helps to provide, in one succinct presentation, a cohesive view of our multi-disciplinary appreciation of inflammation today and how it impacts many disease processes and organs throughout the body.

The editors have also taken care to present current approaches in pharmacotherapy in inflammatory responses as well as the application of mathematical modeling and network analysis to inflammation. These are valuable and can help provide a strong foundation to the readers for appreciating the role of inflammation and its treatment for both personalized and precision medicine. This eBook on ***Basic Biology and Clinical Aspects of Inflammation*** should be of wide interest across disciplines to not only practitioners, health care providers and basic medical scientists, but should also be of interest to the pharmaceutical and cosmetic industries as well as nutrition and economists, because of the tremendous economic burden of diseases where uncontrolled inflammation is a key culprit. Drs. Diegelmann and Chalfant give us a well-integrated eBook and chapters that will enable the reader to increase our present understanding and gain insight to discover new means to marvel and control this important life process.Inflammation is all!

Charles N. Serhan
Brigham and Women's Hospital,
Harvard Medical School,
77 Avenue Louis Pasteur (HIM 829)
Boston, MA 02115,
USA
cnserhan@zeus.bwh.harvard.edu

PREFACE

In recent years, there have been many exciting advances made in the field of inflammation. State of the art scientific technologies have helped make these advances possible. As underlying cellular and biochemical mechanisms responsible for the inflammatory response are better understood, new therapeutic strategies can be developed to treat the spectrum of clinical problems associated with excessive inflammation.

This educational eBook, "Basic Biology and Clinical Aspects of Inflammation" was developed for a wide audience. Basic scientists, academicians, clinicians, health care regulators, industrial and pharmaceutical scientists as well as the lay public can benefit from the expanse of knowledge presented herein.

To help continue promoting cutting edge scientific research and technology, the Editors and all contributing Authors have agreed to donate their royalties from this eBook to the Wound Healing Foundation (http://www.woundhealingfoundation.org) for young investigator research grants. In addition, we recognize and appreciate Bentham Science Publishers for their generous support and contributions to the Wound Healing Foundation.

Dedication: We dedicate this book to our wonderful wives, Penny and Laura and our loving children, Sarah, Laura, Ryan, Stephen, Scott, Isabella, and Alec.

Robert F. Diegelmann & Charles E. Chalfant
Department of Biochemistry and Molecular Biology
Virginia Commonwealth University Medical Center
1101 East Marshall Street
Sanger Hall, room 2-007
Richmond Virginia, 23298-0614
USA
Robert.Diegelmann@vcuhealth.org
cechalfant@vcu.edu

List of Contributors

Agbor Ndip	Centre for Endocrinology and Diabetes, Institute for Human Development, University of Manchester, Manchester, UK Department of Diabetes, Warrington General Hospital, Warrington, UK
Alastair G. Stewart	Department of Pharmacology & Therapeutics and Lung Health Research Centre, University of Melbourne, Parkville, Victoria 3010, Australia
Alexander A. Karakashian	Department of Physiology, University of Kentucky College of Medicine, Lexington, KY, USA
Andrew J.M. Boulton	Centre for Endocrinology and Diabetes, Institute for Human Development, University of Manchester, Manchester, UK Department of Diabetes and Medicine, Manchester Royal Infirmary, Manchester, UK
Angela M. Reynolds	Department of Mathematics and Applied Mathematics, Virginia Commonwealth University, Richmond, Virginia, USA
Bruce D. Spiess	Johnson Institute for Critical Care research, Department of Anesthesiology, Emergency Medicine, VCU Medical Center, Richmond, Virginia, USA
Chang-An Guo	Department of Biochemistry, University of Wisconsin-Madison, Madison, WI, USA
Chao Li	Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, VCU Program in Enteric Neuromuscular Sciences, Medical College of Virginia Campus, Virginia Commonwealth University, Richmond VA, USA
Charles E. Chalfant	Department of Biochemistry and Molecular Biology, Virginia Commonwealth University School of Medicine, Richmond, Virginia, 23298, USA Research and Development, Hunter Holmes McGuire Veterans Administration Medical Center, Richmond, Virginia, 23249, USA The VCU Massey Cancer Center, Virginia Commonwealth University, Richmond, Virginia, 23298, USA VCU Johnson Center, Virginia Commonwealth University, Richmond, Virginia, 23298, USA VCU Institute of Molecular Medicine, Richmond, Virginia, 23298, USA
Daipayan Banerjee	Department of Physiology, University of Kentucky College of Medicine, Lexington, KY, USA
Dayanjan S. Wijesinghe	Department of Pharmacotherapy & Outcomes Sciences, Virginia Commonwealth University School of Medicine, Richmond, Virginia, 23298, USA VCU Johnson Center, Virginia Commonwealth University, Virginia, 23298, USA

Edward B. Jude	Centre for Endocrinology and Diabetes, Institute for Human Development, University of Manchester, Manchester, UK Department of Diabetes, Tameside General Hospital, Ashton-Unde--Lyne, UK
Graham A. Mackay	Department of Pharmacology & Therapeutics and Lung Health Research Centre, University of Melbourne, Parkville, Victoria 3010, Australia
James M. Ntambi	Department of Biochemistry, University of Wisconsin-Madison, Madison, WI, USA Department of Nutritional Sciences, University of Wisconsin-Madison, Madison, WI, USA
Jennifer A. Mietla	Department of Biochemistry and Molecular Biology, Virginia Commonwealth University School of Medicine, Richmond, Virginia, 23298, USA
John F. Kuemmerle	Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, VCU Program in Enteric Neuromuscular Sciences, Medical College of Virginia Campus, Virginia Commonwealth University, Richmond VA, USA
Joshua L. Kennedy	Departments of Internal Medicine and Pediatrics, Division of Allergy and Immunology, University of Arkansas for Medical Sciences, Little Rock, AR, USA
L. Alexis Hoeferlin	Department of Biochemistry and Molecular Biology, Virginia Commonwealth University School of Medicine, Richmond, Virginia, 23298, USA
Laura Bond	Department of Biochemistry, University of Wisconsin-Madison, Madison, WI, USA
Lisa J. Gould	Wound Recovery & Hyperbaric Medicine Center, Kent Hospital, Warwick, Rhode Island, USA
Luisa A. DiPietro	Center for Wound Healing and Tissue Regeneration, University of Illinois at Chicago, Chicago, IL, USA
Mariana N. Nikolova-Karakashian	Department of Physiology, University of Kentucky College of Medicine, Lexington, KY, USA
Mary Elizabeth Hanley	Wound Recovery & Hyperbaric Medicine Center, Kent Hospital, Warwick, Rhode Island, USA
Matthew C. Bell	Departments of Internal Medicine and Pediatrics, Division of Allergy and Immunology, University of Arkansas for Medical Sciences, Little Rock, AR, USA
Matthias Geyer	Department of Rheumatology and Clinical Immunology, Internal Medicine and Rheumatology, Kerckhoff-Klinik, Justus-Liebi--University Gieβen, Bad Nauheim, Germany

Megan E. Schrementi	Department of Biological Sciences, DePaul University, Chicago, IL, USA
Praveen R. Arany	Oral Biology, School of Dental Medicine, University at Buffalo, New York, USA
Rebecca A. Segal	Department of Mathematics and Applied Mathematics, Virginia Commonwealth University, Richmond, Virginia, USA
Robert F. Diegelmann	Department of Biochemistry and Molecular Biology and the VCU Johnson Center, Virginia Commonwealth University Medical Center, Richmond, Virginia, USA
Roger M. Loria	Department of Microbiology and Immunology, Virginia Commonwealth University Medical Center, Richmond, Virginia, USA
Steffen Gay	Department of Rheumatology, Center of Experimental Rheumatology, University of Zürich, Zürich, Switzerland
Tomasz Arodz	Department of Computer Science, School of Engineering, Virginia Commonwealth University, Richmond, VA, USA
Ulf Müller-Ladner	Department of Rheumatology and Clinical Immunology, Internal Medicine and Rheumatology, Kerckhoff-Klinik, Justus-Liebi--University Gieβen, Bad Nauheim, Germany
Unsong Oh	Department of Neurology, Virginia Commonwealth University School of Medicine, Richmond, VA, USA
Xi Gao	Department of Computer Science, School of Engineering, Virginia Commonwealth University, Richmond, VA, USA

CHAPTER 1

Introduction to Basic Biology and Clinical Aspects of Inflammation

Roger M. Loria[1,*], Robert F. Diegelmann[2]

[1] *Department of Microbiology and Immunology, Virginia Commonwealth University Medical Center, Richmond, Virginia, USA*

[2] *Department of Biochemistry and Molecular Biology and the VCU Johnson Center, Virginia Commonwealth University Medical Center, Richmond, Virginia, USA*

Abstract: Abstract: Inflammation has been recognized as biological phenomena for more than 2000 years by the Roman physician Aulus Cornelius Celcus who described the four cardinal signs of inflammation heat (calor), redness (rubor), pain (dolour), and swelling (tumour), a fifth sign, the loss of function was added later [1]. Consequently, there is ample literature on this subject as illustrated by the fact that more than 500,000 publications on this subject are listed in PubMed. Nevertheless, this volume provides new relevant information on the topic of inflammation, demonstrating that we have not yet complete knowledge on this subject. The reader is directed to extensive introduction of the subject of inflammation [2] as well as many other reports which deals with this subject [3 - 10]. This introductory chapter provides a brief summary of the individual chapter contain in this book.

Keywords: Acute and Chronic Inflammation, Systemic Inflammatory Response Syndrome (SIRS), Cell and Biochemical Mediators, Wound Healing, Metabolism and Aging, Allergy, Diabetes, Cardiovascular, Arthritis, Oral and Gastrointestinal, Neuroinflammation, Pharmacotherapy, Math Modeling and Network Analysis .

INTRODUCTION

The inflammatory response is classified into the following categories:

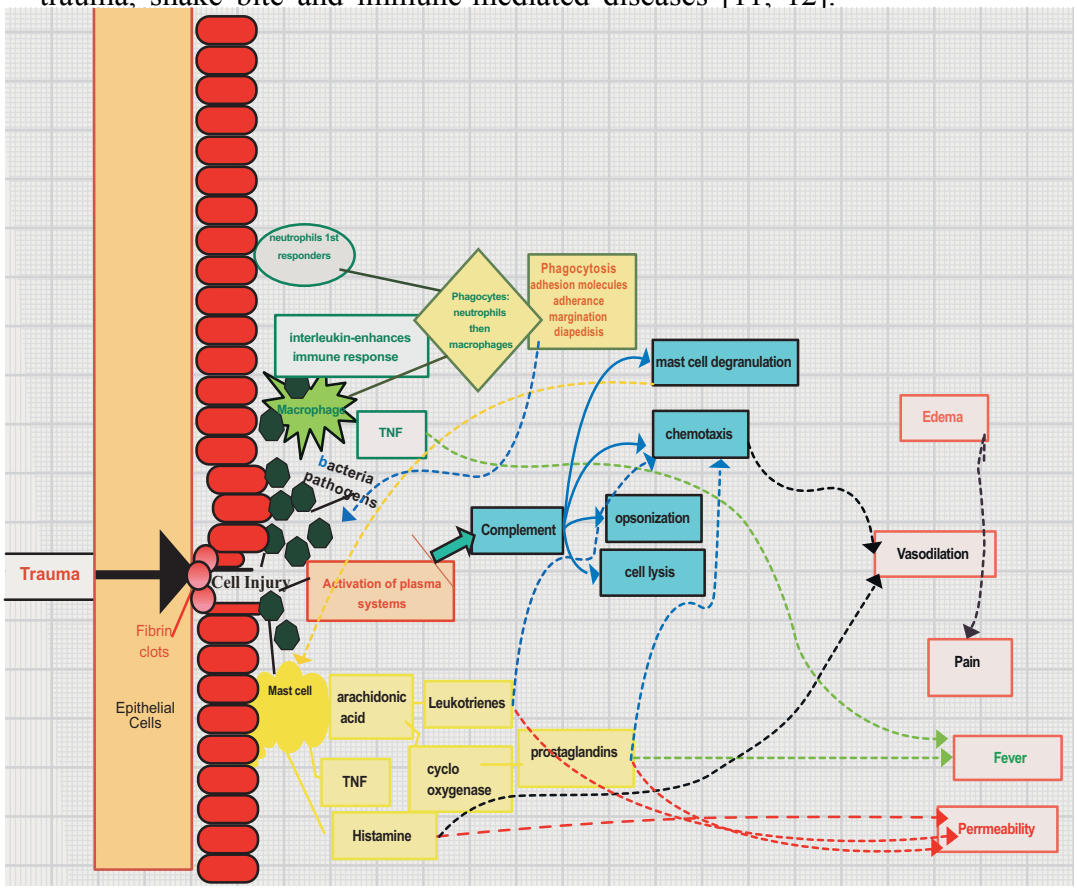
[*] **Address correspondence to Roger M. Loria:** Department of Microbiology and Immunology, PO Box 980678, Virginia Commonwealth University, Richmond, VA 23298-0678, USA; Tel: 804-828-9729; Fax: 804-828-9946; Email: rmloria@vcu.edu

Robert F. Diegelmann & Charles E. Chalfant (Eds.)

