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Review

Emerging aspects of nanotoxicology in health and disease: From agriculture and food sector to cancer therapeutics

Zoi Piperigkou [a, b, 1], Konstantina Karamanou [a, c, 1], Ayse Basak Engin [d, 1], Chrysostomi Gialeli [a, e], Anca Oana Docea [f], Demitrios H. Vynios [a], Mauro S.G. Pavão [c], Kirill S. Golokhvast [g], Mikhail I. Shtilman [h], Athanassios Argiris [i], Ekaterina Shishatskaya [k], Aristidis M. Tsatsakis [j, g, *]

[a] Biochemistry, Biochemical Analysis & Matrix Pathobiology Research Group, Laboratory of Biochemistry, Department of Chemistry, University of Patras, Patras, Greece
[b] Foundation for Research and Technology-Hellas (FORTH), Patras, Greece
[c] Laboratório de Bioquímica e Biologia Cellular de Glicoconjugados, Universidade Federal do Rio de Janeiro, Brazil
[d] Gazi University, Faculty of Pharmacy, Department of Toxicology, Hipodrom, Ankara, Turkey
[e] Lund University, Department of Laboratory Medicine, Malmö University Hospital, Malmö, Sweden
[f] Department of Toxicology, University of Medicine and Pharmacy, Faculty of Pharmacy, Craiova, Romania
[g] Scientific Educational Center of Nanotechnology, Far Eastern Federal University, Engineering School, Vladivostok, Russia
[h] Master School Biomaterials, D.I. Mendeleyev University of Chemical Technology, Moscow, Russia
[i] University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
[j] Center of Toxicology Science & Research, Medical School, University of Crete, Heraklion, Crete, Greece
[k] Medical Biology Department, Siberian Federal University, Russia

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ABSTRACT

Nanotechnology is an evolving scientific field that has allowed the manufacturing of materials with novel physicochemical and biological properties, offering a wide spectrum of potential applications. Properties of nanoparticles that contribute to their usefulness include their markedly increased surface area in relation to mass, surface reactivity and insolubility, ability to agglomerate or change size in different media and enhanced endurance over conventional-scale substance. Here, we review nanoparticle classification and their emerging applications in several fields; from active food packaging to drug delivery and cancer research. Nanotechnology has exciting therapeutic applications, including novel drug delivery for the treatment of cancer. Additionally, we discuss that exposure to nanostructures incorporated to polymer composites, may result in potential human health risks. Therefore, the knowledge of processes, including absorption, distribution, metabolism and excretion, as well as careful toxicological assessment is critical in order to determine the effects of nanomaterials in humans and other biological systems. Expanding the knowledge of nanoparticle toxicity will facilitate designing of safer nanocomposites and their application in a beneficial manner.

Contents

Abbreviations: CNT, carbon nanotube; ECM, extracellular matrix; EGF, epidermal growth factor; ENM, engineered nanomaterial; FGF, fibroblast growth factor; GI, gastrointestinal tract; MWCNTs, multi-walled carbon nanotubes; NP, nanoparticle; NR, nanorod; PHA, polyhydroxyalkanoate; SWCNTS, single-walled carbon nanotubes.

* Corresponding author. Center of Toxicology Science & Research, Medical School, University of Crete, Heraklion, Crete, Greece.
E-mail address: aris@med.uoc.gr (A.M. Tsatsakis).

[1] These authors contributed equally to this work.

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1. Introduction

The evolution of nanotechnology has resulted in a wealth of products containing or using nanomaterials with numerous potential applications. The small size of the particles imparts different properties to nanomaterials relative to those with larger sizes. Unusual physicochemical properties of engineered nanoscale materials (ENMs) are attributable to their small size, chemical composition, surface structure, solubility, shape, and aggregation (Nel et al., 2006). The term ENM is used to describe any manufactured substance at the nanoscale, which ultimately bestows on the substance characteristics and properties. An unequivocal definition of the term 'nanomaterial' is essential in the EU legislation and regulations, particularly taking into regard the management of potential risks of nanomaterials to human health and the environment. In October 2011, the European Commission published the Recommendation on the Definition of Nanomaterial, which defines nanomaterial as a natural, incidental or manufactured material containing particles, in an unbound state 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 is in the size range 1 nm-100 nm (2011/696/EU). Innate and adaptive immune responses provide an efficient protection against invasion by foreign elements, not only for pathogens but also for nanomaterials. Subsequent to entrance into the body ENMs encounter the immune system and may induce desirable or undesirable immunological effects (Dumortier, 2013). At first, innate immune responses facilitate the participation of adaptive immune responses allowing the body to recognize foreign particles; later the adaptive immune system can produce signaling mediators which strengthen the effectiveness of innate immune responses (Wang et al., 2013).

