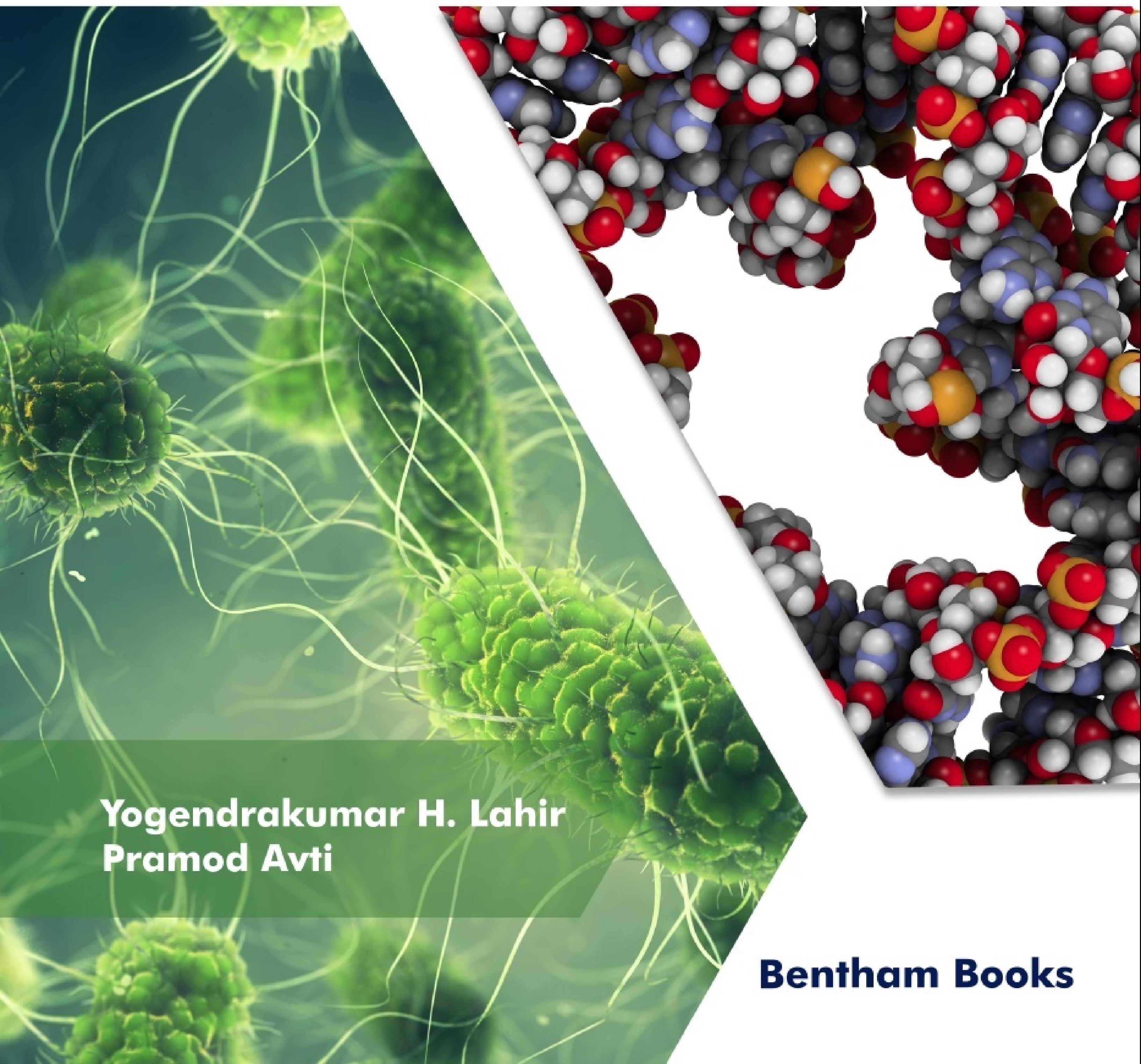
NANOMATERIALS AND THEIR INTERACTIVE BEHAVIOR WITH BIOMOLECULES, CELLS AND TISSUES



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Nanomaterials and their Interactive Behavior with Biomolecules, Cells and Tissues

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Foreword

This book comprises ten chapters; each chapter elucidates specific aspects of nanotechnology, nanoscience, and the basic concepts involved during their multifaceted interactions with and within biological systems and biomolecules.

This presentation elaborates on the introductive remarks on nanotechnology and nanoscience. There is a brief discussion on the definition of nanomaterials, scope, and applications in different fields with emphasis on biological sciences and materials sciences. The interactive behavior of nanomaterials relates to their types and nature. The successful applications of nanomaterials enormously depend on their degree of biocompatibility and bioavailability in the biosystem and at the site of the interface. The physicochemical parameters like inter and intramolecular bonding, hydrophobicity, interactive forces, surface charge, and composition of nanomaterials are well illustrated with suitable examples and supported by the references. When nanomaterials encounter a biosystem, the cellular components like glycocalyx, cell membrane, cytoskeleton, act as the first site of the interface. These components influence the interplay and uptake of the nanomaterials. These entrants form conjugates with ligands, proteins, and cause their effects, and interfere with cellular functioning. Nanomaterials undergo internalization involving phagocytosis, endocytosis. These materials show exclusive interactive behavior with proteins and this depends on the structure of protein, zeta-potential, and nature of binding. This behavior intervenes in cellular physiology and the structure. Protein microchip technology is very useful for analyzing different analytes. The internalized nanomaterials interact with the genetic materials (DNA and RNA) in a biosystem and cause changes in their geometry, physiology, stability, and biophysical aspects. Nanomaterials interact with enzymes *in vitro* and *in vivo*. This feature is used in enzyme technology, enzyme immobilization, biomimetics, and industrial enzymology. The defense mechanism of the biosystem is prone to the impacts of nanomaterials causing immunosuppression or immunostimulation. The nanomaterials intermeddle structurally and functionally with the components of the immune system transforming their roles. Lastly, all these interactive aspects congregate into the wide spectrum of the applications of nanomaterials as detection tools, imaging agents, synthesis, medical implants, and various roles in industries.

A good number of books and reviews report on the specific and selective aspects of nanoscience and nanotechnology. However, there is a need for comprehensive essays that give a consolidated overview of the physical, chemical, biological, biophysical, and molecular aspects of the interactions between nanomaterials and biomolecules, cells, and tissues. This book fulfills this need and offers an incriminated description of the incorporation of basic structural, functional, and physicochemical concepts during the interplays between nanomaterials and biomolecules. The lucid explanation in this book eases the mathematical aspects of the concerned concepts involved. This effort aims to infuse the interest in students, researchers, and foster collaboration through the multidisciplinary approach of nanoscience and nanotechnology in the recent frontiers of biological sciences and nanotechnology.

Each chapter starts with the outline of the chapter, introduction, text, and conclusion; these provide a take-home message of the information contained therein. Throughout the book, suitable examples are presented that support the concepts and are an amalgamation of past and recent research. Lastly, this presentation gives glimpses of the multidisciplinary approach and room to maneuver the various concepts from physical, chemical, applied sciences and technologies, for the betterment of their future applications.

I feel the book will provide a handy but complete reference and review of the nanoworld to students and researchers in this field.

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PREFACE

Nanoscience and nanotechnology both have been utilized by a man during the early days of scientific developments under various civilizations, like ancient India, ancient Mesopotamia, ancient Egypt, ancient China, Japan, *etc*. During these eras, there have been scientific developments and materials in nanoforms that might be in use as it is evident from the monuments and the products found during the excavation. Possibly a common man might not be aware of the terms like nanoparticles, nanomaterials, nano synthesis, *etc*., except the specialized craftspersons. These specialized craftspersons might be using different terminology concerning the particular concept of dimension, size, and other properties of the materials in these eras**.** Nanomaterials are useful in almost all fields of present-day life. These materials have at least one dimension within 1to 100 nm ranges.

The physicochemical features of nanomaterials, mode of their synthesis, duration of exposure, and amount of nanomaterials, *etc*., influence their impacts on the biosystem. Most of the nanomaterials, natural and engineered, both get dispersed in all media and move across almost all types of biological barriers. This ability of nanomaterials exhibits a higher degree of derogative or beneficial interactions. These are of investigatory interest concerning biotic and abiotic components of the environment. These features make them potential agents for their varied applications in industrial, domestic, food-technology, medical, cosmetics, pharmaceutical, and other biomedical fields. Most of the administered nanomaterials get readily disbursed in the biosystem and exhibit a higher degree of metabolic interaction. Such interactions depend on the dose, physicochemical properties of nanomaterials, and cause, either conjugation or dissociation in the interactive biomolecules. The interacting nanomaterials induce changes in the biomolecular conformation, the reactive groups, molecular cross-linkage, hydrophobicity and hydrophilicity, and structural damage, and interrupt cellular functions. The harmful impacts involve micro, macromolecules, cell membrane, cell membrane receptors, cell-organelles, and metabolic pathways. The administered nanomaterials come in contact with the contents of body fluids. The adhesion of nanomaterials onto the cell membrane, even if the biomolecular corona is absent on nanomaterial. The adsorption of proteins on the surface of nanomaterials sharply reduces the adhesion in comparison to the conditions when the nanomaterials are without biological corona. The cellular uptake of the nanomaterials involves two steps: i- initial adherence of nanomaterial to the cell membrane, and ii- internalization of nanomaterial by the cell comprising the energy-dependent pathway.

In most cases, the biomolecules such as proteins, lipids, carbohydrates, *etc*., are present in body fluids of the biosystem. These body fluids include blood, hemolymph, lymph, or any other form of fluid present in the biosystem. The interactions between nanomaterials and biomolecules relate to the specificity of binding ability of biomolecules, the composition of nanomaterial, and their surface physical-chemistry. The effect of the nanomaterial-biomolecular complex formed; generally, the compound formed is with proteins or conjugated proteins that influence the responses of the biosystem. The nanomaterial-protein complex built plays a more significant role in their biodistribution in the biosystem because the protein-nanomaterial-complex formed becomes the identity of the nanomaterials involved within the biological system. Interaction between nanomaterial and biomolecules is a dynamic process. Since proteins are relatively in abundance, they dominate these types of interplay, resulting in the formation of complexes depending on the charge on the surface of protein molecules and nanomaterials. The conformation of the protein at the interface influences the cellular uptake of the nanomaterial. Therefore the interactions between nanomaterial and protein are of great significance in biotechnology and molecular biology.