Acute Inflammation: is defined as a localized protective response elicited by injury or destruction of tissues, which serves to destroy, dilute, or wall off both the injurious agent and the injured tissue.

Chronic Inflammation: is defined as prolonged and persistent inflammation marked chiefly by new connective tissue formation; it may be a continuation of an acute form or a prolonged low-grade form.

Systemic Inflammatory Response Syndrome (SIRS): is defined as a generalized inflammatory response with vasodilation of capillaries and post capillary venules, increased permeability of capillaries, and hypovolemia. Depressed cardiac function and decreased organ perfusion follow. The various initiating stimuli include sepsis and septic shock, hyperthermia, pancreatitis, trauma, snake bite and immune-mediated diseases [11, 12].



An abbreviated schematic of the inflammatory process is provided in (Fig. **1**). This tome further illustrates that Inflammation is both a blessing [13] and a curse [14] and both are described in the following chapters.

CHAPTER 2

Cell Mediators of Acute Inflammation.

Phagocytic cells, including neutrophils and macrophages, produce cytokines that promote inflammation, but are also important for the clearance of microbes and apoptotic cells. This chapter reviews the key functions of these cells in response to an acute insult.

CHAPTER 3

Biochemical Mediators of Inflammation and Resolution.

Some biochemical mediators are specifically pro-inflammatory or pro-resolution, while others perform both functions. These biochemical mediators play key roles and thus the production and inhibition of these inhibitors are often targets for pharmaceutical intervention.

CHAPTER 4

Wound Healing and Dermatologic Aspects of Inflammation.

The chapter examines the normal inflammatory response as well as the factors that lead to chronic non-healing wounds. Identification of abnormal cellular and molecular immune responses may lead to targeted therapeutic strategies that promote harmony in the wound healing symphony.

CHAPTER 5

Metabolic Regulation of Inflammation.

Addresses the metabolic control of inflammation and immunity as well as the molecular aspects of metabolic inflammation converging to insulin resistance.

CHAPTER 2

Cell Mediators of Acute Inflammation

Luisa A. DiPietro[1,*], Megan E. Schrementi[2]

[1] *Center for Wound Healing and Tissue Regeneration, University of Illinois at Chicago, Chicago, IL, USA*

[2] *Department of Biological Sciences, DePaul University, Chicago, IL, USA*

Abstract: The acute inflammatory response that occurs due to tissue injury or infection involves multiple cell types with both overlapping and specific functions. The resident mast cell is an important sentinel and able to rapidly release proinflammatory mediators *via* degranulation. Phagocytic cells, including neutrophils and macrophages, produce cytokines that promote inflammation, but are also important for the clearance of microbes and apoptotic cells. Importantly, macrophages also provide substantial reparative signals to direct the healing process once the inflammatory insult is cleared. Other cells that may mediate acute inflammation include epithelial cells and lymphocytes. This chapter reviews the key functions of these cells in response to an acute insult.

Keywords: Cytokines, Inflammation, Innate immunity, Macrophages, Mast cells, Monocytes, Neutrophils, Phagocytosis.

INTRODUCTION

Acute inflammation, a process that begins within seconds of damage, is a short term process that quickly resolves over hours to days as the insult is removed and tissue is repaired [1]. The cells that are critical to acute inflammation are typically those of the innate immune system. In contrast to adaptive, or specific immune cells (such as lymphocytes), innate immune cells are able to recognize a broad range of microbes and danger-related signals and respond quickly.

[*] **Address correspondence to Luisa A. DiPietro:** Center for Wound Healing and Tissue Regeneration, University of Illinois at Chicago, Chicago, IL, 60612, USA; Tel: 312-355-0432; Email: ldipiet@uic.edu

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Acute inflammation is a short term event that ends when the pathogen or foreign particles are removed. By comparison, chronic inflammation involves both innate and adaptive, or specific, immune cell types, and is generally distinguished by a situation where the insult cannot be removed. In some disease states, such as rheumatoid arthritis, tuberculosis, or liver fibrosis, a chronic inflammatory condition persists for years.

This chapter describes the types of immune cells that initiate and execute the acute inflammatory process. Acute inflammation is initiated by specialized immune cells that reside in tissues and serve as sentinels for damage or infection. These sentinel cells include resident mast cells, macrophages, and certain non-immune cells. Sentinel cells identify injury or microbes *via* specific surface receptors called pattern recognition receptors (PRRs) [2, 3]. PRRs recognize molecules that are commonly found on pathogens (but not normal host cells), as well as molecules that are exposed when tissue is damaged. The activation of PRRs triggers sentinel cells to action, including the release of mediators that attract additional immune cells and further stimulate the acute inflammatory response. Many of the mediators that are released are members of the cytokine family, an important group of proteins that allows cells to signal to one another *via* interaction with receptors. Other mediators include small molecules such as nitric oxide and eicosanoids. The acute inflammatory response is designed to quickly clear the foreign agent or damaged cells, allowing for tissue repair and resolution of the condition. In addition to the cell types described below, certain cells that are not of immune lineage may also contribute to an acute inflammatory response. For example, epithelial cells can respond to damage as well as to inflammatory mediators by producing cytokines that stimulate the immune response. Other “non-immune” cells that can spur inflammation *via* the production of cytokines include endothelial cells and connective tissue cells such as adipocytes and fibroblasts [4, 5]. While this chapter focuses on cells of immune lineage, non-immune cells can be important regulators of the acute immune response in certain disease states.

As the inflammatory insult is cleared, the acute response resolves. Levels of pro-inflammatory mediators drop as do the numbers of acute inflammatory cells in the tissue. The process of resolution also involves the active production of mediators

that resolve inflammation; this process is described further in Chapter 3.

Toll-like Receptors

Toll like receptors (TLRs) are a group of molecules that are present on many immune cells such as macrophages, neutrophils and dendritic cells. They are among the first molecules to respond to a breach in immune protection. The presence of TLRs on the cell surface allows the immune system to sense the attack of foreign invaders and begin to coordinate an appropriate host response. TLRs recognize small segments of pathogens also known as Pathogen Associated Molecular Patterns (PAMPs). To date, there are nine known TLR s. Those found on the cell surface (TLR 1, 2, 4-6) recognize bacterial and fungal components. Intracellular TLRs recognize viral double-stranded RNA (TLR-3), viral single-stranded RNA (TLR-7 and 8) and bacterial DNA (TLR-9) [6]. In the skin, TLRs 2 and 4 are the most abundant and are found on the surface of keratinocytes, fibroblasts, Langerhans cells, macrophages and mast cells [7]. Although TLRs do not normally recognize most host molecules, they can interact with ligands produced by injured or damaged cells [8]. Thus, TLR's present on the surface of sentinel skin cells provide a recognition system for tissue damage and possible infection.

When a TLR on the surface of a cell binds with its cognate PAMP, a conformational change occurs which results in a complex signaling cascade within the cell. The result of the signaling differs depending on the TLR ligand interaction. For example, when LPS, a component of gram-negative bacteria, binds to and is recognized by TLR4, the signaling cascade leads to the production of proinflammatory cytokines that can attract more cells to the area to control a possible infection.

Mast Cells

Mast cells are relatively large, granule filled cells that are found throughout many tissues in the body. Mast cells were first identified more than 100 years ago by the German Nobel awardee, Paul Ehrlich, who named them *mastzellen* from the German word *mast*, to indicate their "fat" appearance [9]. Tissue bound mast cells derive from immature progenitors, and become fully developed and filled with

CHAPTER 3

Biochemical Mediators of Inflammation and Resolution

Jennifer A. Mietla[1], L. Alexis Hoeferlin[1], Dayanjan S. Wijesinghe[2,5], Charles E. Chalfant[1,3,4,5,6,*]

[1] *Department of Biochemistry and Molecular Biology, Virginia Commonwealth University School of Medicine, Richmond, Virginia 23298, USA*

[2] *Department of Pharmacotherapy & Outcomes Sciences, Virginia Commonwealth University School of Medicine, Richmond, Virginia 23298, USA*

[3] *Research and Development, Hunter Holmes McGuire Veterans Administration Medical Center, Richmond, Virginia 23249, USA*

[4] *The VCU Massey Cancer Center, Virginia Commonwealth University, Richmond, Virginia 23298, USA*

[5] *VCU Johnson Center, Richmond, Virginia 23298, USA*

[6] *VCU Institute of Molecular Medicine, Richmond, Virginia 23298, USA*

Abstract: Inflammation is the response of the immune system to injury and infection. As such, it is a critical component of multiple disease states, including anaphylaxis, cancer, cardiovascular disease, obesity, rheumatoid arthritis, diabetes and asthma. Inflammation is a complex process that is composed of multiple stages – the main stages being a pro-inflammatory stage followed by a pro-resolution phase. Eicosanoids and cytokines are critical biochemical mediators involved in both the initiation of the inflammatory response and the resolution of the inflammatory response. Some biochemical mediators are specifically pro-inflammatory or pro-resolution, while others perform both functions. These biochemical mediators play key roles, and thus, the production and inhibition of these mediators are often targets for pharmaceutical intervention.

[*] **Address correspondence to Charles E. Chalfant:** Department of Biochemistry and Molecular Biology, Room 2-016, Sanger Hall, Virginia Commonwealth University, School of Medicine, 1101 East Marshall Street, P.O. Box 980614, Richmond, VA 23298-0614, USA; Tel: 804-828-9526; Fax: 80408281473; Email: cechalfant@vcu.edu

Robert F. Diegelmann & Charles E. Chalfant (Eds.)

Keywords: Chemokines, Cytokines, Eicosanoids, Inflammation, Phospholipase A_2, Resolvins.

INTRODUCTION

Inflammation can be defined as the body's immediate response to damage to its tissues and cells by pathogens, noxious stimuli, or physical injury [1], and it can be acute or chronic. It is composed of many coordinated processes (Fig. **1**) that are actively signaled by both specific protein and lipid molecules [2]. The first step in the immune response involves inflammation and is characterized by the production of pro-inflammatory mediators, an influx of innate immune cells, and tissue destruction [3]. The resolution of inflammation involves the production of anti-inflammatory mediators, an influx of macrophages, and tissue repair [3]. Eicosanoids are well established mediators of both the initiation and the resolution of inflammation, but there is still much to learn as the roles of only few eicosanoids have been well studied. Additionally, cytokines and chemokines play roles in both the initiation and resolution of inflammation.

Inflammation is a critical component of many disease states including anaphylaxis, cancer, cardiovascular disease, obesity, rheumatoid arthritis, diabetes and asthma [4 - 13]. For example, in tumor development, inflammatory responses are involved in infiltration, promotion, malignant conversion, invasion, and metastasis [5]. There is also increasing evidence that prolonged inflammation in the vascular wall results in atherosclerosis [14 - 17].

Another increasing health concern, obesity, is also characterized by an overall inflammatory response in the body, and may impact the ability of the body to utilize insulin effectively [10, 18, 19].

As inflammation is intrinsically involved in multiple disease states, gaining a greater understanding of the mechanisms involved in this process could lead to new strategies for disease treatment and prevention.

BIOSYNTHESIS OF LIPID MEDIATORS

Phospholipase A_2

Phospholipases A_2 (PLA_2s) are enzymes that hydrolyze the sn-2 ester bond of cellular phospholipids to release free fatty acids and, as a result, form lysophospholipids [20, 21].