2. Nanoparticles classification

Recent studies classified nanomaterial types into separate categories (Habibi et al., 2010; Yan et al., 2011) (Table 1):

(i) *By material*: metallic (nanomaterials incorporating metals, transition metals, their compounds or composites, quantum dots, etc.); carbon (SWCNTs, MWCNTs, fullerenes, graphene, etc.); organic (agglomeration or assembly of organic molecules, biomolecules or bio-macromolecules, etc.); boron nitride; mineral (halloysite, etc.) and silicon
(ii) *By shape*: quantum dots; aerogel; nanotubes; nanofibers; nanorods; nanoballs; nanosheets; nanowires and nanofibrils

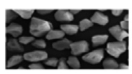
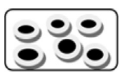
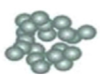
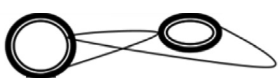
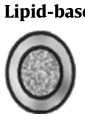
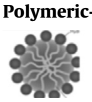
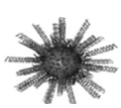
Primary uses of these defined nanomaterial types are to fulfill industrial applications, thus an overview of the behavior, therapeutic approaches and the current toxicity status of these compounds, is of great importance.

2.1. Carbon Nanotubes

Carbon nanotubes (CNTs) possess several unique physicochemical properties that can result in various effects in organisms. The augmented surface area to size ratio leads to the tendency to aggregate, increasing interaction with biomolecules and as a result to higher surface reactivity (Firme and Bandaru, 2010; Fubini et al., 2010; Golokhvast et al., 2015b). As mentioned above, surface chemistry and size play an important role in CNTs' cytotoxicity. Indeed, it has been suggested that the cytotoxic response depends on the degree of functionalization and size, as shorter CNTs are less toxic than longer CNTs due to the ability of macrophages to engulf the former and thus be activated. The two most accepted proposed mechanisms of CNTs internalization are: (a) endocytosis/phagocytosis (b) nanopenetration. CNTs-exposed cells undergo oxidative stress due to the induction of oxidants and toxic enzymes. A higher level of oxidative stress leads to inflammation and cytotoxicity. Thus, decreased cell viability and elevated levels of the pro-inflammatory cytokines interleukin-8 (IL-8) and IL-1β are reported, while apoptosis may result from mitochondrial disruption and release of pro-apoptotic factors (Golokhvast et al., 2015a; Vitkina et al., 2016). Differential effects of single- (SWCNTs), double- and MWCNTs have been described. SWCNTs have been characterized as the most toxic type (Shvedova et al., 2005, 2012). In contrast, orally administered MWCNTs can induce cell reaction in the macula densa of the renal distal tubules and immunostimulating effects (Golokhvast et al., 2013).

CNTs at various particle concentrations, even if they do not result in significant lung inflammation or tissue damage, cause alterations in systemic immune functions. Thus, immunosuppression caused by CNTs exposure is characterized by reduced T-cell-

Table 1
Classification scheme of ENMs. According to their dimensions, structure and surface chemical modifications, NPs are organized into three major groups: a) solid NPs; b) lipid-based vehicle nano-systems, and c) polymeric-based vehicle nano-systems. Main applications of each NP type are also depicted. Adapted by (Champion et al., 2007; Geilich et al., 2015; Letchford and Burt, 2007; Liu et al., 2013).

Particle shape and dimensions	Description	Applications
Solid nanoparticles		
 10-100nm	**Spherical or solid particles** with homogenous composition	Opticoacoustic tomography, catalytic activities
 350-450nm	**Tubular particles** with homogenous composition	Catalytic activities, high-capacity electrochemical capacitors
 60nm-30μm	**Complex non-spherical particles** with homogenous composition	Drug delivery, microfluidics
 >100nm	**Particles of heterogeneous composition** (variation between the same body and the surface)	Industrial catalysis
	**Particles of heterogeneous composition** (changes in the allocation of the composition)	Limited applications due to hazardous waste
	**Homogeneous aggregations** (consisted of different types of particles)	Limited applications due to toxic effects
	**Heterogenous aggregations** (consisted of different types of particles)	Ion batteries
Lipid-based vehicle nano-systems		
 70-100nm	**Nano-liposomes** (lipid bilayer of transfer vehicle)	Drug delivery, dietary and nutritional supplements, stabilizers
	**Micelle** (simple lipidic layer of transfer vehicle)	Solubility enhancement
 >5-100nm	**Nano-cochlea** (the sheet of the lipidic layer wraps in a spiral form)	Formation of fullerenes and nano-onions
Polymeric-based vehicle nano-systems		
 100nm-10μm	**Micelle** (agglomerated copolymers)	Drug delivery
 100nm-10μm	**Nano-spherical particles** (agglomerated copolymers produced in the solid main tank)	Drug enzymatic protection
 250-450nm nano- & micro-scale	**Nano-capsule/polymerosome** (polymeric membrane surrounded by a central cavity) **Nano-capsule** (membrane of simple layer) **Polymerosome** (membranic bilayer)	Drug delivery, nano-encapsulation for food flavoring