Adsorption of the proteins on the surface of nanomaterial is a complex process. It is primarily related to (i) - dielectric properties and pH of the medium, (ii)-surface morphology, and surface heterogeneity of nanomaterials and (iii) -the quaternary structure of the protein involved. This phenomenon indicates the existence of the different types of interactions between more significant multimeric proteins, nanomaterial, and small oligomeric proteins.

There is dissociation or binding of proteins present in lower concentrations, but have a higher affinity, influence the separation of conjugated proteins, and this aspect slows the kinetics. Thus the nanomaterials coated with protein can undergo enhanced cellular uptake specifically by macrophages. In most cases, opsonins are present in blood and body fluids. It enhances the ability of macrophages to recognize the surface of the particles entered the biosystem (opsonization). Opsonins like albumin, immunoglobulins, fibrinogen, and compounds of complementary system and apolipoprotein are present in body fluids. They play an active role in the clearance or elimination process in the biosystem. Apolipoproteins are the proteins that bind to lipid.

Lipids are oil-soluble substances like fat and cholesterol and form lipoproteins. These apolipoproteins transport the lipid through the lymphatic circulatory system in vertebrates and hemolymph in the case of invertebrates. The apolipoprotein and phospholipids exhibit amphipathic features having both hydrophilic and hydrophobic components, hydrophilic head and a hydrophobic tail. The apolipoprotein and phospholipids are water-soluble surround lipids and lipoproteins. These interact with enzyme cofactors, exhibit ligand-surface receptors, and low-density lipoproteins (LDL). The distribution of nanomaterials is explicit in cases, like oriented targets, like cancer cells, diseased cells, DNA, RNA, gene, *etc*. Surface-bound molecules like proteins can promote cell-specific uptake of nanomaterials. There are chances that nanomaterials can activate the intracellular signaling pathways. Their dispersibility in air, aquatic, and solid media depend on their nature and specificity.

Any material natural or engineered having nano dimensions and intend to interact with the biological system to evaluate, treat, augment, replace tissue and organ, and have specific functionality. The biocompatibility of such nanomaterials is the first and for most priority for their successful application. The biocompatibility of such materials is the ability to perform appropriate host-response in a specific application. The biocompatibility of nanomaterials depends on the molecular adsorption, mechanical, biophysical, and chemical cellular pathways during their cellular internalization. These interactions are either defensive, interfering oriented targets. Biocompatibility may concern long term or short term specifically for the implanted devices and tissue-engineered devices and conceptually, concerns with cytotoxicity, sensitization, irritation, genotoxicity, implantation, hemocompatibility, carcinogenicity, and biodegradability, *etc*. When biomaterials and hosts come in contact during surgical implants, infusion, injection, extracorporeal circuits, or *in vivo* bioreactor, *etc*., initiate the response.

The processes like material degradation, cell adhesion, mechanical forces generated as a result of the administration as the host response progress with many possibilities like inadequate resolution, clinically relevant effects, either tolerable or non-tolerable, inflammation, hyperplasia, thrombosis, calcification, resolution of the reactions, clinically acceptable results also play a significant role the responses due to these interplays. Biomaterial components like metal ions, polymers, additives, contaminants of nanomaterials on cellular internalization involving specific mechanism, phagocytosis, endocytosis, pinocytosis, *etc*., affect the ambient intracellular environment; this can include material degradation, generation of free radicals like ROS/RNS, cellular damage, alterations in the functionality of cell organelles, interference with apoptotic and necrotic pathways, the passage into nucleus affecting gene expression or gene damage. This process involves material mediators for interactions, chemical structure, elasticity, shape, volume, topology, *etc*.

This presentation is an effort to understand the mechanisms and the involvement of probable parameters along with different concepts, theories, laws, and applied principles of chemistry, physics, biological sciences, and computational simulation. There is a dedicated effort to present the matter precisely, even for those who may not have a mathematical background.

CONFLICT OF INTEREST

The authors confirm that there is no conflict of interest.

CONSENT FOR PUBLICATION

Declared none.

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DEDICATION

This work is dedicated to

Lahir Family
&
Avti Family.

CHAPTER 1

Nanoscience, Nanotechnology, Nanomaterials and Biological Sciences

Abstract: Nanoscience and nanotechnology help manipulate or maneuver atoms and molecules to enable them to function at the nanoscale. Nanoscaled materials are the products of nanotechnology, and these are synthesized or fabricated based on specific guidelines. Nanomaterials can interact with most of the biomolecules, cell organelles, and cells, and can move across most of the biological barriers. These materials can readily be functionalized and modified as per the required targets. The modified nanomaterials become convenient tools in several fields of biotechnology, enzyme technology, tissue engineering, *etc*. In these fields, modified nanomaterials act as a vehicle for biomolecules, imaging agents, sensors, probes as diagnostic tools, devices, *etc*. The matters in the bulk form and at the nanoscale level show variable physicochemical properties, thereby, showing multifaceted abilities. These features are responsible for their variety of applications in day to day life as well as in specialized fields.

Keywords: Antifungal Agent, Antimicrobial Agent, Nanomaterials, Nanoscience, Nanotechnology, Sensors, Wootz Steel.

OVERVIEW: NANOSCIENCE, NANOTECHNOLOGY, AND NANOMATERIALS

Nanoscience and nanotechnology are multifaceted aspects of science that provide information about the manipulation or maneuvering of atoms and molecules and enable them to function at the nanoscale. Such products readily interact with cell organelles, cells, and most of the biomolecules. Nanoscience guides to design and formulate nanostructures that ensure their feasible applications in various fields such as biomedicine, biomolecules, biochemical, pharmaceuticals, *etc*. In these fields, nanomaterials are applicable as a cargo vehicle (drugs, biomolecules, gene, *etc*.), imaging agents, sensors, diagnostic devices, *etc*. The industrial applications include electronics, energy storage devices, enzyme technology, tissue engineering, *etc*.

Nanoscience is a science of formation and interactions of nanomaterials. Materials that have at least one dimension within the range of 1nm to 100 nm (nm=one-billionth of a meter) are regarded as nanomaterials. The materials at the nanoscale

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have different electrical, optical, thermal, and mechanical properties in comparison to their bulk forms. These properties relate atoms and molecules assembly, and interaction at the nanoscale. Nanoscience is a multidisciplinary aspect of science involving principles of material science, physics, chemistry, biological sciences, biotechnology, electronics, quantum mechanism, *etc* [1, 2]. Nano is a prefix used in metrics (metric system), and it represents anything that is one-billionth of some matter in size. It expresses a specific unit that measures mass and time. Materials at this dimension have different properties and behaviors, and both are different in comparison to the respective materials with larger sizes.

The field of nanotechnology has enormous impacts on human life. Nanoscale structures help to store information on 20 nm thick magnetic strips, dirt-resistant and scratch-resistant surfaces, materials that are suitable for tissue regeneration, *etc*. Researchers all over the world are making untiring efforts to explore advanced applications of such materials using basic and applied principles of physics, chemistry, biology, materials science, *etc*. As a result, there has been an enormous development in the field of nanodevices, microscopic development systems, structural and engineering systems, storage of information, computational investigations, biomedical devices, *etc*. The prime focus of nanoscience is on the properties of materials at the nanoscale, and the methodology involved in the synthesis, fabrication, and, assembly of these nanostructures. This science also facilitates the characterization, applications, and functionality of the nanomaterial, nanodevices, *etc*. The observations and study of these wonder materials need very specialized instruments and methodologies that should have the ability to either magnify or detect the products of chemical interactions that produce such nanomaterials in nature or otherwise.

Some of the fine aspects of nanoscience and nanotechnology include bioengineered materials and bionanoscience, quantum confined nanoscale materials, novel tools for nanoscale device patterning, imaging, and characterization, molecular nanoscience and electronic materials, *etc* [3]. James Tour and his coworkers made a nanoscale car, consisting of phenylene ethynylene (oligo), alkynyl axles, and four spherical fullerenes (C60) in 1906. This car moves on the gold surface as the temperature increases, and above 300ºC, it moves very fast. (This nanoproduct has the chemical formula $C_{430}H_{274}O_{12}$ and molar mass 5632.769). In 1908, the National Nanotechnology Initiative (nano.guv) published a strategy related to nanotechnology. This document is a general guideline that governs the varied aspects involved in this technology.

Generally, nanostructures are the materials in the form of structural elements (particles), clusters, crystallites, or molecules. These products are in high demand as they have significant academic and industrial applications. There have been tremendous efforts to study their properties and changes concerning their infinitely extended solid form to particle size consisting of countable numbers of atoms. The functions of the nanomaterials depend on their size and physicochemical properties. These parameters are of prime concern during their synthesis and investigations. At the nanoscale, the properties and functionalities of matter, such as electrical, optical and magnetic, *etc*., change. These features are related and exhibit variations about the changes in their infinitely extended solid form to an excellent particle state. At this state of materials, their atoms are countable. This condition also exists even in the confinement of nanoscaled semiconductors or metal clusters or colloids. The nonmetallic elements, like carbon-based nanomaterials such as fullerene, nanotubes, *etc*., also exhibit similar behavior. These features make them suitable for their pervasive applications not only in nanoscience but also in other biomedical fields [4].

HISTORICAL ASPECTS OF NANOSCIENCE AND NANOTECHNOLOGY

One of the earlier established applications of nanoscience and nanotechnology has been reported during 600 BC in India. Indian blacksmiths produced wootz steel, mixing specific ingredients like wood from Cassia auriculata and leaves of Calotropis gigantea, and, other ores from the particular Indian mines. These ingredients were used during the forging process in steel industries resulting in the formation of petite cakes. These tiny cakes are called wootz steel, and, the steel formed from these was wootz steel. During this process, and, related ones, like thermal cycling and cyclic forging, catalytic segregation of elements into a different array was induced [5]. Carbon nanotubes and cementite nanowires were noticed in the microstructures of wootz steel. In ancient India, a sophisticated thermomechanical treatment related to forging and annealing had been in practice. This technique has been applied to refine steel with specific qualities. For this purpose, wootz steel cakes were used. This technique was developed and spread globally. The medieval bladesmiths could use a mineral called cohenite to reduce the brittleness of cementite (having carbon contents of 1-2% wt). Mechanical processing makes microstructure of steel to be fine-grained and superplastic at an appropriate high temperature. The addition of tiny amounts of vanadium, chromium, manganese, cobalt, nickel and other, resulted in specific bonding of cementite during thermo-cycling at temperature lowers than the formation of cementite (around 800ºC). Actually, during this treatment, the formation of cementite nanowires takes place at the microstructure level [6, 7]. History of nanoscience and nanotechnology is traced at a much earlier stage. Famous glass, Lycurgus Cup; a product of the 4th century, is known for its dichroic behavior because of the presence of colloidal gold and silver particles in the glass. These

CHAPTER 2

Nanomaterials and their Behavioral Aspects

Abstract: Nanomaterials exhibit some extraordinary features. These features are the bases for their applications in different fields such as biomedical, pharmaceuticals, communication, warfare, clothing, sports industries, automobiles, *etc*. Reports reflect on their interactions with abiotic and biotic components of the environment. It is very imperative to understand their interactions with biomolecules or related materials. These investigations elaborate on their benefits and, damaging effects; these ascertain their appropriate applications. The concerned reactants may be natural, organic, or inorganic. Nanomaterials interact with components of an environment in a medium like air or water, on the bases of their specific structure and functional groups. During such interactions, the physiological and ecological parameters of the environment also play a significant role. The physicochemical properties of nanomaterials and surface functionalities are due to the specific modifications of the nanomaterials. The hydrophobicity or hydrophilicity of nanomaterials influences their interactions between them and the biological and ecological systems. This chapter deals with the behavior of nanomaterials, parameters, and conditions related to their interaction in a biosystem.