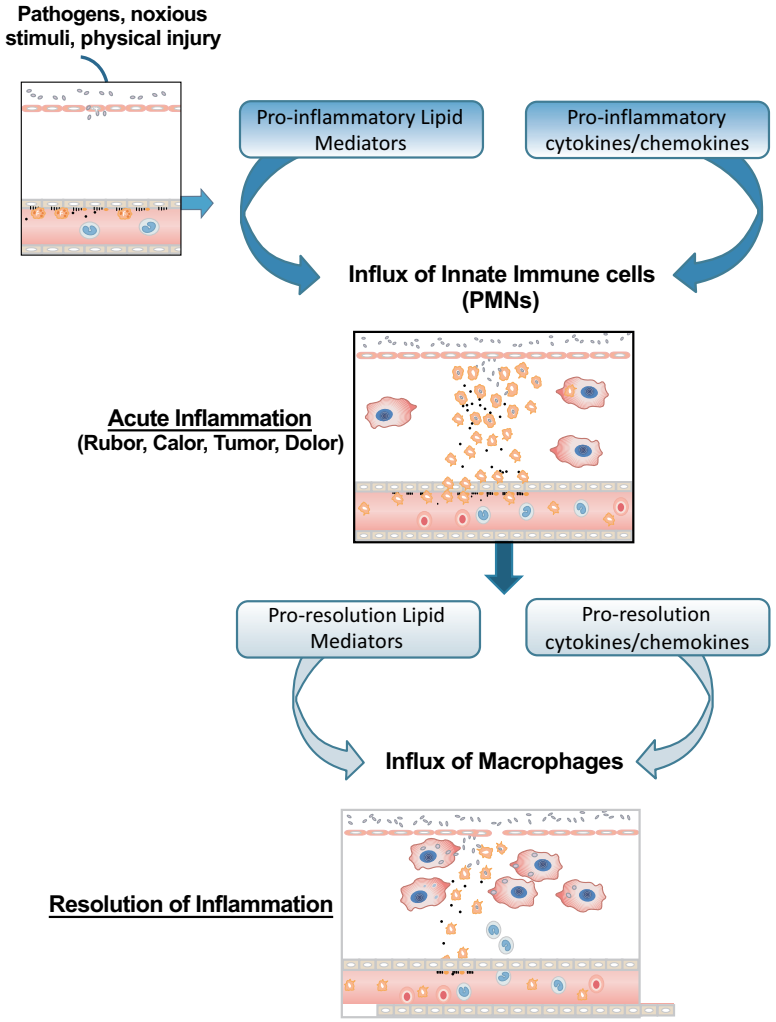

Fig. (1). General Course of Inflammation. Inflammation is a multi-step process that is actively signaled by specific lipid and protein molecules.

CHAPTER 4

Wound Healing and Dermatologic Aspects of Inflammation

Lisa J. Gould, Mary Elizabeth Hanley*

Wound Recovery & Hyperbaric Medicine Center, Kent Hospital, Warwick, Rhode Island, USA

Abstract: The skin is a highly complex organ that provides a wide variety of functions, including protection against toxins, pathogenic organisms and physical insults. When there is a breach in this very important barrier, it becomes clear that the skin is also an immune organ. There is a yin and a yang to the role of inflammation in wound healing. Although most of us take it for granted, normal wound healing requires a rapid inflammatory response with quick resolution. When this basic process is disrupted, either due to systemic illness or local factors, pathologic abnormalities in wound healing occur. This chapter will examine the normal inflammatory response as well as the factors that lead to chronic non-healing wounds. Identification of abnormal cellular and molecular immune responses may lead to targeted therapeutic strategies that promote harmony in the wound healing symphony.

Keywords: Aging, Diabetes, Inflammation, Lymphocytes, Macrophage, Neutrophils, Psoriasis pyoderma gangrenosum, Tumor necrosis factor, Venous insufficiency.

INTRODUCTION

Inflammation and the inflammatory process play key roles both in normal and abnormal wound healing. The absence or inability of a host to mount an inflammatory response will cause a wound to cease to progress through the final stages of healing and lead to development of what is referred to as a "nonhealing"

* **Address correspondence to Mary Elizabeth Hanley:** Wound Recovery & Hyperbaric Medicine Center; Kent Hospital; 455 TollGate Road; Warwick, Rhode Island 02886, USA; Tel: 401-736-4646; Fax: 401-736-4248; Email: mhanley@kentri.org

Robert F. Diegelmann & Charles E. Chalfant (Eds.)

or "problem" wound. Numerous studies in murine models have shown that a lack of pro-inflammatory cells will cause impaired healing in surgical wounds [1 - 3].

The Macrophage has earned the title of "Conductor" of the wound healing symphony for its pivotal role in overseeing the initiation of the inflammatory phase, maintaining the population of phagocytizing cells for debridement and removal of bacteria and for regulating the transition to the non-inflammatory proliferative phase of wound healing.

Despite the fact that inflammatory mediators and the inflammatory process are integral to wound healing, there are pathological conditions in which the inflammation and or its mediators run amok and can cause serious, sometimes permanent, dermatological injury and scarring. These situations can arise when patients have a co-existing autoimmune or rheumatological disorder, or sometimes are idiopathic in nature.

The skin is the largest organ in the mammalian body. It is made up of essentially 2 separate layers separated by a basement membrane. Because the skin is such a large organ system it makes sense that a veritable plethora of disorders (some inflammation driven, others not) will manifest themselves in the dermal structures. Most chronic wounds are ulcers that are associated with ischemia, diabetes mellitus, venous stasis disease or pressure. However, reactive cutaneous disorders such as erythema nodosum, pyoderma gangrenosum, Cutaneous poly-arteritis nodosa, and Sweet's Syndrome are examples of the inflammatory process in wound healing gone awry, either due to lack of inflammatory mediators, or to an overproduction of such. Many of these cutaneous manifestations are associated with systemic inflammatory conditions such as Ulcerative colitis and Crohn's disease and will respond to local or systemic steroids or immunosuppressant therapy aimed at moderating the inflammatory process. In this chapter we examine the inflammatory response that promotes skin wound healing with an emphasis on identifying potential therapeutic targets when inflammation is either deficient, excessive or poorly timed.

NORMAL DERMATOLOGICAL RESPONSE IN WOUND HEALING

Wound healing is a complex process involving interactions with the extracellular

matrix, soluble mediators, resident cells of the skin and transient inflammatory cells. The main goal of this process is to reestablish homeostasis and achieve tissue integrity.

Most authors agree on four overlapping phases to wound healing:

1. Hemostatic
2. Inflammatory
3. Proliferative
4. Remodeling

These occur in most healthy persons in a timely and logical progression. A lack of, or excess of any one mediator may prolong or prevent the stepwise progression the wound needs to progress through in order to fully heal.

Hemostasis occurs immediately after injury and is characterized by vaso-constriction and fibrin clot formation. Platelets not only activate the clotting cascade, they also secrete pro-inflammatory growth factors such as transforming growth factor (TGF)-β, platelet derived growth factor (PDGF), fibroblast growth factor (FGF) and epidermal growth factor (EGF) and cytokines which initiate healing [4].

The Inflammatory Phase of Wound Healing

In addition to establishing control of hemorrhage, the hemostatic phase initiates the signals to re-establish homeostasis. Simultaneous with platelet aggregation, the resident cells (keratinocytes, fibroblasts, endothelial, Langerhans) secrete mediators to recruit leukocytes and skew the process towards rapid wound closure. The inflammatory phase is characterized by the sequential infiltration of neutrophils, macrophages and lymphocytes [5].

Neutrophils

Neutrophils are the first immune cells to reach the injured tissue. Takamiya *et al.* observed that neutrophils begin to accumulate in dermal wounds after 2 hours, reaching a peak after 33-49 hours [6]. In this early phase the soluble mediators most prevalent at the wound site are: IL-10, GM-CSF, IFN-γ and TNF-α, while

CHAPTER 5

Metabolic Regulation of Inflammation

Chang-An Guo[1], Laura Bond[1], James M. Ntambi[1,2,*]

[1] *Department of Biochemistry, University of Wisconsin-Madison, Madison, WI, USA*

[2] *Department of Nutritional Sciences, University of Wisconsin-Madison, Madison, WI, USA*

Abstract: Inflammation and the related immune responses are energetically expensive processes, defending against pathogens and maintaining tissue homeostasis. As a result, immune response and metabolic regulation are highly integrated, allowing organisms to adapt to changes in their internal and external environments. Many nutrient- and pathogen-sensing system share common signaling pathways and have been evolutionarily conserved. Studies over the past decade have demonstrated that inflammation is a key feature of obesity, type 2 diabetes, and various cardiovascular disease states. In the context of over nutrition, shifts in tissue metabolism are accompanied with waves of profound recruitment of inflammatory cells (monocytes and lymphocytes) and high proliferation rates among lymphocyte populations. In this chapter, we review recent work addressing metabolic control of inflammation and immunity as well as the molecular aspects of metabolic inflammation converging to insulin resistance. It is crucial to explore the question of causality between the state of chronic inflammation and metabolic dysfunctions seen in obesity, and therefore developing effective therapeutic strategies to cope with the current worldwide obesity epidemic.

Keywords: Immune cell, Inflammation, Insulin resistance, Metabolism, Obesity, Over nutrition.

INTRODUCTION

The ability to withstand starvation and to fight off infections is critical for species survival. Metabolism fuels all biological programs including development,

* **Address correspondence to James M. Ntambi:** University of Wisconsin-Madison; 433 Babcock Dr, RM 415B, Madison, WI 53706, USA; Tel: 608-265-3700; Fax: 608-265-3272; Email: ntambi@biochem.wisc.edu

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proliferation and differentiation. The immune system continually senses and responds to environmental challenges, a process that is powerful and energetically demanding.

It is now appreciated that immune response and metabolic regulation are highly intertwined and evolutionarily conserved processes, therefore, proper function of one is dependent on the other. One example that represents this active interaction is the *Drosophila* fat body, which incorporates the mammalian homologs of the liver, adipose tissue, and the hematopoietic immune system into one functional unit [1, 2] The fly's fat body carries out a crucial function in sensing energy availability and coordinates the responses to pathogen with metabolic status [1]. It is very possible that, in the fly, common and overlapping molecular pathways regulate both metabolic and immune functions and in higher organisms, tissues or organs that are responsible for metabolism and immunity maintain their developmental heritage. As such, it is conceivable that in the context of obesity epidemic, nutrient surplus might be able to activate a pathogen-sensing system, such as the Toll-like receptors (TLRs) and NOD (nucleotide-binding oligomerization-domain protein)-like receptors (NLRs) [3], and nutritionally induce inflammatory responses.

INFLAMMATION AS A LINK BETWEEN OBESITY AND METABOLIC SYNDROME

Metabolic syndrome, also known as Syndrome X or insulin resistance syndrome, is a combination of medical disorders that, when occurring together, increase the risk of developing cardiovascular disease, stroke, and type 2 diabetes. Gerald Reaven, in his 1988 Banting lecture, described "Syndrome X" as the association of insulin resistance, hyperglycemia, hyperinsulinemia, hypertension, low HDL cholesterol and elevated VLDL triglycerides [4]. Today, obesity, especially abdominal obesity or central obesity, has been added to the list and considered to be one of the most important criteria for evaluating metabolic syndrome.

In the past two decades, the search for a unifying mechanism behind the pathogenesis of obesity-associated metabolic syndrome has revealed a close relationship between nutrient excess and an alternative form of inflammation,

called “metabolic inflammation” or “metainflammation”, which is characterized by the chronic, low-grade inflammation that is observed in obesity [5].

Appreciation of the involvement of inflammation in insulin resistance or type 2 diabetes started with the use of salicylate. In 1876, Wilhelm Ebstein first demonstrated that high doses of sodium salicylate could diminish glycosuria in diabetic patients [6]. Consistently, in 1901, R. T. Williamson reported that “sodium salicylate had a definite influence in greatly diminishing sugar excretion” [7]. However, the hypoglycemic actions of salicylates and the molecular target of salicylates, IκB kinase-β (IKKβ)/NF-κB axis [8, 9], were certainly not known at the time.

The association between insulin resistance and inflammation was later recognized with the identification of insulin resistance in patients with sepsis [10]. We now know that many diseases with active inflammatory responses display insulin resistance as a feature, including hepatitis C, HIV, and arthritis [11 - 13]. Direct proof of the link between inflammation and metabolic responses came from the genetic studies in mice by Hotamisligil and colleagues. They found that adipose tissue from obese mice secretes inflammatory cytokines (such as TNFα) and that these cytokines themselves can inhibit insulin signaling [14, 15] (Fig. **1**).

CLASSIC INFLAMMATION *VS.* METABOLIC INFLAMMATION

Inflammation is usually referred to as classic acute inflammation, an adaptive response to harmful stimuli, such as infection, tissue injury and irritants. Acute inflammation is a protective attempt by the organism to remove the injurious stimuli, followed by a resolution and repair phase to restore homeostasis. The classic response of acute inflammation is a short-term and high-amplitude process, usually appearing within a few minutes or hours and resolving upon the removal of the injurious stimulus. Acute inflammation is characterized by five cardinal signs: pain, heat, redness, swelling and loss of function [16].

Despite sharing similar pathways and mediators, inflammation induced by metabolic surplus or the so called “meta-inflammation” is distinctive and is not caused by the classic instigators of inflammation: infection or injury [17]. Instead, this altered form of inflammation is associated with the malfunction of tissues that

CHAPTER 6

Aging and Inflammation

Daipayan Banerjee, Alexander A. Karakashian, Mariana N. Nikolova-Karakashian*

Department of Physiology, University of Kentucky College of Medicine, Lexington, KY, USA

Abstract: Inflammaging is a term referring to the constitutive low-grade inflammation that underlies the process of aging. The causes of inflammaging stem from an up-regulation of the innate and a decline in the adaptive immune systems and involve chronic induction of the production of inflammatory mediators, including cytokines, chemokines, and bioactive lipids. Damaged DNA and protein that accumulate in the cells of the aging organisms, oxidative stress, and changes in the function of adipose tissue are among the key culprits leading to the onset of inflammaging. Changes in cytokine signaling pathways at cellular levels also occur with aging, contributing to propagation of inflammation. The inflammaging is considered the main contributing factor to the development of various aging-associated diseases, including cancer, atherosclerosis, metabolic, and neurodegenerative diseases. At least in animal models, inflammaging is subdued by common anti-aging therapies like caloric restriction and resveratrol.