dependent antibody response as well as T-cell proliferative ability and increase in interleukin-10 (IL-10) and nicotinamide adenine dinucleotide phosphate [NAD(P)H] oxidoreductase-1 mRNA levels (Mitchell et al., 2007). Additionally, complement activation by CNTs is consistent with adjuvant effects and may also promote damaging effects through excessive complement activation. The first component of the classical complement pathway, C1q, binds directly and selectively to CNTs (Salvador-Morales et al., 2006). Actually, C1q also binds to immune complexes to elicit complement-dependent microbial killing and enhance phagocytosis (Lu et al., 2007). This interaction may influence the adhesion of CNT to phagocytic cells, while the excessive activation of complement can have a harmful effect on adjacent tissues (Rybak-Smith and Sim, 2011). Short-term inhalation of the rod-like CNTs induces novel innate immunity-mediated allergic-like airway inflammation in healthy animals. This is coupled with marked eosinophilia, mucus hypersecretion, airway hyper-responsiveness and the expression of Th2-type cytokines (Rydman et al., 2014). CNTs have various structures, which differ in the induction of immunological responses. Furthermore, the dispersion characteristic of SWCNTs is a dominant factor for the regulation of immunotoxic effects. Although, the low dispersion of SWCNT can suppress the activation of the inflammatory pathways and increase immunotoxicity, highly dispersed SWCNTs reduce this effect, which is related to the decrease of the T-cell population and lower level of immune function (Lee et al., 2015). Likewise, the short linear, thin bundles of SWCNTs elicit delayed pulmonary inflammation with slower recovery, while relatively long linear, thick bundles induce cellular immune activation and trigger acute lung inflammation shortly after inhalation (Fujita et al., 2015).

MWCNTs are rapidly distributed to brain, liver and kidney via vascular transport (Albini et al., 2015). In addition, to stimulating the initiation of phagocytosis, MWCNTs cause the upregulation of CD14, CD11b, toll like receptor-4/myeloid differentiation factor 2 (TLR-4/MD2) and CD206, expression in macrophages. The macrophages that engulf MWCNTs secrete a large amount of macrophage inflammatory protein-1α (MIP-1α) and MIP-2 to recruit naive macrophages and release of angiogenesis-related cytokines matrix metalloprotease-9 (MMP-9) and vascular endothelial growth factor (VEGF). In this manner, the mixed status of M1/M2 macrophages supports angiogenesis (Meng et al., 2015). On the other hand, large MWCNTs agglomerates/aggregates, which are found in granulomas in the allergic rats, decrease serum IgE levels and the number of lymphocytes in bronchoalveolar lavage. This event indicates the modulatory action of MWCNTs in the allergy-associated immune response (Staal et al., 2014). Thus, the diverse abilities of CNT to impact the immune system should be taken into consideration for hazard assessment (Fujita et al., 2015; Rydman et al., 2014).

2.2. Metal oxide nanoparticles

Metal oxide nanomaterials are increasingly being used as catalysts with very wide industrial and commercial applications, especially as pigments and sunscreen ingredients for UV protection. Zinc oxide (ZnO) and titanium oxide (TiO_2) NPs have proven to be more transparent compared with the normal-scale sunscreen particles; however, the potential toxicity of these NPs is not well understood. A variety of *in vitro* studies have been performed to assess the toxicity of several NPs using different cellular systems and tests (Donaldson et al., 2006; Hardman, 2006; Sayes et al., 2006). TiO_2 NPs have been correlated with chromosome segregation, centrosome duplication, cytokinesis and functional regulation of mitotic checkpoint protein PLK1. Short-term exposure to NPs was reported to enhance cell survival, cell proliferation, ERK signaling activation and reactive oxygen species (ROS) production, while long-term exposure produces disturbances in cell cycle progression, chromosomal instability and cell transformation in cultured human fibroblasts (Huang et al., 2009; Rim et al., 2013). Such genotoxic effects are thought to be mediated through lipid peroxidation and oxidative stress mechanisms. On the other hand, the presence of ZnO NPs in human lung fibroblasts culture induced a concentration- and time-dependent increase in oxidative stress, intracellular Ca^{2+} levels and cell membrane damage. Alterations in gene expression due to oxidative stress and resulting apoptosis were considered to be the mechanisms for their cytotoxicity (Huang et al., 2010). Comparative studies performed for the evaluation of the relative toxicity of ZnO and TiO_2 NPs indicate that both NPs have a tendency to induce apoptosis- and necrosis-like cell death in human neural cells and in human fibroblasts, with ZnO NPs being more cytotoxic than TiO_2 NPs (Lai et al., 2008).