Keywords: Absorption, Applications, Drug delivery Systems, Nanomaterials, Physicochemical Properties, Plasmonic Nanoparticles, Scattering, Surface Energy, Tissues Engineering.

INTRODUCTION AND OVERVIEW

Nanomaterials are present in the environment and influence its abiotic and biotic components. Although the world nano is relatively recent, the term, minimal particulate matter, as earlier conceived, has left its impact on animals, fungi, microbes, and plants. These particles are the products of human and natural activities or processes such as combustion, volcanic eruptions, forest fire, dust storms, tornado, domestic dust, and anthropogenic activities, *etc*. Many misconceptions or miss apprehensions, like bad air, bad/evil spirits, phobia, *etc*., are associated with the nanomaterials. Research about nanomaterials reveals their link with respiratory, cancerous, cardiovascular diseases and mortality, *etc* [1]. During this period, these particles have not been precisely defined, characterized, or classified. Their impacts are also not technically analyzed or understood. Such particles differentiate as coarse, ultra-fine, and very fine-textured particles, (bhasm). These are used in different medical branches like Ayurveda, Homeo-

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pathy, or Unani Medicine for the treatments. The inception of the nanoscale is helpful in the characterization of nanomaterials, and the related investigations enhance the understanding of mechanisms concerning their interactions with biotic and abiotic components of the environment [1].

Studies related to nanomaterials involve size, shape, and, physical features, and, characterization under the guidance of the principle of materials science and metrology (the science of measuring). Such investigations reflect on the term nanoscale (material with at least one dimension in the range 10^{-9} m or 1-100 nm). Studies related to the structural and functional aspects of nanomaterials elaborate on the unique physicochemical, optical, electronic, electrical, and thermal conduction and mechanical properties, *etc*. These understandings lead to the successful micro and macro fabrications and strengthen the concept of nanotechnology, its commercialization, and commoditization [2 - 4].

DEFINING NANOMATERIALS

Usually, a state or a phase of matter is defined to ease its detailed description and for identification or nomenclature. This process is solemnized based on the specific features or properties or the impacts of that matter or state. Defining nanomaterials is relatively an area of active scientific and policy-related debate [5]. Maynard (2011) expressed his view against characterizing the manufactured nanomaterials. Related definitions are helpful in identification, description (at least to some extent) of the mater under consideration to assign them a specific nature or impact as benign or hazardous. Understandably, matter at nanoscale exhibits different specific properties as compared to their corresponding bulk forms. Defining the nanomaterials helps to know about their safety, impacts, and concern precautions against their derogative effects. This topic is subjected to legitimate public concern, adaptation, and political acceptance or response and overall industrial applications. Hence, an appropriate definition is a need, even though nanomaterials show heterogeneous nature. Their category defines nanomaterials, impact on human health, and environmental risk. There are chances that technical definitions based on parameters like size, maybe deficient or insufficient but may be helpful to evaluate the risks involved in their commercial production, investment, and marketing aspects [6 - 8].

The following are the definitions approved by some of the global regulatory authorities.

1-”Nanomaterials are insoluble or biopersistent. These materials are either intentionally manufactured or fabricated with one or more external dimensions or an internal structure with the scale from 1 to 100 nm”. This definition is regulatory and is proposed by the European Commission on cosmetics Directives. Nanomaterials include under the cosmetic category [9].

2-"The products under FDA regulation are useful in engineered nanomaterials. The prime parameters include dimension and that should be within 1nm to 100 nm range or the physical and chemical properties or biological effects that change the dimension of the nanomaterial". This definition is a piece of advice, but this agency suggests no formal description. Cosmetics, pharmaceuticals, food, and food packaging materials come under these guidelines [10].

3-"There are mostly only outlines that are advisory definitions related to the nanomaterials that are involved in products. Such materials should be solid at 25ºC and atmospheric pressure with particle size within 1nm to 100 nm at least one dimension. The materials should show unique and novel properties because of the size, the engineered particles or the aggregates and agglomerates should be within the range but not greater than 10% by weight and dimension less than 100 nm". These are advisory definitions and applicable to all products excluding cosmetics, pharmaceuticals, food, and food packaging materials [11 - 13].

4-"Nanomaterials means a natural or manufactured active or non-active substances containing such particles, in an unbound or as an aggregate or as an agglomerate and where for 50% or more of the particles in the number, size distribution, one or more external dimensions having the size range 1nm- 100nm. The particles of fullerene, graphene flakes, and single-walled carbon nanotubes and that have one or more external dimensions below 1nm are grouped as nanomaterials" [14].

5-"Substances produced in the nanoparticular state define as substances containing unbound particles or aggregates or agglomerate of those particles where 50% or more of the particles in number, size distribution have one or more external dimensions within the size range of 1nm -100 nm. The definition excludes natural, non-chemically modified substances and those for which the fraction in the 1nm-100nm range is a by-product of human activity". These are the regulatory definitions based on a complex set of exemptions [15].

USES OF NANOMATERIALS

Nanomaterials are of multi-utilities and are in use in varieties of industries. The silver, silicon dioxide, potassium, calcium, iron, zinc, phosphorous, boron, zinc oxide, and molybdenum nanomaterials are applicable in the field of agriculture. Tungsten, disulfide silicon dioxide, boron, clay, titanium dioxide, diamond, copper, cobalt oxide, zinc oxide, boron nitride, zirconium dioxide, γ-aluminum oxide, palladium, platinum, cerium-IV oxide, carnauba, aluminum oxide, silver, calcium carbonate, and calcium sulfonate are useful in the automotive/automobile industries. Silver, titanium dioxide, gold, carbon, zinc oxide, silicon dioxide, clay, sodium silicate, kojic acid, hydroxy acid, *etc*., are used in the cosmetics either

CHAPTER 3

Biocompatibility and Bioavailability of Nanomaterials Outline

Abstract: Biocompatibility, biodistribution, and bioavailability are essential aspects of those nanomaterials that are used in the field of biological, biomedical, and biotechnological sciences. These are applicable like agents for the drug delivery system, biomolecules, biomedical applicants, biosensors, theranostics, *etc*. These aspects are intricately interdependent and play prime roles in successful applications of nanomaterials. The physicochemical features of cell, biosystem, and nanomaterials play a significant part in these processes. The nanomaterials can be modified or functionalized by various techniques or by conjugating with a variety of molecules that have specific functional groups or phase transfer of the nanomaterials. The highest degree of biocompatibility of the nanomaterials is attained by minimizing the cytotoxic, genotoxic, and other derogative impacts of nanomaterials with respect to the physiology of a biosystem. Bionanomaterials should be hemocompatible, histocompatible, and cytocompatible for their successful performance. Nanomaterials are functionalized or modified suitably to achieve the selected performances. This aspect needs to alter the physicochemical properties, the surface topography of the nanomaterials that permit the smooth functioning of fabricated nanomaterials. In this chapter, the biocompatibility of nanomaterials, strategies involved, probable pathways along with some examples have been reviewed. This will provide an overview of these significant aspects related to the interaction between nanomaterials and the biosystem.

Keywords: Bioavailability, Biocompatibility, Biodistribution, Biodispersibility, Functionalization of nanomaterials Hydrophilicity, Hydrophobicity, Wettability.

BIOCOMPATIBILITY, BIODISTRIBUTION, AND BIOAVAILABILITY OF NANOMATERIALS IN BIOSYSTEM: AN OVERVIEW

Biocompatibility is the ability of any material to accomplish specific functions safely within a biosystem [1]. Biocompatible materials are considered to exhibit non-interfering behavior towards the biological system. The non-interfering response is related to non-thrombogenicity, non-allergenicity, non-carcinogenicity, and non-toxicity [2]. Biocompatibility is either long term or short term, explicitly concerning tissue-engineered and biomedical devices. The biomedical devices are used to evaluate, treat, augment, and replace tissue/organ and to either rectify or support the functional aspects of the organ or tissue. The

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surfaces of the bionanomaterials act as an interface when these interact with biomolecules, like proteins, and cell, and cell organelles. Under these conditions, biocompatibility relates to the contextual concepts like cytotoxicity, sensitization, irritation, and genotoxicity, the success of implants, hemocompatibility, carcinogenicity, tissue engineering, biodegradability, and biodistribution. Williams suggested that there is nothing like biocompatibility, but it is the response of the biosystem towards the structure and functional components of administered nanobiomaterials [3].

Properties like hydrophilicity and hydrophobicity depend on the nature of the surface of the nanomaterials and the medium. The surface topography or presences of adsorbed, crystalline, or amorphous molecules also play significant roles in biocompatibility, biodistribution, and bioavailability of nanomaterials in a biosystem. Hydrophilic molecules containing groups like COO^{-}, OH^{-}, NH^{-2} or SO_3H^{-}, influence the hydrophilic nature of nanomaterial, while groups like CH^{-3}, CH_2-CH^{-2}, chains, and rings of hydrocarbons, elevate the degree of hydrophobicity of nanomaterials [4].