Keywords: Adipose tissue, Bioactive lipids, Caloric restriction, Ceramide, Cytokine signaling, Inflammaging, Innate immune response, Interleukin 1, Oxidative stress, Resveratrol, Senescence, Tumor necrosis factor.

INTRODUCTION

In 350 B.C, Aristotle wrote: “It remains for us to discuss youth and age, and life and death. To come to a definite understanding about these matters would complete our course of study on animals”. Understanding the matters of old age is

* **Address correspondence to Mariana N. Nikolova-Karakashian:** University of Kentucky College of Medicine; Department of Physiology, MS508, 800 Rose Str. Lexington, KY, 40536; Tel: (859)323-8210, Fax: (859) 323-1070; Email: mariana.nikolova-karakashian@uky.edu

Robert F. Diegelmann & Charles E. Chalfant (Eds.)

far from complete. We are still trying to determine the fundamental causes of aging and what the maximum possible life span of the human species is. Nevertheless, the concept that aging and inflammation are intrinsically interwoven has become a centerpiece of contemporary gerontology and geriatrics. This is based on two complementary doctrines: immunosenescence and inflammaging. The latter is considered key factor behind numerous serious diseases associated with old age.

Immunosenescence

The term immunosenescence is strictly defined as a decline in the adaptive immune response of the host in response to antigenic challenge. It is exemplified by changes in T-cell subpopulation size, cell-intrinsic defects in B-cells, abnormal secretion patterns of several cytokines, and decreased antibody production [1]. The causes for the impairment of the adaptive immune system in the elderly are not entirely clear. Replicative senescence of hematopoietic stem cells, adaptation of the immune system to persistent intrinsic and extrinsic challenges, and intrinsic de-regulation of signaling pathways *via* changes in the lipid rafts, are just some of the proposed causes for the onset of immunosenescence [2]. Regardless the cause, this decline in the adaptive immunity is directly linked to increased susceptibility of the elderly to infectious diseases, as well as poor response to vaccination and increased infection-related mortality and morbidity. The elevated incidence of cancers in the elderly is also linked to some extent to the reduced immuno-surveillance for cancerous cells [3]. Somewhat paradoxically, age-related immuno-senescence has also been linked to increased autoimmunity (the loss of self-tolerance) in the elderly. Finally, the onset of a state of chronic low-grade inflammation in the elderly has been suggested to be at least in part, the result of declining adaptive immune system.

Inflammaging

The state of perpetual low-level inflammation is another characteristic of the aging process and is often referred to as “inflammaging”, a term coined in 2000 by Franceschi *et al.* [4]. It is thought to contribute to a plethora of degenerative illnesses, including cardiovascular diseases, neurodegenerative syndromes, and

cancer as well as ailments such as muscle cachexia. While immunosenescence refers to the decline in the adaptive component of the immune system, inflammaging is a loosely defined term that denotes an increased activity and hyperresponsiveness of the innate arm of the immune system. Inflammaging is associated with subtle increases in local and/or systemic concentrations of inflammatory markers. Those include pro-inflammatory cytokines, chemokines, acute phase proteins, and bioactive lipids. The process is accompanied by intrinsic, cell autonomous changes in the cellular response to inflammation, typically in the direction of hyperresponsiveness. The probable cause for this hyperresponsiveness is age-related changes in the cytokine signaling pathways that cause hyper-sensitization of cells to even small amounts of agonists (amounts that typically have no effect in young organisms) resulting in propagation of pro-inflammatory signaling. All this contributes to the onset of tissue inflammation and to the increased incidence of aging-associated diseases.

While immunosenescence certainly has a role in the onset of inflammaging, numerous other factors are also essential. These include: changes in the neuro-endocrine axes, increased oxidative stress, intrinsic changes in the TLR signaling cascades in various cell types, metabolic stress, and the inability of cells to repair and clear damaged cellular components (like DNA, protein, and lipids). Although the exact causes of inflammaging may be debatable, the link to various aging-associated diseases like cancer, Alzheimer's, and cardiovascular disease is not. Many of the proposed anti-aging remedies such as caloric restriction, resveratrol supplementation, and others seemingly subdue the pro-inflammatory state in the elderly in parallel to a decreasing incidence of some aging-associated diseases. Significant research efforts are currently targeted at furthering our understanding of the association between inflammaging and disease, as well as elucidating the fundamental reasons for the onset of inflammaging. The goal of this chapter is to summarize the current knowledge regarding the causes, manifestation, and consequences of the state of inflammaging in the elderly, focusing on changes related to the innate immune system.

CHAPTER 7

Allergic Inflammation

Joshua L. Kennedy*, Matthew C. Bell

Departments of Internal Medicine and Pediatrics, Division of Allergy and Immunology, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Abstract: Atopic diseases, including seasonal and perennial allergic rhinitis, asthma, atopic dermatitis, and food allergy, affect a significant proportion of the United States population. Specific host inflammatory patterns characterize these allergic responses. Whether the innate or adaptive immune responses are recruited for a specific antigen, the signature of cytokines secreted will identify this inflammatory pattern and, in the presence of the correct cellular infiltrate, will yield enhanced T helper 2 (Th2), or allergic, inflammation. A description of the various cell types involved in allergic inflammation and the inflammatory responses leading to allergy, including innate and adaptive immunity, are presented in this chapter. Specific pharmacologic modulation utilizing monoclonal antibodies is also discussed.

Keywords: Adaptive Immunity, Allergic Inflammation, Cytokines and Allergy, Pharmacologic Modulation, Th2 inflammation.

INTRODUCTION

Allergic diseases, including allergic rhinitis (seasonal and perennial), asthma, atopic dermatitis, and food allergy, affect approximately 1 in 5 adults in the United States [1]. In sensitized individuals, exposure to specific allergens (antigens) leads to symptoms of runny nose, sneezing, itchy eyes, cough, itchy skin, and rash, and, in some patients, more severe symptoms, including anaphylaxis. Anaphylaxis is defined as a severe allergic reaction with acute onset involving two or more body systems. These symptoms can include respiratory

* **Address correspondence to Joshua L. Kennedy:** University of Arkansas for Medical Sciences, 13 Children's Way, Slot 512-13, Little Rock, AR 72202, USA; Tel: 501-364-1060; Fax: 501-686-8765; Email: kennedyjoshual@uams.edu

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compromise, wheezing, reduced blood pressure (hypotension), involvement of the skin (urticaria or hives), swelling (angioedema), persistent gastrointestinal symptoms (abdominal pain, vomiting, and diarrhea) after exposure to an allergen that may progress to death if not treated quickly and appropriately with intramuscular epinephrine [2].

A distinct inflammatory pattern can be delineated in atopic, or allergic, individuals based upon characteristic cytokine profiles and cellular infiltrates. Cytokines are secreted proteins with growth, differentiation, and activation functions that regulate and direct the nature of immune responses, subsequently leading to inflammation [3]. Distinct antigens (allergen)-specific cytokine profiles within a given individual polarize the inflammatory environment and, in atopic subjects, promote "pro-allergic" responses. In allergic individuals, a combination of innate and adaptive immune signals produces a distinctive cytokine milieu, enhancing a predominant T helper type 2 (T_H2) response and production of the allergic antibody, IgE. Because cytokines serve as critical mediators of the immune response, they are attractive targets for therapeutic intervention in a variety of allergic disorders. For this chapter, distinct cell types involved in generating and maintaining allergic inflammation will be discussed. In addition, cytokines leading to T_H2 immune responses and IgE production are categorized as those predominantly associated with innate and adaptive immune responses (Table **1**).

CELLS INVOLVED IN ALLERGIC INFLAMMATION

Allergic inflammation begins with the exposure of an allergen at the epithelial cell surface of the nose, lung, gastrointestinal mucosa, and/or skin, triggering a cascade of inflammatory signals. First, through stimulation of various receptors on the surface of the epithelial cells, innate cytokines are secreted that may bias toward a T_H2 response (see section Innate Cytokines Involved in Allergic Inflammation) [4 - 6]. Second, dendritic cells (DCs), which function as professional antigen presenting cells (APCs), will capture the allergen and travel to regional lymph nodes. The allergen is subsequently presented to naïve T cells within the lymph node through major histocompatibility complex (MHC) class II receptors (Signal 1). Signal 2 is a verification step, which requires the interaction

of CD80/86 on the surface of DCs to CD28 on T cells. If this step does not occur, the T cell presumes that it is recognizing self-antigen and becomes anergic, or turns off.

Table 1. Summary of Innate and Adaptive Cytokines their receptors and targets.

Allergic Inflammation	Cytokine	Chromosome (Human)	Receptor	Sources	Targets
Innate cytokines					
	TSLP	Chr 5	TSLPR/ IL7R-chain	Epithelial cells Fibroblasts	**Dendritic cells**: increased ability to attract T_H2 cells **Eosinophils**: Induced release of proinflammatory cytokines and chemokines **Mast: Cells**: Increased production of $T_H2$cytokines T Cells: Increased differentiation to T_H2 cells **Basophils**: Increased production of T_H2 cytokines and increased responsiveness to IL-33
	IL-25 (IL-17E)	Chr 14	IL17R	Epithelial cells Fibroblasts Eosinophils Mast Cells	**T cells**: Increased differentiation to T_H2 cells **Basophils**: Increased production of T_H2 cytokines **Mast cells**: Increased production of T_H2 cytokines **ILC2**: Release of IL-5 and IL-13
	IL-33	Chr 9	IL1RL1 (ST2)	Epithelial cells Smooth muscle cells Keratinocytes Dendritic cells Macrophages	**T cells**: Increased differentiation to T_H2 cells **Macrophages**: increased cytokine production **Dendritic cells**: Increased cytokine production, up regulation of MHC and co-stimulatory molecules **Eosinophils**: Increased proliferation, survival, and chemokine production **Basophils**: Increased production of T_H2 cytokines **Mast cells**: Increased production of T_H2 cytokines **ILC2**: Release of IL-5 and IL-13

CHAPTER 8

Inflammation in Type 2 Diabetes

Agbor Ndip[1,2,*], Edward B. Jude[1,3], Andrew J.M. Boulton[1,4]

[1] *Centre for Endocrinology and Diabetes, Institute for Human Development, University of Manchester, Manchester, UK*

[2] *Department of Diabetes, Warrington General Hospital, Warrington, UK*

[3] *Department of Diabetes Tameside General Hospital, Ashton-Under-Lyne, UK*

[4] *Department of Diabetes and Medicine, Manchester Royal Infirmary, Manchester, UK*

Abstract: Accumulating evidence has demonstrated that intensive glucose control improves microvascular complications in type 2 diabetes; however, such interventions have limited value in reducing macrovascular outcomes. Diabetes is in fact a heterogeneous disorder, with subclinical inflammation playing a significant role. An overview of the key inflammatory mediators and signalling pathways driving the onset of diabetes (beta cell failure and insulin resistance) and the development of complications is presented in this chapter. The inflammatory pathways involving interleukins (IL-1β and IL-6), tumour necrosis factor (TNF-α), AGE/RAGE and NLRP3 inflammasome all play important and different roles. Further careful characterisation of these pathways is warranted in order to inform novel lines of therapeutic interventions to reduce the burden of disease. As diabetes affects various target organs, topics covered elsewhere in this book have been deliberately omitted, but the reader is encouraged to read those chapters to gain a more comprehensive picture.

Keywords: Diabetes, IL-1β, IL-6, Inflammasome, Inflammation, Interleukins, NLRP3, TNF-α.

INTRODUCTION

Diabetes is clinically defined and characterised by hyperglycaemia predisposing

[*] **Address correspondence to Agbor Ndip:** Warrington General Hospital, Lovely Lane, Warrington, WA5 1QG, UK; Tel: +44 (0) 1925662582; Fax: +44 (0)1925662042; Email: agbor.ako@manchester.ac.uk

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individuals to long term microvascular (nephropathy, neuropathy, and retinopathy) and macrovascular (cerebrovascular, cardiovascular, peripheral vascular disease) complications. In a nested case-control analysis of participants in the ADVANCE study, interleukin-6, a major proinflammatory cytokine was found to be independently predictive of macrovascular events and mortality in individuals with type 2 diabetes who had baseline CVD or risk factors [1].

The importance of inflammation in cardiovascular disease in general cannot be overstated; major trials are underway targeting IL-6 system (CIRT; Cardiovascular Inflammation Reduction Trial) and CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) [2]. It should be noted that inflammatory pathways involved in the pathogenesis of diabetes (IL-1β) are not necessarily the same as those driving the development of diabetes-related complications (IL-6) [3, 4]. For example, a multiprotein complex called the inflammasome (NLRP3) drives inflammation in the kidneys and in pancreatic beta cells while MMPs and TNF-based inflammatory pathways are seen in neuronal inflammation.