NPs rapidly ids. Thus, the coating proteins on the NP surface largely define the immunological identity of the particles (Cedervall et al., 2007). Despite the fact that metal oxide particles have similar surface charges in buffers, they bound different plasma proteins. TiO_2 and ZnO NPs tend to form agglomerates in biological media and this leads to an increase bound of proteins, as immunoglobulins, lipoproteins, acute-phase proteins and proteins involved in complement pathways and coagulation, to these nanoparticles (Deng et al., 2009). *In vitro* exposure of the TiO_2 NPs, increase the expression of IL-6, IL-8, tumor necrosis factor-alpha (TNF-alpha) and p53 genes in peripheral human lymphocytes (Baranova et al., 2015). On the other hand, the increase of neopterin production upon treatment of peripheral blood mononuclear cells (PBMC) with TiO_2 NPs implies that these compounds induce pro-inflammatory immune-regulatory pathways in T-cells and macrophages. The observation that the rates of tryptophan breakdown and interferon- γ (IFN-γ) production declined with increasing exposure to TiO_2 materials indicate that TiO_2 NPs target macrophages directly and that they have combined effects on promoting neopterin production and at the same time suppressing indoleamine 2,3-dioxygenase (IDO) activity.

TiO_2 NPs exert their cytotoxicity on the human macrophage and B lymphocyte cell lines dose- and size-dependently, via stimulation of the oxidative stress pathways (Becker et al., 2014). ZnO NPs induce a dose-dependent cell death and caspase activity in PBMC. ZnO but not TiO_2 NPs induce a downregulation of CD16 expression on natural killer (NK)-cells in the PBMC population, suggesting that subtoxic concentrations of ZnO NPs might have an effect on FcγR-mediated immune responses (Andersson-Willman et al., 2012). Nevertheless, the immunotoxicity of the ZnO NPs are contradictory. The variety of the size and charge causes differential effects on the immune system; the positively charged ZnO NPs exert higher cytotoxicity than the negatively charged ones in the murine macrophage cell lines (Kim et al., 2014a). ZnO NPs release free Zn ions that can be taken up by immune cells resulting in cell death. It was shown that the release of Zn ions from ZnO NPs triggers the production of excessive intracellular ROS, resulting in autophagic death (Johnson et al., 2015). Eventually, exposure to ZnO NPs can impair innate immune responses and attenuate macrophage responses to bacterial infection (Lin et al., 2014). Furthermore, inhalation of TiO_2 NPs in rats was followed by an imbalance of Th1/Th2 cytokines (Chang et al., 2014). Titanium accumulation in spleen and thymus caused histopathological changes and splenocyte apoptosis. Moreover, the exposure of TiO_2 NPs could significantly increase the levels of MIP-1α, MIP-2, Monocyte Chemoattractant Protein-1 (MCP-1), vascular cell adhesion molecule-1 (VCAM-1), IL-13, while it can markedly decrease the levels of NKG2D (Killer cell lectin-like receptor subfamily K, member 1) expression (Sang et al., 2014). Intratracheal inhalation of TiO_2 NPs by rats significantly decreases the CD3+, CD4+, and CD8+ cells, while the ratio of CD4+ to CD8+ significantly increases, indicating a disturbance of cellular immune function (Chang et al., 2015). However, the oral administration of TiO_2 NPs results in significant increases in the levels of IL-12, IL-4, IL-23, TNF-α, IFN-γ and transforming growth factor-β (TGF-β) in the ileum of mice (Nogueira et al., 2012). When orally administered to mice, ZnO NPs caused a slight decrease in the CD4+/CD8+, indicating an alteration in the T-cell maturation and suppression of natural killer cell activity. Consistently, serum levels of pro/anti-inflammatory IL-1β, TNF-α, and IL-10, and IFN-γ, and IL-12 are also suppressed (Kim et al., 2014a).