Biological membranes exhibit attractive and repulsive responses towards water molecules. The compositional material of the layer and the corresponding surface chemistry plays a significant role during the interaction with water. One aspect of this interaction is wettability. Wettability of a material is related to a particular surface property that yields a unique value for that material. The value of the surface tension of a substance is an essential factor when wettability is under consideration. Wettability of a given substance in the specific liquid helps to measure the contact angle between a solid surface and a droplet on that surface. The surface tension is a product of internal forces that exist between two different materials. When two materials, say liquid droplet and solid surfaces, come in contact with each other and form an interface or a boundary. The force of surface tension is due to the tendency of all materials to reduce their surface area in response to the unbalanced state among the intermolecular forces. These forces are active at the point of contact between the two materials. The significant fundamental comparison of surface tension helps to understand the principle of wettability. Generally, liquids having lower values of surface tension readily spread on materials (liquids/solids). Liquids having higher amounts of surface tension do not show this tendency. This feature of a material affects its hydrophilic and hydrophobic behavior. When the multi-component solution is under consideration, its expression relates to the surface tension that depends on solubility complications of the said solution [5, 6].

The nature of a membrane and the wettability of any materials play a significant role in the degree of biocompatibility, biodistribution, and bioavailability of nanomaterials in a biosystem. Particles that foul in the aqueous medium tend to be hydrophobic in behavior. Colloids, starch, metal colloids, complex-ion aggregates, groups of molecules, liquid-solid; and liquid-liquid suspensions or environment exhibit hydrophobic behavior. Proteins have positive and negative charges but also have a hydrophobic region and behave like hydrophobic materials. Other hydrophobic materials include clays, silicates, alumina, ferric hydroxide, oil particles, paraffin, surfactants, and greases, *etc* [5, 6].

Particles that foul in the aqueous medium tend to be hydrophobic in behavior. Colloids, starch, metal colloids, complex-ion aggregates, groups of molecules, liquid-solid; and liquid-liquid suspensions or environment exhibit hydrophobic behavior. Proteins have positive and negative charges but also have a hydrophobic region and behave like hydrophobic materials. Other hydrophobic materials include clays, silicates, alumina, ferric hydroxide, oil particles, paraffin, surfactants, and greases, *etc* [5, 6]. Generally, hydrophobic particles tend to cluster or group. This behavior lowers the interfacial free energy, *i.e.*, surface tension. There is a formation of bigger spherical particles because the spherical shape has the minimum surface area, and its exposure is limited to the hydrophilic environment. Utilizing modified surface chemistry that functions like the hydrophilic component is a useful technique to regulate the process of fouling of membrane [7, 8]. The probable pathways of intracellular biocompatibility of nanomaterials are shown in Fig. (**1**).

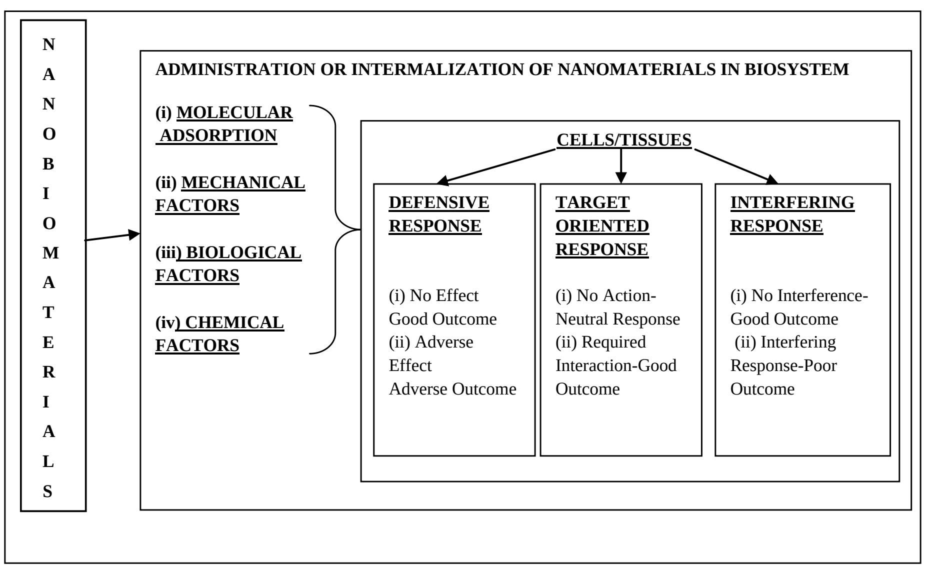

Fig. (1). The probable pathways of intracellular biocompatibility of nanomaterials.

CHAPTER 4

Physicochemical Aspects that Influence the Interactive Behavior of Nanomaterials

Abstract: Nanomaterials have occupied ubiquitous status in present-day life. Nanotechnology has become the backbone for technical aspects of energy-storing, communication industries, domestic, health, and safety, *etc*. Interactions and behavior of nanomaterials are the primary concern among the related research fraternity. The main focus is on the mechanisms involved in the interactions and the responses of nanomaterials concerning abiotic and biotic components of the environment during the pertinent research. The interactions and behavior of nanomaterials follow the basic principles of physics, chemistry, material science, biological sciences, *etc*. Nanomaterials abridge the atomic and molecular state of the matter and the respective bulk forms. In such interactions, the quantum mechanics and tunneling effect, parameters like, inter and intramolecular binding forces, hydrophobicity, and hydrophilicity, net charges, *etc*., have functional significance. Nanomaterials exhibit the ability to get precisely designed as per the assigned functions. As a result, such nanomaterials act as preferred options in different fields like vehicles for cargo and diagnostic tools, *etc*. In this chapter, the functional roles of the physicochemical parameters and related forces are reviewed regarding the behavior of nanomaterials in the biosystem.

Keywords: Coulomb Forces, Electrostatic Forces, Hydrophilicity, Hydrophobicity, Intermolecular Bonding, Magnetic Properties of Nanomaterials: Quantum Mechanism, Optical Properties of Nanomaterials, Tunneling Effect.

INTRODUCTION AND OVERVIEW

Currently, nanomaterials and nanotechnology act as the backbone in current industrial, biomedical, and academic research scenarios because nanomaterials are in use for most of the day to day life products. The behavior of nanomaterials in the biosystem is ambiguous and needs investigation concerning mechanisms involved in nanomaterials, and biomolecules, and cellular components. Nanomaterials have the advantage of being designed as per the required assigned functions to enhance avidity for interactions with a specific target such as biomolecules and cellular components. These materials interact in a derogative or helpful manner within a biological system based on their unique reactivity. The probable derogative impacts are on biomolecules, cells and tissues, and potential

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interferences during these interactions. Natural and engineered nanomaterials pose challenges regarding the uncertainty about their health-hazardous potential and approvals from various regulatory authorities at different levels, *etc*.

Nanotechnology ensures appropriate designing, fabrication, and synthesis of nanomaterials with maximum precision so that engineered nanomaterials perform the designated functions. The features of engineered nanomaterials, such as surface properties, charge modifications, size, and shape, enable them to interact with the target moieties. The half-life of nanomaterials is affected while they are in circulation within a biosystem. This parameter implies that such nanoparticles and adducts formed during their interaction require prolonged duration for clearance from the biosystem.

The mechanism and severity of the interactions and behavior of nanomaterials are unpredictable, thereby making it essential to understand the mechanism involved. The current detailed investigations are concerning size, shape, chemical functionality, surface charge, composition, and biomolecular signaling, kinetics, transportation, and toxicity in cell culture and experimental animal models [1]. Properties like chemical composition or surface modification, hydrophobicity, hydrophilicity, and presence of lipophilic groups, *etc*., of nanomaterials, play a significant role in their interactions and behavior. The ability of nanomaterials to move across most of the biological barriers and to bind with biomolecules specifically, factors or components that inhibit enzyme activity and immune system are the main points that need attention. The presence of metallic group and toxic compounds induces their respective effects during such interactions [2]. Features, like dimensions, shape, the tendency to agglomerate, crystallinity, surface coating, *etc*., of the nanomaterials, have relatively more cytological capabilities. In a given biological system, nanomaterials having a spherical, tubular, rod, and needle-like shapes, *etc*., exhibit kinetics of deposition and adsorption [3].

NATURAL AND ENGINEERED NANOMATERIALS

Some of the common examples of natural nanomaterials are present in nature. Nanostructures present in the wings of a butterfly (morph) and peacock modify the interaction between the light waves, and the result is a brilliant blue and green hue. Soap bubbles exhibit iridescence causing varied coloration because the wall of a soap bubble is within the range of nano dimensions. Lotus plants possess some water-resistant nanostructures, *i.e*., hydrophobic, and water molecules do not adhere to the parts of this plant. An invisible spray of water at the waterfalls or oceanic waves has the nano dimensions. Fine products of the combustion of fuel (soot) are examples of natural nanomaterials. Natural nanomaterials are produced in nature by natural processes like combustion, volcanic eruption, mining activities, forest fires, anthropogenic physical processes, *etc*. The ambiguous behavior of nanomaterials raises doubts about the validity of their use. Engineered nanomaterials are appropriately designed, fabricated as per the requirements; this reduces the real enigma. Aspects related to derogative or beneficial effects, appropriate utility, half-life, and the clearance form biosystem, *etc*., and the approvals from a competent authority, are primarily considered during their applications and research. These parameters should get administrative support while designing and fabricating nanomaterials for the set targeted tissue, moiety, or functions. Nanomaterials exhibit unique and intermediate dimensions between atoms and molecules, and the corresponding bulk materials. This feature has a significant role during the behavior of nanomaterials and their applications in various fields like biological, biomedical, theranostics, and other industrial applications [4].

SOME FUNDAMENTALS RELATED TO PHYSICS THAT AFFECT THE BEHAVIOR OF NANOMATERIALS

The behavior of nanomaterials follows some of the fundamentals of physics. Thus, it is appropriate to enumerate some of the prime fundamentals.

Quantum Mechanics

This mechanism comes quite handy in explaining or understanding the behavior of nanomaterials because the principles involved are relatively strictly applicable to atoms and molecules. Surface to volume ratio gets enhanced at the nanoscale. The quantum mechanism is related to the motion and energy of atom along with the electrons. Since nanomaterials are low dimensional materials, their mass becomes extremely less, and as a result, the gravitational force comes to a negligible level. Under this condition, electromagnetic force becomes the regulatory parameter in controlling the behavior of atoms, molecules, and nanomaterials. Nanomaterials are elementary particles with nano size or elementary particles, and negligible mass exhibits the wave-particle duality concept. Under these conditions, such particles exhibit a wave-like nature, and it may be relatively in a distinct manner. Electrons show wave behavior, and their wave function shows their probable position. Nanomaterials exhibit quantum mechanism and manifest quantum confinement, *i.e*., nanoparticles of specific metal have electrons restricted within the particular space. This condition of electrons does not exist in the corresponding bulk metal form. Furthermore, electrons exist at a discrete energy level; this is evident in the case of quantum dots where the impact of quantization of energy is displayed [5, 6].