INFLAMMATORY MECHANISMS IN THE PATHOGENESIS OF DIABETES

Type 2 diabetes is characterised by a reduced insulin-stimulated glucose uptake in peripheral tissues (insulin resistance) and beta cell failure. Insulin resistance occurs early in the disease, including in pre-diabetes states. The pancreatic beta cells compensate for insulin resistance by increasing their functional mass (leading to increased insulin secretion); therefore, not every obese or insulin resistant person eventually develops diabetes. However, overt diabetes – and certainly in the later stage of the disease - is characterised by failure of expansion of functional beta cell mass to compensate for insulin resistance. The pathogenesis of diabetes is diverse but inflammation plays an important role in both insulin resistance and beta cell failure (reduced beta cell mass and/or reduced ability to secrete insulin).

Inflammatory Mechanisms of Beta Cell Dysfunction/Failure in Diabetes

The mechanisms underlining beta cell failure in type 2 diabetes is driven by

inflammation, a process called *auto-inflammatory insulitis*. This is mediated by interleukin-1 beta (IL-1β). Exposure of human islets to glucose, leptin, or free fatty acids (FFA) stimulates the production and release of IL-1β [5 - 8]. Hyperglycaemia also activates thioredoxin-interacting protein (TXNIP), while reactive oxygen species and oxidative stress enhance the dissociation of TXNIP from thioredoxin [9]. The liberated TXNIP subsequently binds to nucleotide-binding domain and leucine-rich repeat containing protein 3 (NLRP3), sometimes called the NLRP3 inflammasome, which in turn activates caspase 1 leading to a conversion of inactive IL-1β precursors to the mature active IL-1β [10]. Glucose-induced oxidative stress also leads directly to the expression of NLRP3 inflammasome and it should be recalled that human beta cells have low anti-oxidative capacity. High glucose also induces beta cell expression of the apoptotic system FAS (CD95) while beta-cell production of IL-1β further induces FAS expression. FAS stimulate beta-cell IL-1β production and IL-1β enters a vicious cycle of auto-activation/auto-stimulation ultimately resulting in recruitment of inflammatory macrophages (auto-inflammation) (see Fig. **1**). Unfortunately human beta cells express high levels of IL-1β receptors rendering them vulnerable to this cascade. The central role of IL-1β in driving beta cell failure has led some investigators to propose this system as a potential target in the treatment of type 2 diabetes [3]. In fact, the IL-1 system acts as a sensor of metabolic stress (high glucose, oxidative stress) but also as the common final effector pathway in islet and tissue inflammation.

Additional to these inflammatory signals, adipocytokines such as leptin and adiponectin have a deleterious effect on beta-cell mass and function through mechanisms that are as yet unclear. It is noteworthy that auto-inflammatory insulitis in type 2 diabetes is different from autoimmune insulitis seen in type 1 diabetes where beta cell failure is orchestrated by circulating autoantibodies that attack and destroy beta cells in the pancreatic islets. Also, beta cell death during compensatory islet expansion plays a limited role in islet inflammation in type 2 diabetes as islet failure tends to occurs while beta cell mass is still expanding and certainly before cell death.

CHAPTER 9

The Vascular Tree and Heart with Relationship to Inflammation

Bruce D. Spiess*

Johnson Institute for Critical Care Research, Department of Anesthesiology, Emergency Medicine, VCU Medical Center, Richmond, Virginia, USA

Abstract: The circulatory system is made up of blood, the heart (a pump) and miles of biologically dynamically involved conduit- the vasculature. The interaction of cellular elements of the blood with the endothelial lining of the vasculature controls so many short and long term inflammatory processes that this system is complex and just now being understood in terms of its cellular biology and biochemistry. Atherosclerosis is the largest killer of persons in developed cultures. The inflammation of atherosclerosis is indicative of the complexity that can occur within the vascular tree. This chapter will examine the dynamic interactions of endothelium, coagulation and inflammation with a focus upon how perturbations of these systems play in creating disease. We will mention a bit about systemic inflammatory autoimmune diseases and note how these create vascular manifestations.

Keywords: Atherosclerosis, Chemokine, Coagulation, Endothelium, Glycocalyx, Heart, Inflammation, Neutrophil, Oxidative stress, Platelet, Vasculitis.

INTRODUCTION

This chapter will provide an overview of the complexity of the relationships between blood, its circulation, the cells lining/controlling the vasculature (endothelial cells- EC) and inflammation [1]. Blood is a complex fluid made up of multiple cell lines, over 2500 known proteins, thousands of lipids, electrolytes,

* **Address correspondence to Bruce D. Spiess:** Johnson Institute for Critical Care Research, Department of Anesthesiology, Emergency Medicine, VCU Medical Center, 1101 East Marshall St, Richmond, VA 23298-0695, USA; Email: bruce.spiess@vcuhealth.org

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dissolved gases, nutrients and wastes [1]. We, in medicine use blood to transport medicines thereby delivering targeted therapies but also creating a number of unintended consequences to those cell lines and proteins. In the last one hundred and fifteen years wide spread use of transfusion therapy has not only become a mainstay of medicine but has allowed us to transfer cells from individual to individual, with that a number of inflammatory consequences and notably DNA. Physicians have had a focus upon the O_2 delivery by blood as they have studied the circulation. To say that the vascular tree's "main function" is to deliver O_2 is tremendously over simplified, perhaps a biased view. The evolution of coagulation and inflammation through the biome is fascinating and probably tells us a great deal about what proteins have been selected by nature as vitally important for organism survival [2].

For example, the serine proteases can be traced back to the horseshoe crab (*Limulus*) as well as some of the interleukins. The complement system seems to be a higher mammalian evolutionary event. The reader is referred to the reference but it is important to understand that the close control and interaction of inflammation, coagulation and endothelial cell interactions has arisen over millions of years. Our knowledge of this interaction is itself evolutionary and probably quite primitive [2].

The combined arterial, venous, capillary and pulmonary vasculature constitutes a network of over 60,000 miles of conduits [3 - 5]. Wonderment arises when we realize that pulmonary capillary bed alone has a surface area larger than that of an American football field. Blood is pumped to all organ systems by a fluid dependent pump, the heart, at a rate of 40-150 beats per minute for up to 100 years or longer. The pump is load dependent and integrated to react to the organisms stresses. The heart and great vessels provide the pumping chambers and conduits to circulate blood, but they react to inflammation, indeed cause inflammation when diseased and ultimately cause the demise for most of us.

The anatomy and physiology of the heart and great vessels fills textbooks as do many medical interventions upon its valves, myocardial cells, electrical conduits and vascular supply [3 - 5]. The myocardium has, as expected, the highest O_2 demand of the body as well as the most efficient O_2 extraction. The myocardial

cycle requires a great deal of ATP and is therefore highly O_2 supply dependent. The heart has the ability to extract up to 85% of O_2 supplied from its micro-circulation, leading to a very low O_2 saturation in the great cardiac vein/coronary sinus [3 - 5]. The heart has no ability to open new vascular channels which the microcirculation in striated muscles can control dynamically to increase O_2 supply. O_2 supply to the myocardium is dependent upon coronary blood flow, diastolic blood pressure (the left ventricle perfuses only during diastole), the time in diastole and the myocardial wall tension (restricting flow) [5 - 7]. The heart is the only tissue in the body that actually metabolizes lactate to ATP. Therefore, it can continue to create cellular energy during periods so limited O_2 supply. Furthermore during periods of low O_2 supply or in regional portions of myocardium with limited blood supply the myocardial tissue can "hibernate" doing not contractile work but existing to maintain cellular integrity. Once O_2 supply is restored these areas of myocardium undergo O_2 reperfusion physiology which can be quite inflammatory.

Each of the sub-components of the heart (myocardial cells, electrical conduits, valves and tough connective tissue "skeleton") and vasculature has both acute and chronic risks of inflammation [8]. Death of heart tissue (myocardial infarction-MI) and/or chronic congestive heart failure (CHF) occur due to lack of O_2 delivery. Heart failure itself is not just a simple in-balance between O_2 supply and demand [9 - 12]. Rather, CHF itself triggers a long term inflammatory state with wide spread biochemical changes leading to many inflammatory changes throughout the body [9 - 12]. A number of biomarkers, apoptotic signaling molecules and diffuse inflammation affect tissues all over the body when CHF occurs. CHF can result from many causes but in the end creates a state of partially compensated chronic shock. When a MI occurs tremendous forces come to bear creating a local and systemic inflammatory response. Within the structure of the heart the valves- particularly the aortic and mitral valves, special risks for bacterial colonization with establishment of biofilms that lead to valve destruction do exist. Today we are learning more and more about how certain bacterial strains can attach, implant and survive/thrive on the tissues of these valves [8 - 16]. It would seem that the blood flow and shear forces exerted on the major cardiac valves would flush clean these structures, but eddy currents and the shear forces

CHAPTER 10

Rheumatoid and Degenerative Arthritis-Associated Inflammation

Matthias Geyer[1,*], Steffen Gay[2], Ulf Müller-Ladner[1]

[1] *Department of Rheumatology and Clinical Immunology, Internal Medicine and Rheumatology, Kerckhoff-Klinik, Justus-Liebig-University Gießen, Bad Nauheim, Germany*

[2] *Department of Rheumatology, Center of Experimental Rheumatology, University of Zürich, Zürich, Switzerland*

Abstract: Among a diversity of localizations throughout the human organism, inflammation may also manifest within joints. It is an important feature of rheumatoid and degenerative arthritis, two major rheumatic joint disorders with high individual disease burden and tremendous socio-economic costs. Their etiologies and pathogenic mechanisms are quite diverse. Many aspects are still not fully understood today, and this often compromises instant and adequate individual therapy. However, continuing research efforts seem to succeed in gathering novel insights that also pertain to the inflammatory aspect, which represents a major player in painful and rather disabling joint destruction. However, it turns out to constitute the common final path within a complexity of initiating and perpetuating processes. Even though lacking total completeness, the different contributions of genetics, the immune system and environmental factors are well investigated to a far extent in rheumatoid arthritis, while in degenerative arthritis correlating elucidations lag behind these achievements, which might be due to a minor immunological but the more enigmatic pathology. Nevertheless, growing investigative efforts to similarly distil key mechanisms of disease are also quite well under way in osteoarthritis. The present review aims to give a selected overview over the current knowledge about rheumatoid and degenerative arthritis. Although this includes aspects on disease management in the clinical routine, the main focus is given by shedding light on the etiopathogenic context including establishment of inflammation in both entities.

[*] **Address correspondence to Matthias Geyer:** Kerckhoff-Klinik, Abteilung für Rheumatologie und klinische Immunologie, Benekestr. 2-8, D-61231 Bad Nauheim, Germany; Tel: +49 6032 996 2101; Fax: +49 6032 996 2104; Email: m.geyer@kerckhoff-klinik.de

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Keywords: Degenerative arthritis, Disease management, Etiopathogenesis, Immunology, Inflammation, Joint destruction, Osteoarthritis, Pathogenic mechanisms, Pathology, Rheumatic joint disorder, Rheumatoid arthritis.

INTRODUCTION

Rheumatoid and degenerative arthritis constitute two major rheumatic joint disorders with inflammation as one of several important features of different individual value. While degenerative arthritides represent the most frequently diagnosed disorders of the musculoskeletal system in general with manifestations of the spine ranging higher than those of peripheral joints such as the hand, knee or hip, rheumatoid arthritis, in contrast, constitutes the most frequent primary systemic inflammatory autoimmune joint disease.

It usually favours the small peripheral joints, but is not restricted to them. Both diseases account for a large percentage of physical disability in affected patients as well as for tremendous masses of direct and indirect socio-economic costs. With turn of the past millennium, musculoskeletal disorders ranged on third position after coronary heart disease and cerebrovascular conditions according to data collected by the World Health Organization in this regard [1, 2]. Thus, due to the demographic changes to be expected for the future, not only further attention has to be paid to such musculoskeletal disorders, but also money to adjunct research considerations, since the etiology and pathogenesis of both conditions are quite diverse and many aspects still not fully understood today. This also often compromises instant and adequate individual therapy. However, arising from sincere intentions to mitigate the burden of rheumatic disease and to substantially overcome all these eminent impasses, researchers throughout the world are continuously struggling to unravel the mysteries of pathogenic pathways. Thus, although still not being elucidated in all aspects and to the last definite extents, more and more pieces can be added to the complex picture of pathogenic circumstances participating in the development of uncomfortable and painful disability associated with joint disorders as outlined herein. While the different contributions of genetics, immunological and environmental factors combined by chance are well investigated in rheumatoid arthritis, suchlike achievements in degenerative arthritis lag behind, which might be due to the less immunological

and thus the more enigmatic pathology. The review of this chapter aims to selectively summarize the current knowledge on both rheumatoid arthritis and osteoarthritis, each ultimately leading to joint destruction with loss of function. Although the major focus will shed light on the etiopathogenic context including inflammation this e-book is dedicated to, the authors also intend to briefly add some rather practical aspects on disease management pertaining to symptoms, diagnosis and treatment of affected individuals in the daily clinical routine to round the overall prospect.

ANATOMICAL AND PHYSIOLOGICAL BACKGROUND

Defining the Joint

Composed of the bony skeleton and many muscles executing moving actions under nerval control, the musculoskeletal system is as prerequisite that enables the human organism to move over distance. Its flexibility is ensured by the multiplicity of distinctively configured single large and small bones. When they converge with their ends at specific sites of articulation, they must be linked to each other to be stabilized and to withstand mechanical load. This becomes anatomically realized by three different modes. (i) When connected by connective tissue, this constitutes fibrous joints or syndesmoses as is the case in *e. g.* radio-ulnar or distal tibio-fibular articulation; (ii) cartilagineous tissue forms cartilagineous joints like the manubriosternal synchondrosis or the symphyses; (iii) a particular capsule with a layered architecture encompasses synovial joints. In these the bones are not directly bound to each other and have a joint cavity. The term “joint” henceforth used always refers to these synovial joints. Some joints may further encompass additional supplemental structures. An articular disc, menisci or a labrum built of fibrous cartilage, for instance, help to optimize articular contacts or expand flexibility. Apart from these genuine joint compartments, adjunct ligaments, tendons and skeletal muscles supportively contribute to joint stability. In case of diseased joints, however, the extent of mobility can often be extremely limited. The causes may be found in each of the participating tissues, but most likely within the genuine joint tissues such as synovium, cartilage or subchondral bone.

CHAPTER 11

Inflammation in Oral Diseases

Praveen R. Arany*

Oral Biology, School of Dental Medicine, University at Buffalo, New York, USA

Abstract: The oral cavity is a unique anatomical niche with its complex milieu of factors that has developed an intricate and elaborate network of pathophysiological responses. This chapter provides a brief overview of the fundamental pathophysiology of oral cavity with an emphasis on the inflammation and immune responses that regulate various oral diseases. The compounding nature of microbial and mechanical insults adds intriguing facets to the role of inflammation in the etiopathogenesis of oral pathologies. Finally, current and future strategies to prevent, reduce or reverse the injurious nature of inflammation in various oral diseases are briefly discussed.

Keywords: Inflammation, Microbial biofilms, Oral immunology, Oral Mucosa, Wound healing.

INTRODUCTION

a. The Unique Niche of the Oral Cavity

The cornerstone of overall human health lies centrally with the ability of the oral food intake and processing the daily nutritional requirements. The oral cavity is unique anatomical niche with intricate biological mechanisms enabling a harmonious function of hard and soft tissue in a moist environment. The complex morphology and synchronized dynamic motion of teeth and jaw bones along with the adjacent soft tissues provide rigorous and sensitive functions such as mastication, taste and phonation. The evolution of the craniofacial skeleton included rugged, sharp teeth for the roughage-filled diet to smoother,

* **Address correspondence to Praveen R. Arany:** Oral Biology, School of Dental Medicine, University at Buffalo, 3435 Main Street, B36A Foster Hall, Buffalo, NY 14214, USA; Tel: 617-785-1868; Email: prarany@buffalo.edu

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blunter forms for our current softer, processed diet.

Moreover, there exists an unique interaction between the hard tissues of the tooth hard and gingival soft tissues termed junctional epithelium within a narrow crevice around teeth [1]. This semi-permeable interactive zone allows hematopoetic elements form a transudate arising from the gingival capillaries that provides serum proteins and immune cells easy access to the extrinsic oral environment. This transudative secretion is termed Gingival Crevicular Fluid (GCF) and forms a continuous outward flow that performs a physical flushing function, keeping the gingival crevice around the tooth awash with antimicrobial secretions and limits plaque and debris build up.

The major oral secretions are contributed by the three major salivary glands (Parotid, Submandibular and Sublingual) and numerous minor salivary glands predominantly concentrated in tongue, mucosal surface of the lips and palate. These secretions together provide a moist environment allowing for the effective process of mastication and phonation among other oral functions. Besides their critical lubricating function performed by these secretions, they also secrete various enzymes such as lysozymes, lactoferrin as well as immunoglobulins such as IgG, IgA and IgM that have key immune functions [2]. Among various immunoglobulins secreted in the saliva, IgA in particularly significant for its wide range of functions in the oral mucosa. The major contribution to the oral IgA is from the salivary gland secretions while minor contributions are from the circulatory system *via* the GCF. There are two forms of the IgA, the secretory component (J chain) of IgA (sIgA) distinguishes it from the circulating serum form that also protects it from proteolytic cleavage. Oligomeric sIgA has been noted to activate the complement system and opsonization very poorly. The polysaccharide chains of sIgA can bind the mucous layer of lining epithelium blocking surface receptors preventing pathogen adhesion.

b. Microbial Environment

The oral cavity forms one of the three main entryways, all of which are lined by specialized mucosa, into the human body that bring in nutrition and perform key sensory functions. The extrinsic interactive nature of the oral cavity, elevated

temperature from the surrounding environment as well as the presence of a moist and food-laden environment explicity ensures there are plenty of microbial flora. The oral cavity contains thousands of different bacterial, viral and fungal species in healthy individuals. The predominance of certain species among 600 distinct bacterial species alone, often appears to determine the balance between the healthy and diseased states [3]. The secretion of a complex polysaccharide matrix from the saliva and food debris contributes to a physical haven for these conglomerates of microorganisms forming biofilms [4]. These biofilms are resistant to many of the usual mechanical actions during oral functions as well as provide resistance to many of the antimicrobial agents naturally present in the mouth. Individual species of microorganisms appear to have evolved specific sets of surface receptors that enable them to effectively interact with the salivary and biofilm matrix components. These colonies of microorganisms communicate *via* secreting small molecules referred to as Quorum Sensing [5, 6]. These interspecies interactions can be either synergistic or antagonistic to both organisms. A preponderance of certain less abundant forms often results in pathogenic, disease states. One such classic example is the naturally present, low abundance mycotic species, *Candida albicans* that can have exaggerated growth during low saliva or lack of mechanical cleansing resulting in Candidiasis. Another commonly seen example is *Porphyromonas gingivalis* that is usually present in low quantities in healthy individuals but is increased significantly during gingivitis.

A significant effort is being made currently to understand the crosstalk between various species as well as their pathophysiological interactions with normal oral cells and their immune responses. The rapid advances in genomics, molecular biology and microbiology have aided the field to move past a single or multi-gene approach to a *metagenomics* focus [7 - 9]. The global genomic interaction of the abundant prokaryotic microorganisms compared to fewer host oral cells is revealing startling new insights into oral health and disease [10, 11].

c. Oral Mucosal Inflammation and Immune Responses

There is an inherent overlap between inflammation and immune responses as the non-specific effector inflammatory pathways are utilized by both the non-specific

CHAPTER 12

Intestinal Inflammation and Inflammatory Bowel Disease

Chao Li, John F. Kuemmerle*

Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, VCU Program in Enteric Neuromuscular Sciences, Medical College of Virginia Campus, Virginia Commonwealth University, Richmond VA, USA

Abstract: Inflammatory bowel diseases, Crohn's disease and ulcerative colitis, are characterized by uncontrolled inflammation of the intestine. Recent advances in the pathogenesis of inflammatory bowel disease have identified over 160 genetic variants conferring risk of disease. Analysis of the intestinal microbiome has also revealed alterations in the diversity in the composition of commensal and pathogenic bacteria. The combined effects of genetic polymorphisms and dysbiosis combine to result in altered activation and regulation of the intestine's innate immune and adaptive immune systems that result in sustained inflammation. In this review we highlight advances that have elucidated the complex alterations and interactions that shape the inflammatory response of the intestine in the setting of inflammatory bowel disease.

Keywords: Adaptive immunity, Bacterial antigen, Damage-associated molecular pattern molecules, Gut microbiota, Innate immunity, Intestinal barrier function, Pathogen-associated molecular pattern molecules, Th1 cytokines, Th2 cytokines, Th17 cytokines, Toll-like receptors, Treg cytokines.

INTRODUCTION

Inflammatory bowel disease (IBD), Crohn's disease and ulcerative colitis, are characterized by uncontrolled inflammation in the intestine. While the

* **Address correspondence to John F. Kuemmerle:** Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, VCU Program in Enteric Neuromuscular Sciences, Medical College of Virginia Campus, Virginia Commonwealth University, Richmond VA, USA; Tel: (804) 828-4060; Fax: (804) 828-5348; Email: john.kuemmerle@vcu.edu

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pathogenesis of Crohn's disease and ulcerative colitis remain incompletely understood, recent advances reveal several key processes that are involved.

The risk of developing IBD has long been recognized to have a genetic contribution. Recent genome-wide association studies (GWAS) have identified more than 160 loci that are linked to IBD susceptibility. While genetic studies indicate the involvement of key regulatory pathways that are associated with risk variants they also reveal that risk alleles, by themselves, are not sufficient to result in inflammation or clinical disease. Dysregulation of the innate and adaptive immune systems directed against luminal gut microbiota or their products, and immune responses to commensal and pathogenic microbiota are the result of altered intestinal permeability and mucosal barrier function. In this review we highlight advances that have elucidated the complex alterations and interactions that shape the inflammatory response of the intestine in the setting of inflammatory bowel disease.

LESSONS LEARNED FROM LINKAGE ANALYSIS AND GWAS

In 2001, the first susceptibility gene for Crohn's disease, nucleotide oligomerization domain (NOD)-2 was identified [1]. Since then genome-wide association studies (GWAS), and immunochip data have increased the number of IBD susceptibility loci to 163 [2]. Of the 163 recognized single nucleotide polymorphisms (SNPs), 30 are risk loci for Crohn's disease, 23 risk loci are specific to ulcerative colitis, while 110 risk loci overlap between the two. Many are associated with other diseases of autoimmunity as highlighted by immunochip analysis. These genetic studies have not only supported the role of gene polymorphisms in IBD pathogenesis and the regulatory pathways involved but also opened the door to pathway analysis and identification of new mechanisms involved in IBD pathogenesis.

Key pathways that are implicated by genetic studies include intestinal barrier function, subsets of specific T-cells and cytokines, and autophagy. Several of the most highly associated risk loci identified implicate key pathways involved in the intestinal inflammatory response. *NOD2* encodes the intracellular receptor for the common bacterial peptidoglycan, muramyl dipeptide (MDP). MDP stimulation of

NOD2 induces autophagy to control bacterial replication and antigen presentation and modulates innate and adaptive immunity particularly in Paneth cells [3 - 5]. *NOD2* can modulate T-cell responses independently of MDP as well [6]. Deep resequencing of GWAS loci have revealed additional rare variants of NOD2 that are also risk loci in Crohn's disease [7].

The role of defective autophagy in pathogenesis of IBD is also evident from other highly associated risk loci, *ATG16L1* and *IRGM* [8, 9]. *ATG16L1* is essential for auto phagosome formation and thus crucial to all forms of autophagy. I*RGM* belongs to the p47 immunity-related GTPase family.

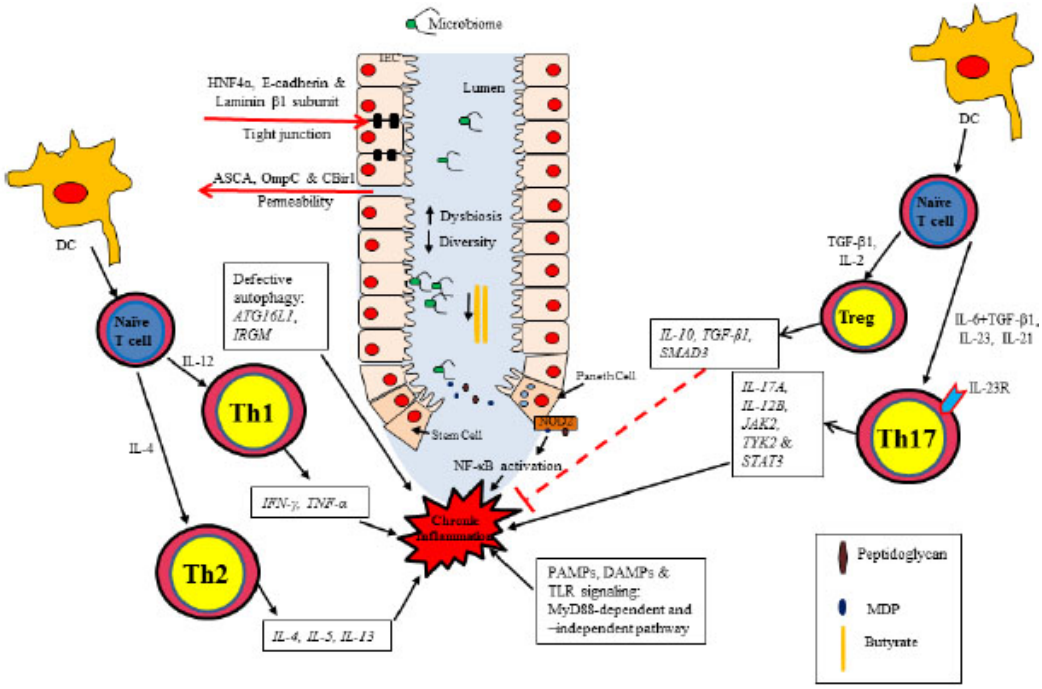

Fig. (1). Intestinal inflammation in the setting of inflammatory bowel disease results from the complex interplay of genetic risk, dysbiosis and decreased diversity of the intestinal microbiome, alterations in barrier function and activation of the innate immune system and adaptive immune system. Inflammation involves crosstalk and interactions between numerous cell types in the gut including intestinal epithelial cells(IEC), Paneth cells, Dendritic cells (DC) that respond to alterations in microbial flora and microbial products including PAMPs and DAMPs to initiate and perpetuate intestinal inflammation. Maintenance of intestinal barrier function, and activation of the innate and adaptive immune systems are altered the functional genomics of the risk variants present in patients with inflammatory bowel disease.