CHAPTER 5

Interaction Between Nanomaterials and Glycocalyx, Cell Membrane, Cytoskeleton, Cell Organelles and Tissues

Abstract: Biosystems are responsive to almost all types of stimuli. These stimuli are in the form of fluctuations in their internal and external environments. Abiota, biota, and nanomaterials are interactive components of the environment. These units exhibit a wide range of reactivity because of their respective physicochemical, biomolecular, biochemical, and biophysical features. Biosystem is a complex unit of biota and these are acellular, cellular, unicellular and multicellular structurally and functionally in nature. Cell being the structural and functional unit of the biosystem, is a well-organized structure exhibiting wide variety, nature, and functions that bring about the sustenance of the biosystem. Nanomaterials are some of the most desired novel materials to be used as agents to carry drugs, as a component of biomedical aids, diagnostic tools, biomedical imaging, *etc*. Inter-actions between nanomaterials and the biosystem are very ubiquitous and at the same time ambiguous. Most of the physicochemical properties of nanomaterials play significant roles and cause impacts on interacting materials. These materials are inorganic, organic, or living. Cellular uptake of nanoparticles is a common phenomenon and has a wide range of applications in the field of nanomedicine from cell tracking, cellular to molecular imaging, disease targeting, drug/gene delivery, diagnosis, and therapy. Nanoparticle-based diagnostic or therapeutic applications are mainly attributed to the various methods of functionalization and localization in the cellular and subcellular compartments. The pre-requisite for the nanoparticle-based therapeutic applications mainly involves the mechanisms of the uptake of the nanoparticles which also determines the fate of these nanoparticles for effective efficacy. Applications of nanomaterials are dependent on the regulated interaction between biota and abiota of the environment. The wide range of functionality of nanoparticles is because of their physicochemical properties, ability to get modified or formulated readily, as per the need, and the greatest flexibility among the adaptability of biota. The potential use of nanomaterials may be the cause of their derogative impacts on abiota and biota. It is one of the prime concerns during development, formulation, and applications in varied fields to provide insight into the interactions between nanomaterials and the biosystem. One must understand the intricacies of their interactions within biosystems.

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Keywords: Biocompatibility, Cellular-uptake, Cell membrane, Cytoskeleton, Cellular-uptake, Caveolae-mediated endocytosis, Clathrin-mediated endocytosis, Enhanced permeable and retention effect, Glycocalyx, Internationalization of nanoparticles, Phagocytosis, Proton sponge effect.

OVERVIEW – NANOMATERIALS AND BIOSYSTEMS

Interaction between nanomaterials and biosystems is very unique. Most of the physicochemical properties of nanomaterials have their impacts on interacting material may it be inorganic, organic, or living beings. Applications of nanomaterials are dependent on the regulated interaction between biota and abiota of the environment. Biosystems are basically very responsive to the external as well as internal stimulations and the fluctuations. Let us label abiota, biota, and the nanomaterials as the reactive components of the environment. Biological reactive components and the nanomaterials exhibit a wide range of reactivity because of their physicochemical, biomolecular, biochemical, and biophysical features. This overall complex phenomenon needs a thorough understanding to make the best of the situation. In the last few decades, nanoscience and nanotechnology have made enormous progress and made nanomaterials as most suitable options for almost all aspects of industries, food technology, agriculture, pharmaceutics, cosmetics, clothing/garment, military ware fare, chemical technology, *etc*., the list seems to be endless. This range of functionality of nanoparticles is dedicated to their physicochemical properties, ability to get formulated and modified as per the need, and the highest degree of adaptability of biota. Increasing concern about the potential use of nanomaterials may be the cause of their derogative impacts on abiota and biota. To provide insight into the interactions between nanomaterials and biosystems, one must understand the intricacies of their interactions with biosystems.

Biosystem itself is a complex unit of biota. This unit is acellular, cellular, unicellular and multicellular structurally and functionally in nature. The cell is the structural and functional unit of the biosystem is a well-organized structure exhibiting wide variety, nature, and functions that bring about the sustenance of the biosystem. The cell is bounded by a cell membrane that is enveloped by glycocalyx externally and strengthened by the cytoskeleton internally. The component of the cell membrane is in communication with external as well as internal environment. Within the cell, cell-organelles are organized depending on the type of the cell involving endoplasmic reticulum, cytosol, cytoskeleton, and the ambient physiological fluid in and around each cell organelles and the cell itself. The interaction between nanomaterials and cells, tissue seems to be very crucial in nature.

Nanomaterials are some of the most desired novel materials to be used as agents to carry drugs, as a component of biomedical aids, diagnostic tools, biomedical imaging, *etc*. This reflects on the probable biocompatibility of varied nanomaterials to the biosystem. Thus nanomaterials should be biocompatible and should exhibit fairly good biodistribution. These aspects play major roles during designing and formulation of natural nanomaterials and also the engineered nanomaterials to accomplish the set target, may it be a cancerous cell, diseased tissue, and should not harm the normal or nontargeted tissues. Currently, there are many types of nanoparticles that are synthesized and being used for a variety of biological and biomedical applications. Among them to name a few are the iron oxide nanoparticles, gold and silver nanoparticles, quantum dots, polymeric nanoparticles, lipid-based nanoparticles, carbon-based nanoparticles, *etc*. Most of these nanoparticles are prepared either by a bottom-up approach or a top-down approach. The most important aspect of the synthesized nanoparticles is that they are immiscible in water and have very less water solubility due to which they cannot be used directly for the biological applications due to a variety of changing physiochemical properties such as their aggregation in the solution or at physiological pH which leads to toxicity, or aggregation based macromolecular formation losing their inherent properties for which they are synthesized. This ultimately leads to non-biocompatibility and cause toxicity when used for any biological applications. Therefore, the nascent synthesized nanoparticles cannot be directly used for the biological applications unless they are surface modified to make them more biocompatible. The surface of nanomaterials, polymer, and bulk materials are different. In the dry state, there is minimal surface energy. There is a shift of groups referred to as the group mobility. The non–polar groups move to the phase boundary formed with air while under aqueous conditions, the polar groups move to the phase of the boundary, *i.e*., at the periphery. The surface modifications approaches include either covalent modification or non-covalent modification. In case of covalent modification either the small molecule carbohydrates, surfactants, proteins, DNA, RNA, lipids or any synthesized molecule is linked covalently to enhance their water solubility at the physiological conditions.

Compounds having low molecular weight move towards the phase boundary or away from it. As a result, there is a change in the properties of the materials under consideration. On administration of synthetic and engineered nanomaterials may face some of the conditions in the biosystem. The first component of the biosystem that comes in contact with the administered nanomaterials is its body fluids. The biochemical components like proteins, lipids, and related molecules present in these body fluids interact with biomaterials either physically or chemically. In blood, the interaction between nanobiomaterials and protein involves adsorption leading to the formation of a layer. This reflects on the hemocompatibility. But this interaction depends on the nature of the protein and

CHAPTER 6

Interactions Between Proteins and Nanomaterials

Abstract: Proteins are among the significant biomolecular constituents in a biosystem. The structure of proteins and the nanomaterials, intracellular interactions, type of the cell, cell organelles, cell signaling and sensation, *etc*., affect the interactions between proteins and the nanomaterials. The interface formed between proteins and nanomaterials is the original site of contact and the interplay. The behavior of the interacting components reflects on the regulatory aspects, assembly of biomolecules, and various applications in the normal functioning of a biosystem. The fundamentals related to the tendency of biomolecules and nanomaterials help to retain their stable physicochemical conformations. The interactions involving proteins and nanomaterials bring changes in both. It is essential and beneficial to understand the mechanism of these interactions and their impacts on each other. This chapter deals with the nature, structure, and behavior of protein in general and nanomaterials, their stability, the significance of zeta potential, opsonins and their role, protein corona, and the factors influencing their dynamics.

Keywords: Biodistribution, Bionanointerface, Nanomaterials, Opsonization, Protein Structure, Protein Corona, Protein Chip, Zeta Potential.

OVERVIEW OF STRUCTURAL ASPECTS OF PROTEINS

In a biosystem, the prime share of the biomolecules is proteins and protein-related molecules. The internalized nanomaterials encounter proteins and interact with them within a biosystem. These interactions involve the molecular assembly of specific proteins, inter and intracellular communication, and sensation related to the cell and cell organelles. The physicochemical features of nanomaterials, proteins, and adducts formed, affect the beneficial or derogative interplay [1]. A protein molecule is a polymer made up of a specific monomer called amino acids. Generally, a protein molecule is a peptide having a minimum of 40 amino acid residues arranged in an unpredictable linear pattern. A molecule of an amino acid is basic and acidic because it has a primary group $-NH_2$ at one end and acidic group $–COOH^-$ at the other end. Thus, each amino acid exhibits a double function, *i.e.*, bifunctionality. This feature of amino acids tends to link linearly forming peptide bonds involving an amine group of one amino acid and the carboxyl group of another amino acid. The structural, physical, chemical, bio-

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chemical properties are related to the substituent present on the side chain of the amino acid. Further, the side-chain substituent plays a vital role in the functionality of the amino acids as acidic, basic, and neutral molecules. This feature also ensures the functions of amino acids as essential amino acids, and these are essential for an individual [2].

A protein may not be a polypeptide as it is a structurally very long polypeptide. Generally, there can be about 40 or 100 amino acids residues to 10,000 amino acids in various proteins. Monomeric and the multimeric proteins are the two categories of protein molecules. Monomeric proteins and multimeric protein classes depend on the type of nature and the number of peptides present in it. A protein molecule having one peptide chain is monomeric protein, while protein molecules having more than one peptide chain is multimeric protein. The peptide chains of multimeric protein are the protein subunits. These sub-units are either identical to each other or different. Insulin is a multimeric protein and consists of two sub-units. Of the two sub-units, one consists of 21 amino acid residues, and the second sub-unit consists of 30 amino acid residues [3, 4].

Proteins are also grouped based on their chemical composition. Simple proteins consist of only amino acid residues and can have more than one sub-unit. All these sub-units are amino acids. The conjugated proteins have one or more non-amino acid entities as their structural components. These components may be either inorganic or organic. These components act as additional fundamental aspects of the protein. Such parts are the prosthetic groups. Proteins are also classified based on the types of prosthetic groups present in their molecules. If a prosthetic group present in a protein molecule is a lipid, the protein is called lipoprotein; when a prosthetic group present in protein is a carbohydrate, the protein is a glycoprotein. Some of the proteins have metal-ion; such proteins are the metalloproteins. Prosthetic groups are a very significant component of a conjugated protein [4].