CHAPTER 13

Neuroinflammation

Unsong Oh*

Department of Neurology, Virginia Commonwealth University School of Medicine,Richmond VA, USA

Abstract: Neuroinflammation is a ubiquitous component of central nervous system (CNS) response to injury. In addition to the disorders traditionally considered inflammatory in nature, neuroinflammation contributes to CNS response in ischemic, traumatic and neurodegenerative disorders. Depending on the particular disorder, both innate and adaptive immune responses may contribute to neuroinflammation. This chapter outlines the basic mechanisms relevant to CNS inflammation. The cells of the CNS innate immune response, including microglia, astrocytes, their mechanisms of activation and innate effector mechanisms such as the production of reactive oxygen and nitrogen species and cytokines are discussed. Features unique to the CNS such as the blood-brain barrier and other mechanisms of CNS immune privilege are outlined. Cells and mechanisms of CNS adaptive immune response such as T lymphocytes, B lymphocytes, activation and effector mechanisms are discussed.

Keywords: Astrocyte, Central nervous system, Microglia, Inflammation.

INTRODUCTION

Neuroinflammation encompasses the process by which immune and glial cells respond to pathogens or damage signals within the nervous system. Traditionally invoked in the setting of CNS infections or immune-mediated inflammatory disorders, there is now recognition and interest in the contribution of neuroinflammation to the pathophysiology of a wider range of neurological disorders including stroke, trauma and neurodegenerative disorders such as

* **Address correspondence to Unsong Oh:** Department of Neurology, Virginia Commonwealth University School of Medicine, Richmond, VA, Box 980599, 23298-0599, USA; Tel: (804) 828-3067; Fax: (804) 828-6499; Email: uoh@vcu.edu

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Alzheimer and Parkinson disease. This chapter will focus on basic mechanisms relevant to CNS inflammation.

Conceptually, neuroinflammation can be categorized based on the extent to which the *adaptive immune response* is engaged in addition to the *innate immune response*. Microglia and, to some extent, astrocytes are the innate immune cells of the CNS. Peripheral innate immune cells that may be recruited into the CNS include macrophages, neutrophils and dendritic cells. The T and B lymphocytes are cells of the adaptive immune system, and their presence in the CNS typically indicates the establishment of an adaptive immune response. Features unique to the CNS limit the interaction between CNS innate immune cells and cells of the adaptive immune response, thereby restricting the establishment of adaptive immunity against CNS antigens. These features include the blood-brain barrier and the mechanisms that underlie CNS immune privilege. The establishment of CNS adaptive immune response does occur, nevertheless, and rely on cellular and molecular mechanisms that reside at the anatomical interface between the CNS and the peripheral immune system such as the perivascular space, leptomeninges, choroid plexus and the circumventricular organs.

A common feature of practically all CNS inflammatory conditions is the activation of microglia, the resident innate immune cells of the CNS. Mechanisms that govern microglial activity are, therefore, of central importance in understanding neuroinflammation. Pattern recognition receptors are the basis of key sensor mechanisms for the microglia, detecting both microbial pathogens and cellular distress signals provided by injured neurons and glia. Both neurotoxic and neuroprotective effects have been ascribed to microglia, whose functions include surveillance, phagocytosis, release of cytokines, chemokines, neurotrophic factors and the production of reactive oxygen and nitrogen species. Attributing either a neurotoxic or a neuroprotective role to microglia in the context of specific neuroinflammatory diseases remains a challenge, but is increasingly important as microglia emerge as targets for therapeutic intervention in neuro-inflammatory diseases.

In CNS inflammatory disorders where the adaptive immune response is also engaged, mechanisms that control immune cell trafficking into the CNS are

important targets of intervention in neuro-inflammatory disorders. In addition, distinguishing between contributions from cell-mediated immunity *versus* humoral immunity becomes useful. With respect to cell-mediated (T lymphocyte-mediated) neuroinflammation, identifying the T lymphocyte receptor specificity and T helper lineage bias has been the focus of intense investigation. Humoral (antibody-mediated) immunity may involve the establishment of intrathecal population of B cells and plasma cells, notably in the leptomeningeal compartment [1]. Alternatively humoral immunity affecting the CNS may involve passive diffusion of circulating antibodies through a disrupted blood-brain barrier.

CENTRAL NERVOUS SYSTEM INNATE IMMUNE RESPONSE

The innate immune system is comprised of cells and mechanisms that can mount immediate response to invading microorganisms or cellular injury in the form of physical or biochemical barriers. In the CNS parenchyma, the microglia and, to some extent, astrocytes are the innate immune cells.

Microglia

Microglia are resident innate immune cells of the CNS. They are cells of the myeloid lineage that arise from the extra-embryonic yolk sack, migrate to the CNS early in development and are locally self-renewing [2 - 4]. The microglia survey the CNS, making frequent contact with neurons, and are activated by specific signals associated with pathogens or cellular distress. The microglia possess a multitude of sensor mechanisms to process these signals, enabling the microglia to respond to a variety of forms of injury. In response to these signals, the microglia activate a variety of effector mechanisms, which include phagocytosis, production and release of reactive oxygen and nitrogen species, inflammatory cytokines and chemokines, and neurotrophic factors. The consequences of these effector mechanisms range from elimination of pathogen or cellular debris to conditioning of the extent and type of subsequent immune response, and may include bystander CNS injury. The presence of activated microglia has come to define neuroinflammation, leading to the assertion that neuroinflammation contributes to virtually all neurological disorders [5].

The concept of reactive microgliosis (reviewed in [6]) is a mechanistic

CHAPTER 14

Pharmacotherapy for Inflammatory Processes

Graham A. Mackay*, Alastair G. Stewart

Department of Pharmacology & Therapeutics and Lung Health Research Centre, University of Melbourne, Parkville, Victoria 3010, Australia

Abstract: Drugs that dampen acute and chronic inflammation and their sequelae are currently some of the most widely utilised therapeutic agents. With the increasing appreciation that inflammation is involved in the pathobiology of most of the serious and complex disorders that affect mankind, the development and therapeutic uses of anti-inflammatory drugs will likely grow with increasing demand for precision interventions in inflammatory pathways. In this article, we examine commonly utilised anti-inflammatory drugs with a view to how their efficacy has informed our fundamental understanding of inflammatory mediators and pathways. We then look at more recently developed, or developing, targeted strategies that have emerged from a deeper appreciation of these pathways.

Keywords: Anti-inflammatory drugs, Asthma, Biologicals, COPD, DMARDs, Glucocorticoids, Inflammatory cells, Inflammation, Inflammatory disease, Inflammatory mediators, NSAIDs, Rheumatoid arthritis.

INTRODUCTION AND SCOPE OF THE CHAPTER

Whilst critical for life, aberrant or inappropriately sustained inflammation is also responsible for an enormous health burden as it contributes to, or in many instances drives, a broad spectrum of diseases (Fig. **1**). These disease states extend across virtually all tissue and organ systems. Understanding inflammation, with a view to controlling its harmful potential, is one of the most pressing medical research priorities. The multifaceted contribution of inflammation to disease

* **Address correspondence to Graham A. Mackay:** Department of Pharmacology & Therapeutics and Lung Health Research Centre, Medical Building, Grattan Street, University of Melbourne, Parkville, Victoria 3010, Australia; Tel: 61 3 8344 3932; Fax: 61 3 8344 0241; Email: gmackay@unimelb.edu.au

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contributed to the rationale behind large-scale, multi-centre clinical trials, such as ASPREE, that examines the broad health benefits of taking the most commonly used non-steroidal anti-inflammatory drug (NSAID), aspirin.

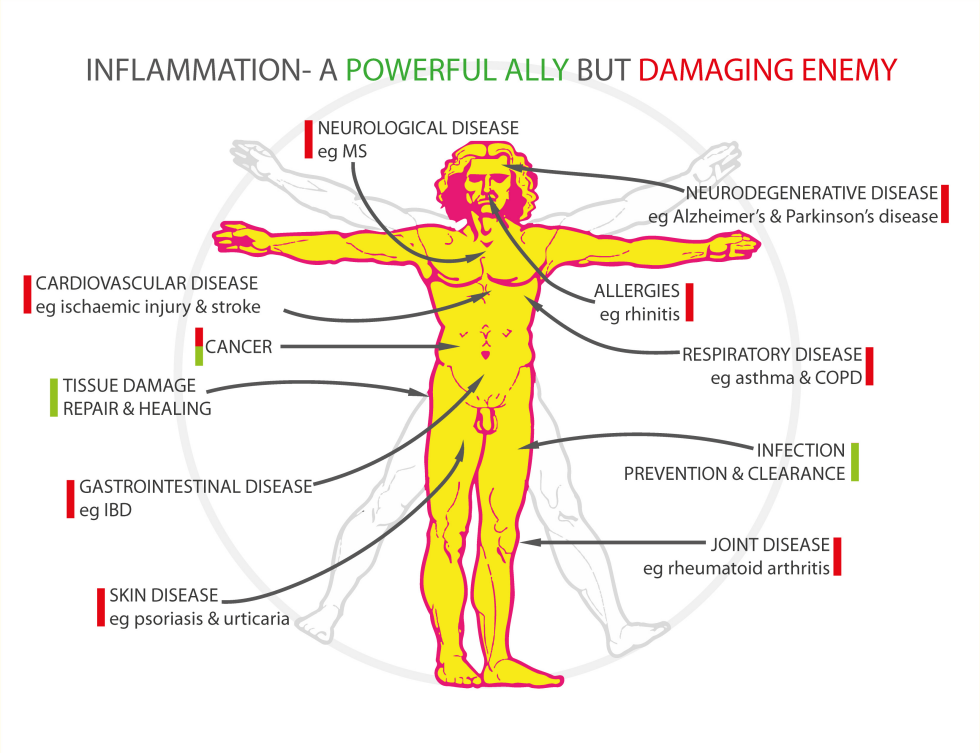

Fig. (1). The broad and varied contribution of inflammation to health and disease.
Whilst inflammation is an essential process to protect us from infection and to facilitate tissue repair, it can go astray triggering or contributing to wide ranging disease states with enormous burden to mankind.

The process of inflammation is initiated upon tissue damage. Whilst this damage may have been caused by exposure to a pathogen that provides a danger signal to encourage inflammation (*i.e.* at a mucosal surface), in many instances this is not the case and the initiator of the inflammatory response is a 'sterile' stimulus. What has become increasingly evident is that upon tissue damage many diverse, but normally intracellular elements can be released to initiate inflammatory pathways that are often common with those triggered by pathogens [1]. Research in this area has uncovered a range of core signalling elements, including the so-called 'inflammasome' pathways. A focus on proteins participating in these pathways

has and continues to highlight gene polymorphisms that are linked to a modified susceptibility to developing inflammatory disease or to exacerbated inflammatory responses. Moreover, these proteins might represent novel drug targets to treat inflammation, the prospects of which will be discussed later in this chapter.

The initiating tissue damage may result from: mechanical insult, ischemic injury leading to cell death; exposure to allergens or irritant/sensitising chemicals or toxins; the formation of aberrant peptides/proteins; local infection with a pathogen that initiates an immune response; or, an autoimmune/autoinflammatory response. Whatever the trigger, or in many instances triggers, 'mediators' are released producing the canonical features of inflammation, with a rapid (seconds to minutes) vascular, followed by a delayed and protracted (hours to days) cellular (leucocyte) response. Inflammation in the skin triggered by tissue damage provides the most clearly visible signs of an inflammatory response. The regional dilatation of blood vessels results in an increase in blood flow that produces reddening. The blood vessels also become leaky through the actions of many of the same mediators that also cause vasodilatation. There are both mechanical and biochemical *sequelae* of this increase in plasma flow into the tissue. The accumulation of leaked plasma fluid increases the pressure in the tissue and causes swelling that may restrict function, in a joint for instance. The swelling can also lead to pain *via* activation of mechano-transduction receptors on sensory nerves. The biochemical consequences include activation of nascent proteases, through exposure to non-vascular tissue components, which can then act on precursors in the inflammatory exudate to generate powerful inflammatory peptide mediators, including thrombin (as well as other coagulation factors), bradykinin and activated complement.