THE STRUCTURAL ASPECTS OF PROTEIN

The structural aspects of proteins include primary, secondary, tertiary, and quaternary structural components.

The Primary Structure

The primary structure of protein consists of amino acids organized in a linear sequence and constitutes peptide or protein. This sequential arrangement starts with amino-terminal N- and ends at the C-carboxyl terminal of amino acid. There are two terminals on an amino acid residue, one terminal residue shows a free amino group, while the other terminal amino acid has a free carboxyl group.

According to the peptide theory, there are three types of peptides. These are open peptides, cyclic peptides, and branched peptides [5]. The open peptide includes amino acids linked by a peptide bond to form a polypeptide chain. Each amino acid as a unit is residue. A polypeptide chain formed by the same sub-units is an open peptide. Cyclic peptides are composed of mixtures of amino acids containing L and D oliguria residues and glycine. The backbone is composed of H-bonds. These are also cyclic compounds having a peptide bond along with primarily L-amino acids and non-protein amino acids. The cyclic peptides also referred to as cyclotides, are disulfide-rich sub-macro cyclic proteins having around 28 to 37 amino acids. It contains an amide head, and the tail is cyclized peptide as a backbone having cyclic cystine knot. Structurally these sub-macromolecules are chains of polypeptides containing a circular sequence of bonds, *e.g*. cyclosporine [6, 7]. The branched peptides represent a non-continuous chain of carbon bonds and compulsorily have a carbon atom; the carbon atoms show a linear pattern, and it acts as a branching point or branching site. All branches have one or more aspects of the non-continuous link. Such cases are most common in plants [8].

Secondary Structure of Protein

The secondary structure of the protein includes α-helix and β-sheet (β-pleated sheets). These two components interact with each other, involving a hydrogen atom of an amino group and oxygen atom of the carboxyl group resulting in the formation of peptide linkage. This type of linkage ensures a strong structural and functional backbone of the protein. Alpha (α) helix, a component of the secondary structure of protein adopts a coiled spring-like shape; it has an established coiled structure based on hydrogen bonds. Hydrogen bonds are present between the =N-H of amide group and =O of the carboxyl group. This helix is right-handed spirally coiled clockwise. The hydrogen bonds formed are oriented parallel to the axis of the helix formed. One turn of this coiled structure or spiral consists of 3.6 amino acid residues. The H-bond is present between the carboxyl group of one amino acid and the amino group of other amino acid oriented with four amino acid residues. In a given spiral of the helix group, R- is always on the outer side, not within the spiral [4, 9].

The (β) beta-pleated sheets constitute the second component of the secondary aspect of protein. Two β-pleated sheets are either the same or different in a protein molecule. The two β-pleated sheets are bonded with each other by H-bonds. The H-bonds in peptide linkage and atoms involved are of different regions of a single chain that folds or bends on itself, forming an intrachain bond or comprise atoms that belong to different peptides chain in a given protein molecule. Proteins have more than one intra-chain. A single protein molecule containing a β-sheet should

CHAPTER 7

Interactions Between Nanomaterials and Genetic Material (DNA and RNA)

Abstract: Genetic material is a stable biomolecule in an organism. The intact and integrated transfer of genetic information from the parental generation to the offspring (daughter cells) is essential. This transfer acts as a basis and ensures the conveyance of somatic and sex-linked traits from generation to generation. The DNA contains genetic information and is present in eukaryotes and prokaryotes, while viruses have genetic information either in DNA or RNA. The genetic information plays a prime role in maintaining structural, physiological originality and modifications by retaining the specific pattern of transcription, translation, and replication of genetic material during cell proliferation, cell cycle, cell differentiation, *etc*. Cellular behavior reflects on the structural, functional, and genetic health of a cell, tissues, and an organism. The formulations of nanomaterials are in concern with the targeted moieties. The nanomaterials have spread their tentacles in most of the fields following the functional and procedural aspects of the biological and non-biological sciences. Different types of nanomaterials are produced in order to meet the demands of various domains like biotechnology, biomedical sciences, industrial, material sciences, *etc*. Nanomaterials cause either beneficial or harmful effects in a biosystem and the environment. The disoriented biochemical, biophysical, and biomolecular impacts are due to the adverse effects of nanomaterials on genetic contents. This condition brings disorganized functionality of the genetic information and the cell. The evaluation of their implications on biomolecules like DNA and RNA is essential to understand the mechanism involved. This chapter deals with the overall biochemical, physiological, and biophysical aspects of genetic contents, along with the impacts of various types of nanomaterials

Keywords: Annealing, Bionanointerface, Carbon Nanomaterials, Dendrimers, DNA, Histone- Proteins, Hydrophobicity And Hydrophilicity, Quantum Dots.

INTRODUCTION

Genetic integrity is the foundation of morphological, physiological, and genetic functionality of all the organisms. This genetic information also maintains the phylogenetic status of a species. Studies related to genetics help in understanding the number of malfunctioning in a life form. Genetic integrity appears to be a significant aspect related to the synthesis of proteins that are needed from time to time in the life of a creature. The genetic materials play a prime role in maint-

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aining the structural, physiological originality during the transcription, translation, and replication of genetic elements, and the normal cellular functions like cell proliferation, cell cycle, and cell differentiation [1]. There are natural processes like repairing DNA damages; this process retains and restores the originality of genetic materials in species. The rate of repair or restoration of genetic information varies in different cells, tissues, and organisms. Parameters like age, physiological, and pathological status of a species are also related to genetic integrity. A biological cell with damaged genetic material is likely to undergo irreparable dormancy state, senescence, apoptosis, and uncontrolled defective cell division, *etc* [1].

Nanotechnology and nanoscience have made exceptional advancements, and their products have found suitable applications in most of the fields. The nanomaterials are useful and beneficial because of their specific features like small size, the higher surface to volume ratio, ease of modifications of surface chemistry, and their ability to conjugate with multivalent ligands. These physicochemical features enhance the degree of avidity of the fabricated nanomaterials for targets like biological tissues, cells, biomolecules, and cell organelles [2]. DNA forms several alternative structures like non-B forms of DNA. These forms are more in numbers and detected in a genome. These non-B forms of DNA play an active role in the varied cellular processes and cause instability in the genetic information of an organism. These non-B Forms of DNA influence gene functions, regulation of immune response, telomere maintenance, and recombination in a cell. The antigen variations in human concerning pathogens and developmental conditions result in the diversity in the genome of a biosystem. These non-B forms of DNA are concerned with transcription and translation also [3].

The polymorphic form-DNA exhibits different assemblies and conformational forms like right-handed A form, left-handed Z form, triplex, G-quadruplex forms, i-motif forms under different physiological conditions [4]. Sathees and Leiber mentioned the existence of cruciform-DNA, Z- DNA, sticky DNA, slipped DNA structure (RNA–DNA hybrid), E DNA (e-motif) [5]. Different conformational and assembled forms of DNA are potential agents for human diseases. The cruciform (hairpin) form of DNA concerns with genetic instability, male infertility, recurrent abortions, Emanuel syndrome, and polycystic kidney disease. The triplet form causes hereditary neurological disorders, follicular lymphoma, and other types of cancers [5].

AN OVERVIEW OF BIOCHEMICAL AND BIOPHYSICAL ASPECTS OF DNA

A genetic material, *i.e.*, DNA, is bestowed with storing information related to the originality of the cells, species, and also for the functionality of specific cells in an organism. Generally, the genetic material in a life form is stable and intact and is essential for the DNA to maintain its structural, functional, and phylogenetic integrity and identity. This fundamental and technical originality of the genetic information in totality is an essential aspect during normal processes, such as transcription, translation, replication, even during the hereditary transfer from one generation to another. This feature is functionally significant to avoid erroneous genetic configuration. DNA is among one of the macro biomolecules correctly attributed to genetic aspects of an organism and protein synthesis. DNA is a double-stranded bipolar helical structure. The two strands are polymer composed of monomer units referred to as the nucleotide. The monomer unit consists of one of the nitrogen nucleobases among cytosine, adenine, guanine, thymine, pentose sugar (deoxyribose and ribose), and phosphate groups. Phosphate groups and sugar are bounded, and nitrogen nucleobases involving covalent bond and hydrogen bonds. These nitrogen bases are pyrimidines (thymine and cytosine) and purines (adenine and guanine).

The backbone of DNA resists cleavage. Each strand is anti-parallel and coiled around the same axis having pitch 34 Å (3.4 nm) and radius 10 Å (1.0 nm). Mendelkerm and co-workers reported the width of DNA between 22 to 26 Å (2.2 to 2.6 nm) and the size of one monomer unit 3.3Å (0.33nm) [6 - 8]. Primarily two forces maintain the stability of the DNA molecule. The hydrogen bonds are present between nucleotides, and base stacking interactions involving aromatic nucleobases are also responsible. Nucleotide bases align at a right angle to the axis of the DNA, forming π-bonds, thereby reducing the interactions between them [9].

PHYSICOCHEMICAL FEATURES OF DNA IMPACT OF TEMPERATURE

Melting temperature is an essential parameter during its interaction with nanomaterials [10]. DNA is prone to fluctuations in temperature. DNA gets denatured when its double-stranded structure is disturbed or the double-stranded changes into two single-stranded conformations. The denatured DNA elevates the degree of absorption of UV radiation. It is a potential parameter to denature DNA molecules. As temperature increases, the frequency of breaking of Hydrogen bonds between the two strands also increases. A temperature at which 50% of DNA gets denatured, *i.e.*, the double-stranded DNA sample becomes 50% single-

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CHAPTER 8

Interactions Between Enzymes and Nanomaterials

Abstract: Enzymes are proteins, but all proteins are not enzymes. Enzyme interactions concern with the biochemical and physiological transformations encompassing most of the life activities. Understanding such events will help to predict particular biochemical, biocatalytic, and enzyme reactions involved. These investigations also help to predict clinical and remedial aspects of dysfunctionalities of physiological processes. Chemical enzymes have their impediments that pose difficulties during their industrial applications. Biological enzymes also referred to as biocatalysts, are chemospecific, and applicable conveniently to carry out varied biological activities. This feature is related to the identification and selection of a particular functional group, among others. This selection is physical or chemical but depends on parameters like the nature of the solvent, atomic orbitals, concentration, pH, temperature, *etc*. Their industrial and biological applications increase using the enzyme immobilization technique. Nanomaterials have occupied significant status in the present day scenario. These materials are better options for this technique because these materials offer features like high specific surface area, improved dispersibility, low mass transfer resistance, *etc*. The mechanism of enzyme activity is quite complicated. The necessary steps incriminated are binding of the enzyme with the specific substrate. The complementary shape, size, charge, hydrophobicity, and hydrophilicity, *etc*., of a substrate, play a significant role in its binding with an enzyme. Nanomaterials are potential components that act as a matrix during the process of enzyme immobilization. These nanostructures elevate the efficacy of biocatalyst, specific surface area, mass transfer resistance, and loading of the capable enzyme, *etc*. The unique physicochemical features like size, surface properties, ease of modulation of nanomaterials, *etc*., ensure better performance of enzymes and improve their applications in different fields likes biomedical, pharmaceuticals, biomolecular, food, and packaging technology, agricultural practice, and biochemical investigations *in vitro* as well as *in vivo*. Some of the fundamental properties of enzymes can be modified to suit the functionality concerning the set targets. This chapter deals with the structure, nature, and regulatory dynamics of the enzyme. The enzyme immobilization technique, its advantages, and interactions with different nanomaterials along with biomimicking agents are also discussed.