The actions of inflammatory mediators released early in the response, especially those with chemoattractant actions, also serve as a trigger for the influx and activation of leucocytes initiating a potent immune cell-driven inflammatory component. Infiltration of these cells into the tissues is assisted by the vascular changes described above. Leukocytes migrate from the blood to the area of tissue damage. Whilst commonly the initial cellular infiltrate has a strong neutrophilic bias, some inflammatory diseases (*e.g.* asthma) show a more dominant eosinophilic infiltrate. The profile of infiltrating leucocyte populations is thus

CHAPTER 15

Mathematical Modeling of Inflammation

Angela M. Reynolds, Rebecca A. Segal*

Department of Mathematics and Applied Mathematics, Virginia Commonwealth University, Richmond, Virginia, USA

Abstract: Mathematical modeling can be a valuable tool for examining complex biological systems. Modeling can allow researchers to focus on important interactions, identify critical behavior thresholds, explore treatment dosage and timing as well as test new investigational approaches. As will be discussed in this chapter, mathematical modeling has been used to investigate the body's dynamic response to inflammation within the context of a wide variety of conditions and diseases. We describe a variety of mathematical models that are used to explore inflammation and then enumerate the ways these modeling paradigms have been used to investigate inflammation in specific organs and diseases.

Keywords: Agent based models, Cancer, Gastrointestinal track, Lung, Ordinary differential equations, Partial differential equations, Periodontal, Rheumatoid arthritis, Skin.

INTRODUCTION

Mathematical modeling is a broad term and can take many forms. We discuss several different types of models within the context of the investigation of the inflammation, but the general paradigms and principles of modeling can extend to other context. Historically, much of the machinery of mathematical modeling was developed in conjunction with explorations and discoveries in the physical sciences. Systems that are externally observable have been more tenable and easier to discover consistent relationships for Beginning in the late 1960s and

* **Address correspondence to Rebecca A. Segal:** Virginia Commonwealth University, Department of Mathematics and Applied Mathematics, Richmond, VA, USA; Email: rasegal@vcu.edu

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early 1970s, mathematicians began using biology as fodder for research topics and the field of Mathematical Biology was born in earnest. Since then, an explosion of research has transpired in the areas of investigation of biological phenomena through the use of mathematics. New mathematical tools and methodologies have been developed to help address the complexities that have become apparent when working in biological problems.

In the following chapter, we give a brief overview of the typical mathematical approaches used to investigate biological phenomena. We then delve into specific models related to understanding the role of inflammation in the human body. We conclude by suggesting possible directions for future work.

MODELING OVERVIEW

Mathematical models can be of two broad types: deterministic or stochastic. We are purposefully ignoring statistical models. These types of models are different creature altogether and, while useful, are not the subject of this chapter. Here, we are focused on mechanistic models, that is, models that are based on known or hypothesized interactions and dynamics for a particular system. This allows for the investigation of questions for which little data has been collected.

Deterministic models are ones that have the same outcome for each run of the model. If the starting state of the system is the same, then the ending state of the system will be the same. These types of models are powerful for understanding the underlying dynamics of a system. They are useful for settling on the set of properties which best describe the essence of the system. While it may seem that a model with a set outcome would not be too helpful, these models can be quite useful. It can be the case that accounting for the specific underlying dynamics gives rise to non-intuitive system level outcomes that are revealed by the model. Additionally, these models are useful for determining how tweaks to the starting point can lead to different outcomes, how overall behaviors of the system conform or diverge from known biology, and how important each component of the system is to overall performance of the system.

Stochastic models incorporate the effects of noise on the system. Noise is modeled as a random input that affects the system at each time step. It can be used

to model the effects of temperature fluctuations on the rate at which component of the system interact or a high order behavior that affects the system but is not modeled explicitly. The incorporation of randomness into the model gives rise to different transients for every realization of the model. Therefore, the same initial setup will not give rise to the same time dependent transient and in some models may actually give rise to significantly different behavior.

DETERMINISTIC MODELS

Continuous Time

When mathematically modeling a biological process it is necessary to account for how the key components interact over a particular time interval. For example, to model a wound healing response, a set of equations would be developed that track the inflammatory cells, fibroblasts, and collagen over a two week time frame. This type of model focuses on the development of the system with respect to time and does not explicitly account for the spatial location of the components. To model a system with respect to time only, the typical mathematical framework to use are ordinary differential equations (ODE). Theoretical studies of ordinary differential equation system is available from Cain and Reynolds [1] and Perko [2]. The term ordinary emphasizes that there is only one independent variable, which in these models, is time. These are differential equations, so each key component of the system is represented by a variable and the equations track the derivative (or rate of change) of these variables with respect to continuous time. There are models that do not track the variables using continuous time. Instead, these equations use a discrete time frame work that map the variables from time unit to the next (*e.g.* year to year or month to month) without explicitly tracking the component levels between those time points.

ODE models are a common framework in mathematical biology, and have been used to address many aspects of the inflammatory response [3 - 9]. To explore this framework in more detail consider the basic model that accounts for an acute inflammatory response triggered by pathogen, developed by Reynolds *et al.* [4, 5]. This four equation model tracks pathogen (P), inflammatory cells (N, neutrophils and macrophages), tissue damage (D, late state pro-inflammatory) and anti-

CHAPTER 16

Network Analysis of Inflammation

Tomasz Arodz*, Xi Gao

Department of Computer Science, School of Engineering, Virginia Commonwealth University, Richmond, VA, USA

Abstract: Analysis of normal and pathological behavior of biological systems has greatly benefited from incorporating networks that capture knowledge about interactions among genes, proteins or metabolites into explorations of data from high-throughput techniques such as microarrays, next-generation sequencing, or mass spectrometry. Signaling, metabolic and regulatory networks can help make results from statistical data analysis techniques more interpretable to biologists, and can serve as a regularizing factor narrowing the search space for statistical models that determine differences between different states of biological systems. However, knowledge about the underlying biological networks is still incomplete, with false negatives and false positives, which may affect outcomes of systems biology studies. Thus, results of network modeling need to be critically evaluated by domain experts, and followed by additional experimental or computational validation.

Keywords: Biological networks, Computational methods, Differential network analysis, Network inference.

INTRODUCTION

Experimental results concerning individual genes, proteins, metabolites and lipids or other molecular endpoints were always analyzed in the context of existing knowledge about their relationships with other molecular entities. In essence, the approaches that came to be known as network analysis, network biology, or systems biology aim at making the process automatic or semi-automatic with the

* **Address correspondence to Tomasz Arodz:** Department of Computer Science, School of Engineering, Virginia Commonwealth University, 401 W. Main St., Room E4252, Richmond, VA 23284-3019, USA; Tel: 804-827-3989; Fax: 804-828-2771; Email: tarodz@vcu.edu

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use of computer algorithms and computer knowledge repositories.

The move towards network analysis is shaped by three factors. First, it is now possible to construct cell-wide networks of metabolism, gene regulation, and interactions between proteins involved in signaling and other cellular processes, and represent them in a form that can be used by computer algorithms. Results from many assays for discovering interactions are disseminated in electronic form. Also, advances in natural language processing facilitated mining scientific literature for information about interactions. The second factor behind the advent of network analyses was the introduction of high-throughput measurement techniques, most prominently the gene expression microarrays. Interpretation of results that span thousands or even more endpoints without any computer-aided assistance became problematic. The third, most fundamental factor behind network analysis comes from observations that the level of pathways, not individual genes, is often the appropriate analysis level for complex pathologies such as cancer.

Currently available tools and methods for network analysis can bring three main benefits to the exploration of biological data: increased interpretability, discovery of new relationships, and increased robustness of discoveries of inter-group difference with respect to experimental noise.

Increased Interpretability of Experimental Results from Profiling Experiments

Data from high-throughput profiling experiments contain large number of variables, ranging from hundreds endpoints in proteomic studies, to tens of thousands probes in gene expression experiments. In a typical study that involves two or more groups, for example patients with a particular disease and a healthy control, a number of endpoints with statistically significant change in expression will be discovered by statistical tests. Network analysis, in its simplest form, can be used to illustrate relationships between those differentially expressed endpoints. More advanced tools can give statistical estimate as to which known pathways contain more differentially expressed genes than would be expected by chance, and thus can be assumed to play a role in the differences.

Another group of tools can move beyond known pathways, which to some extent are delineated in an arbitrary way, and discover new small networks of relationships based on known interactions.

Discovery of New Relationships between Endpoints in Profiling Experiments

Apart from finding differences between different patient cohorts, another goal of profiling studies is to find novel relationships between individual endpoints. In its most simple form, this takes form of clustering of the endpoints into groups, or a hierarchy of decreasing similarity. In addition, simultaneous clustering of genes and samples, referred to as bi-clustering, is often used, with results presented in a form of a heat map. More advanced methods move beyond clustering towards network inference. Instead of returning a cluster of genes with correlated expression, network inference methods aim to identify direct connections between pairs of endpoints that correspond to causal relationships.

Increased Robustness of Discoveries with respect to Experimental Noise

The analysis of molecular profiles with high number of endpoints is typically confounded by the small number of samples. This often leads to situations where differentially expressed genes do not pass the stringent statistical significance thresholds mandated by multiple-hypothesis testing. Network analysis can use known inter-gene interactions to define groups that may contain differentially expressed genes that fail the statistical tests individually, but as a group are highly significant. Conversely, it can help eliminate false discoveries by discarding genes that pass the significance threshold, but are not connected to any other differentially expressed genes.

BIOLOGICAL NETWORKS: TYPES OF INTERACTIONS AND MAJOR REPOSITORIES AND DATABASES

Biological networks typically use two formalisms to represent the relationships. The most popular one is a graph, a mathematical structure used to represent objects as nodes and their relationships as edges. Nodes typically correspond to genes, proteins, microRNAs or other molecular entities. Edges can represent physical interactions, for example protein-protein binding or complex formation.

SUBJECT INDEX

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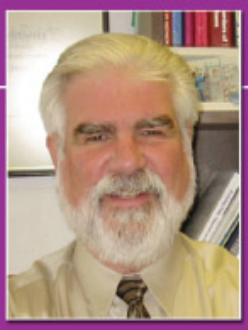
This is an excellent series on inflammation encompassing a range of chapters on mediators, wound healing, metabolism, bowel disease, arthritis, the nervous system, and pharmacotherapy. It is an e-book with the permanence of traditional books and the immediacy of editorial comments, written by experts with the rest of us in mind. The authors have agreed to donate their royalties to the Wound Healing Foundation to foster research by young investigators. What better value; buy it!

Gabriel Makhlouf, M.D., Ph.D.



ROBERT F. DIEGELMANN, PH.D.

Dr. Diegelmann received his PhD in Microbiology from Georgetown University in Washington, DC. Following a postdoctoral fellowship at the National Cancer Institute at the N.I.H. in Bethesda MD he established the Laboratory of Tissue Repair at the Medical College of Virginia in Richmond, VA. He continues to serve as the lab's director and is a Professor of Biochemistry & Molecular Biology at the V C U Medical Center. Dr. Diegelmann co-edited the textbook entitled "Wound Healing: Biochemical and Clinical Aspects", he has published over 200 scientific manuscripts and book chapters on wound healing and has given numerous lectures on the topic at both national and international meetings. His research has been funded by the N.I.H. and the Department of Defense as well as by industry. He is a Founding Member of the Wound Healing Society, had several terms on the Board of Directors and was the society's President in 2013. His current research interests are focused on the impact of trauma and inflammation on wound healing.

CHARLES E. CHALFANT, PH.D.

Dr. Chalfant received his PhD in Biochemistry and Molecular Biology in 1997 from the University of South Florida-College of Medicine under the mentorship of Dr. Denise Cooper. He then joined the laboratory of Dr. Yusuf Hannun at Duke University Medical Center and later the Medical University of South Carolina. Currently, he is a Research Career Scientist in the Veterans Administration and Vice Chair and Professor of Biochemistry and Molecular Biology at VCU. He holds the Endowed Chair in Cancer Cell Signaling from the VCU Massey Cancer Center, and he is currently the Deputy Director of the VCU Johnson Center for Critical Care and Pulmonary Research. His research program has been funded by the NIH and/or the Veterans Administration beginning in 1998. A central focus of his current research program is the sphingolipid metabolites, ceramide and ceramide-1-phosphate (C1P), as well as the biosynthesis of eicosanoids and 3- PUFA-derived lipid mediators. This research led to the communication of the 2011 Avanti Young Investigator Award for Lipid Research.