Keywords: Active Energy, Biocatalysis, Biomimicking, Enzymes-Action, Enzyme-Immobilization, Free Energy, Nanomaterials, Toxic-Impacts.

BIOCATALYSIS

It is a challenge to know about biological activities. Most of the biological activ-

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ities are related to or involve proteins, and organic enzymes are proteins. The interactions involving proteins form a considerable umbrella and encompass most of the biological activities and interactions. The catalysts comprise the biocatalysts and regulate such interplays. The biocatalytic events help to predict a particular biochemical, biomolecular reaction that takes place during physiological functionalities. These interactions take place involving either change at the bond level or the reaction center level or similarity at the reaction center. The studies concerning biocatalysts help to understand their potential applications and biomolecular transformations. These transformations assign functions to an enzyme in a sequential biological, biochemical, and chemical reaction [1]. This feature is related to the identification and selection of a particular functional group, among others present on the substrate and enzyme molecule. The choice is physical or chemical but is dependent on parameters like the nature of the solvent, atomic orbitals, concentration, pH, temperature, *etc*. Prediction of such selectivity is quite tricky [2]. The biological catalytic interactions are generally harmless in the sense that they do not form any unwanted by-products. These interactions are occurring in a specific direction; *i.e*., these prefer to either make or break a chemical bond in one direction. These interactions take place because of the three-dimensional conformation of the reactants. The enzyme and biocatalysts can differentiate between the varied groups present in different zones of the molecule of a substrate. Sometimes two or more compounds have non-identical structural aspects but are not mirror images of each other and exhibit two different conformations [3]. The biocatalysis concerns the enhancement of the rate of the interaction or transformation of biomolecules, organic compounds within the biosystem. The ability of microorganisms to produce enzymes is useful in food technology, beverage, fermentation technology to get the desired commercial products, and to maintain a specific state of the food and other merchandise of economic importance, *etc*. There is a need to produce fine chemicals and other chemicals that are useful in pharmaceutical and related industries, and these based on biocatalytic and enzymatic interactions [1].

There are two types of enzymes namely, endoenzymes and exoenzymes. The secretory cells are the site of the production and location of actions for biocatalyst. Most of the biocatalysts are considered to be endoenzymes. Sometimes an endoenzyme (single molecule) acts as an exoenzyme also. The endoamylase splits larger amylose molecules into smaller chains of dextrin, while exoenzymes operate on the subunits of a polymer at one end of the polymer [4]. The prokaryotic and eukaryotic cells produce exoenzyme. These biological molecules are the product of cells, but these function outside the cell. Exoenzymes are secreted in the cell but act outside the cell. Most of these enzymes break down macromolecules, add a specific group, conjugate temporarily. These act as participants in a multiplex reaction or associated with two or more subunits of a complex molecule or biological macromolecule. Exoenzymes break down the macromolecules and help in the movements of the smaller micromolecules across the membrane. The subunit molecules conveniently move across the cell membrane or biological membrane. Generally, digestive enzymes come under this group [5 - 9]. The flowchart representing the cellular release of protein enzyme is shown in Fig. (**1**).

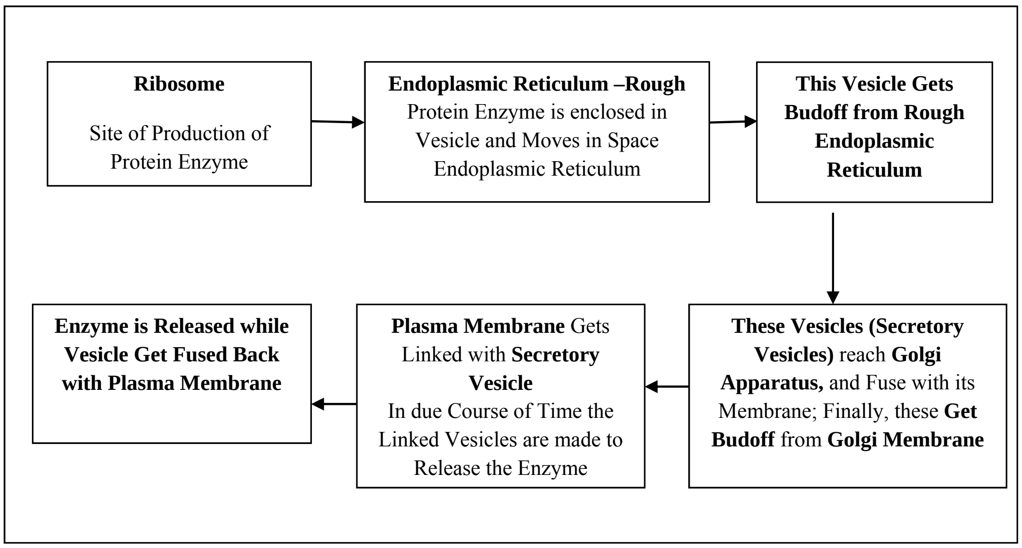

Fig. (1). The flowchart representing the cellular release of protein enzyme.

The biological enzymes are either anabolic or catabolic in action. The anabolic biocatalysts regulate the building up processes leading to the formation of a complex biomolecule from the respective simpler subunits. The resultant complex has a higher molecular weight than the subunits. The photosynthesis, synthesis of proteins, and other macro biomolecules are the products of anabolic enzyme activities. The formation of glucose is one such example. Other examples include synthesis of proteins, nucleic acids, biomolecules, or organic and inorganic molecules having very high molecular weight, complex conformations. During this process, molecular energy in the form of ATP is used up. Catabolic enzymes break the complex molecule with high molecular weight and complex conformation into its sub-units. Such processes release molecular energy in the form of ATP.

The enzymes are macromolecules and regulate specific chemical, biochemical, and biomolecular interactions. These macromolecules act on particular chemicals

CHAPTER 9

Nanomaterials and Immune System: Interactions

Abstract: Drug delivery systems, vaccination, and diagnostic imaging are the main aspects that enhance the effectiveness of human health and safety. This system protects an organism against microbes, viruses, parasites, and allergens. The immune system represents the level of the ontogenic and phylogenetic development of a biosystem. The degree of efficiency to protect against infection varies in different organisms. Overall, the functional mechanism of the immune system is complicated. Any molecule, or a pathogen entering the human body or a biosystem, has to face various components of the immune system. It is imperative to understand the concept of the interactions between nanomaterials and the components of the immune system. This understanding will improve, improvise, and elevate the degree of clinical translation of nanomedicine in the field of human health and safety. There seems to be an enormous scope of studies related to the intricacies of interaction occurring at the bio-nano-interface. These efforts will guide to design the rational nanomaterials that are either fabricated or synthesized with specific targets. The study of the modes or the patterns involved during the interactions between nanomaterials and the immune system can maintain the appropriate defense system of the individual against infections, xenobiotics, and any foreign molecule. This chapter deals with the applications of nanomaterials in the delivery system, competence of nanomaterials concerning the immune system, immunomodulation, immunosuppression, immunostimulation, and interactions between various nanomaterials and the components of the immune system.

Keywords: Immunomodulation, Immunosuppression, Immunostimulation, Immunological Memory, Nanomaterials.

INTRODUCTION: OVERVIEW-IMMUNE SYSTEM IN HUMANS, NANOTECHNOLOGY, NANOSCIENCE, AND NANOMATERIALS

All organisms have some defense system and specialized mechanism dedicated to the protection against the derogative impacts of microbes, viruses, and parasites, and any agent (xenobiotics) that causes sickness or any form of infection. This protective system exhibits the ontogenic and phylogenic development in different organisms. The mechanism and functionality of the immune system are complicated. Despite enormous research in the field of immunology, still, there exist some lacunae concerning the mechanism involved during the interactions between nanomaterials and components of the immune system. Further, this mechanism becomes more ambiguous because of the wide variety of nanomate-

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rials. Nanomaterials are the products of nanoscience either fabricated or formulated, as per the targeted applications in pharmaceutical, imaging, biomedical implants, and other related applications.

The blood cells like monocytes, platelets, leukocytes, and dendritic cells in tissues, and macrophages in the lungs, tend to engulf the internalized nanoparticles involving phagocytosis among humans and the vertebrates. The fluid components, like plasma proteins, opsonins, and related complements, also get involved in the interactions between nanomaterials, immune cells, and proteins. These interactions can influence the uptake, biodistribution, and the clearance of the internalized nanomaterials. This response can cause a disturbance in the distribution of nanomaterials and divert them from the target tissue and organ [1]. The immune system has two sub-components, namely, innate and adaptive resistant components. The main features of the innate component (network) are non-specificity and cell-mediated responses. Its humeral parts are present in body fluids. An appropriate exposure causes immediate remedial reactions that may not have immunological memory. The features of adaptive immune system concern with the pathogen and are antigen-specific in function. There is a lag time between exposure and duration of maximal response. The exposure leads to immunological memory. There is a complex conglomerating functionality between protein and the cells that regulate the short term and long term efficacies of the immune system. The innate immunity stands for fast and broad response spectrum affectivity. It utilizes proteins present in the blood, body fluids, and tissues.

Cells, such as macrophages, dendritic cells, neutrophils, mast cells, and natural killer cells participate in innate immunity [2, 3]. Innate immunity is the first line of defense among human beings and is non-specific. Its function depends on the Pattern Recognition Receptors (PRPs) that identifies a broad and conserved molecular pattern of the target. This innate immune system recognizes the foreign bodies that enter in a biosystem. It is also responsible for proinflammatory responses [2]. The adaptive immunity has a high degree of specificity, but slow functionality and antibodies identify the antigen. The cells like B-cells and T-cells play their role in antigen-antibody interaction [2, 3].

Nanomaterials activate the complement system-a component of the innate immune system, significantly. It is a complex system comprising of about thirty proteins; some of these are functionally protease enzymes, and the proteolytic dissociation induces these proteins. These all have a functional role that involves binding interaction with the surfaces of the foreign body. During the process of activation of complement, the third complement protein referred to as (C3), undergoes proteolytic cleavage, resulting in the formation of two opsonic complements called (C3b) and (iC3b)]. Macrophages identify nanoparticles or administered materials. The distributed materials in the human body bind with this opsonic complement [C3b] and [iC3b], involving corresponding complement receptors 1 and 3 present in the recipient. Nanoparticles follow three primary pathways, namely classical, lectin, and alternative pathways during their cellular internalization. As the activation of complement system progresses, anaphylatoxins (also referred to as biologically active complement peptides namely, C4a, C3a, C5a), are the action of the product of proteolytic enzyme causing cleavage of the original molecules (C3, C4, and C5). These anaphylatoxins induce the release of histamine from immune cells, like mast cells. These immune cells also participate in allergic reactions. The histamine increases the permeability of vascular cells and even during the contraction of smooth muscle. Anaphylatoxins promote some of the physiological conditions, like distressed breathing, acute changes in blood pressure, chest pain, declined output from heat and cardiac arrest, *etc*., (Fig. **1**) [4 - 6].

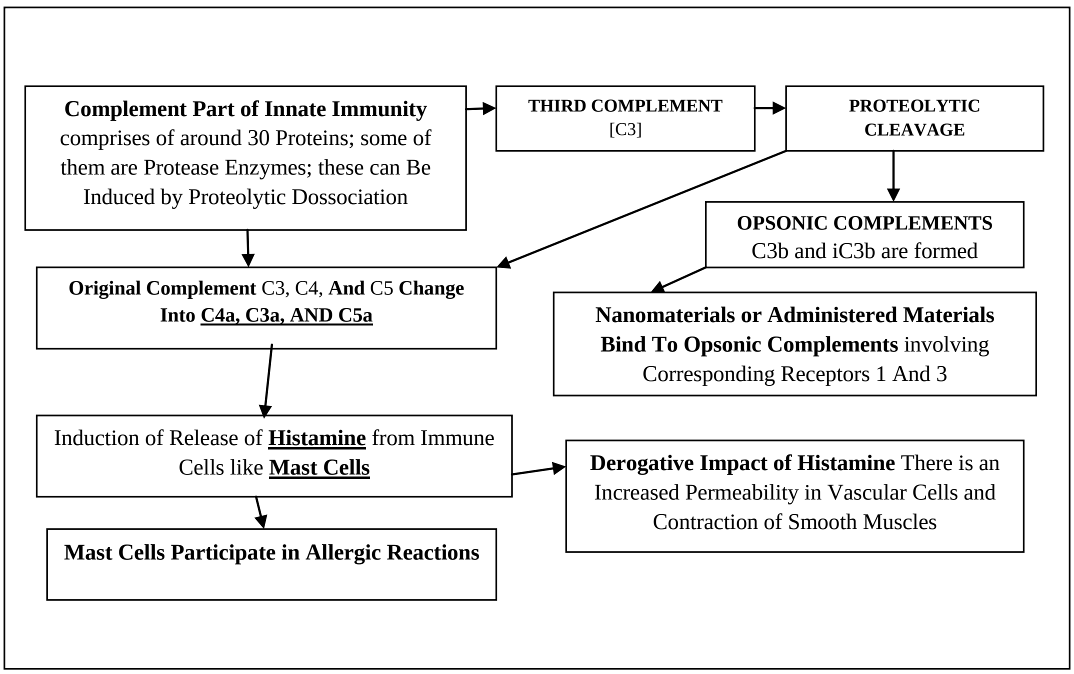

Fig. (1). The flow chart representing the probable process of activation of complement peptides (also called biological active complement peptides).

CHAPTER 10

Broad Spectra of Applications Based Interactions of Nanomaterials

Abstract: Advancements in the nanoscience, nanotechnology and material science involve the principles of fundamental physical, chemical, and biological sciences. These scientific advancements have opened a vast horizon for understanding the mechanisms of the physiology of life and the environment. This progress has also provided suitable materials and appropriate methodology concerning the developments. Nanomaterials are the bridge between the atomic and molecular and bulk form of matter. These nanoscaled materials are modified, fabricated, and reach most of the biological targets in life forms. As a result, these become useful materials for applications in medical sciences, industrial processes, health care, and home security. The biological components, such as cells and tissues in the biosystem and nanomaterials, interact amicably with restrictions concerning their physicochemical features. Nanomaterials exhibit biocompatibility and bioavailability within the physiological environment. This ability is the primary basis of their applications in almost every sphere of investigation, diagnosis, and treatment of ailments. Enzyme technology, DNA and RNA technology, tissue engineering, military, and communications, energy, and many industrial processes are the fields where different nanomaterials are useful and provide beneficial and desired results. In this chapter, various potential application based interactions related to medical sciences, biomolecular investigations, biotechnology, genetic engineering, tissue engineering, environmental aspects, military, *etc*., have been envisaged.

Keywords: Antibacterial nanomaterials, Antifungal nanomaterials, Antiviral nanomaterials, Bladder and cartilage implants, Drug delivery, Nanomaterials and defense, Nanomaterials as biocomposites, nanomaterials as neural, nanotechnology, Nanomaterials for tissue culture, Vascular tracheal implants,.

OVERVIEW

The nanoscience, nanotechnology, and materials sciences are the basis for the ever-increasing pace of development. These developments meet the challenges related to industrial, health, agricultural, natural, manufacturing, energy, digital expression and communication, neuronal, and cognitive fields. These make provisions for long-lasting technologies that take care of the problems related to these fields and also digital currencies, hydrogen energy storage, brain to brain in-

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terface and robotics, *etc*. These fields reflect on many interdependent technologies that influence the society, economy, and the environment. The advancements in the area of nanoscience, nanotechnology, and materials science are the fast-paced changes in materials science. The materials science perceives the matter to be recognizable as functional materials, next-generation materials, and self-assembling materials. The substances that function on the borrowed principles from biological aspects and adopt a new behavior pattern accordingly are considered to be functional materials. Super light and active materials get affected or react in accordance to the environmental changes and generally culminate as smart materials. These original materials come under next-generation substances; can stimulate the components of the environment, the central users. Materials that exhibit self-assembly behavior constitute a large scale, very precise, able to improve their properties concerning strength, tear resistance, conductivity, *etc*., and are included in next-generation substances [1].

Maters get organized in different types and this organizing concerns with the current advancements in materials science. Smart materials are the material with one or more specifically modified properties. The external changes or stimuli like stress, electric or magnetic field, temperature, pH, moisture, *etc*., help in such modifications during the designing of these materials. Thermo bimetals self-regulate and consume energy for a more extended period. Furthermore, these bimetals are activated thermally and can make glass to shade after being exposed to sunlight. Superomniphobic materials can float on aqueous fluid and repel oil. These behave like water bugs on the surface of the water pond. Auxetic contents change their thickness under force. These become thicker in the perpendicular direction to the direction of force applied. These materials either have hinge-like structures, or some of their parts act like a hinge, which gets flexed under stretch. Such auxetic materials are suitable for packaging, pads for knee and elbow, robust shock absorbing material, sponge materials for mops, and materials for body armor, *etc*. Aerogels are ultra-light porous materials, and they are modifications from the gel after replacing the liquid present by air or gas. Aerogels have extremely low density, conductivity, and give polystyrene (Styrofoam) feel when touched. These materials are useful to improve thermal insulation, as chemical absorbents to clean the spills, these are suitable materials for electrochemical supercapacitors, and shock absorbers. Biomaterials are derived from natural sources or synthesized in the laboratory. These materials are appropriate to replace or increase the inherent functionality of the organ or body part. These are the potential materials to improve the drug delivery system and degree of acceptance of graft among transplants. Graphene consists of only carbon elements. The arrangement of the carbon atoms in a typical hexagonal pattern, forming a single sheet with thickness, equals the thickness of one atom. These materials are very light but strong and similar to graphite [2]. These nanomaterials are suitable for the use of low-cost solar cells and display screens in inexpensive mobile devices. These are suitable to store hydrogen for cars powered by the fuel cell, like biomedical and chemical sensors, ultracapacitors and faster-charging batteries, *etc*. Graphene nanomaterials are advantageous for use in integrated transistors. These form the functional components of actuators, nanoelectromechanical systems (the devices that integrate electrical and mechanical systems functionally). These systems also include pumps or motors and good options for physical, chemical, and biological sensors.

Nano-factories are the devices that act as nanomachines. These interact with reactive molecules involving mechanosynthesis and form correct assembled structures of organic products. These products follow a specific arrangement of the macroscopic sized pattern with atomic precision. A material product with large scale assembly exhibit specific behavior, *i.e*., in an organized system, the components form an organized structure with its local parts in a particular sequence. Thus, the bottom-up approach results in the formation of 3D sequenced structures like DNA, RNA, and protein that come in this category. Substances under metamaterial have specifically and precisely arranged geometrical shaped materials and influence light and sound unconventionally. Such materials are useful in aerospace devices, devices to monitor fractures, and to manage smart solar power devices. Self-healing materials are referred to as intelligent materials work as a biological system, and incorporate a repair mechanism helping the healing of damaged tissues. These materials include polymers, ceramics, and can rectify intrinsic damage caused due to the devices. These materials also reduce the impact of degradation, enhance life span, and are cost-effective [1, 3]

VARIOUS APPLICATIONS OF NANOMATERIALS

Tremendous advancement has taken place in all spheres of life due to the innovative technologies in recent times. Improvements in the fields of nanotechnology and materials science have played significant roles in these advancements. These two disciplines provide methodologies and suitable materials for specific applications for such developments. Nanomaterials are aptly modified or fabricated those help involvements in different investigations and brought successful and useful applications in industries, health care, and home security in addition to the cosmetics and pharmaceutical advancements.

Nanomaterials for Drug Delivery and Biomedical Applications

Drug delivery is the fundamental aspect of health care and safety; it delivers genes, biomolecules, and drugs to a specific site in a biosystem. Parameters like an increased area of the reactants that offers a more significant number of atoms and molecules that interact, bind, adsorb, and facilitate the delivery process.

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