2.3. Metal nanoparticles

Metallic NPs, such as Ag, Au, Cu, and others, are widely used due to their antimicrobial properties. The toxicity of these NPs generally results from their chemical nature or from their dissolution products and/or agglomeration. *In vitro* studies revealed that Au and Ag NPs at concentrations between 5 and 100 μg/ml were non-toxic to primary cultures of human bone marrow hematopoietic progenitor cells, while Co NPs caused toxicity in the same concentration range (Bregoli et al., 2009). The effects of metal oxides in *in vivo* models are different (Venkataramanan et al., 2016). The reactions of dermal structures to subcutaneous injections of Au-NPs were studied in CBA mice. It was demonstrated that injected NPs were phagocytosed by macrophages; some of them migrated to lymphoid follicles of the node, while others migrated into blood vessels. The endothelium was destroyed as a result of the toxic activity of macrophages loaded with metal NPs. The oxide compounds of metal NPs may exert their immunotoxic effects by releasing free ions that can be taken up by immune cells (Engin et al., 2012). Hence, the dose responses display maximum stimulation or biphasic dose–response relationship. The aggregation/agglomeration tendency of elemental metals and their oxides compounds (Borm et al., 2006) plays a potential role in their immunotoxicity which is evident by activation/dysregulation of macrophages and antigen presenting cells (APC) (Xia et al., 2013). Even in nontoxic concentrations of nanosize, copper (II) oxide (Nano-CuO) particles cause a dose- and time-dependent increase in p38 phosphorylation-mediated plasminogen activator inhibitor-1 (PAI-1) expression due to oxidative stress (Yu et al., 2010). IgG is decreased by silver NP exposure, whereas IgM is increased. Immunoglobulin class switching from IgM to IgG requires T-helper cells and also APCs; therefore, IgG rather than IgM depends on the functional immune system, functionality is due to not only B-cells but also T-helper cells. In that manner, the effects of the silver NPs are likely exerted by the silver ions that are released from the NPs (Vandebriel et al., 2014). In addition, key factors contributing to toxicity are the size, shape, surface coating, surface charge, and conditions of silver ion release (Sharma et al., 2014). Thus, both the silver ions and TiO_2 NPs increase the stimulation of the immune system and of apoptosis due to expression of IL-6, IL-8, TNF-α and p53 genes respectively under the effect of NPs, indicating that different forms of metal NPs may have similar immunotoxicity (Baranova et al., 2015). Furthermore, the smaller metal NPs induce significant immunotoxic effects at lower concentrations and shorter times. Ag NPs produces the following pro-inflammatory response: IL-1β expression preceding both TNF and prostaglandin E2 (PGE2) expression for 25 nm particles; and only significant TNF responses with no detectable PEG2 response for 40 and 80 nm Ag NPs (Trickler et al., 2010). Moreover, exposure to metallic NPs causes increased oxidative injury mediated by cytokine regulation. The phagocytic function of alveolar macrophages is dose-dependently reduced by silver ions, ZnO, and TiO_2 NPs. ZnO NPs induce greater cytotoxicity than the other NPs. Particle composition and chemical stability have primary roles in the immunotoxicity of different NPs.

In some cases, the use of core–shell NPs consisting of metal and metal oxide provides the optimal combination of properties (Li et al., 2011). Depending on the production method, such NPs may have two, three or more layers. Core-shell NPs are produced through sequential synthesis by depositing a shell consisting of a metal or metal oxide on the surface of the NP cores that have been prepared in advance (Rudakovskaya et al., 2015). Often, due to the significant differences in the properties of the core and shell surface, it is necessary to use “crosslinking” materials in the form of polymers. The core–shell NPs, the core of which consists of magnetite, have magnetic properties and they are of the greatest practical importance. Since grafting of ligands directly to the surface of magnetite is difficult, the latter is modified by applying metals that are capable of forming strong bonds with ligands. The core determines the magnetic properties of NPs, and the shell is used for the grafting of ligands at the same time, ensuring their stabilization and specific properties. The gold-coated magnetite particles are the most significant members of this category, and they are utilized for increasing the image contrast in magnetic resonance imaging (Wang, 2011), and as carriers for certain biomolecules and antibody sensors in immunoassays (Vickery et al., 2013). Another area of application is drug delivery and hyperthermia in cancer therapy (Widder et al., 1978). When injected the core–shell NPs become opsonized and then rapidly captured from the vascular space by the liver, spleen and bone marrow macrophages (Reddy et al., 2012). Magnetite NPs are rather toxic and cause disruption of cell membranes, impair mitochondrial function, DNA damage, oxidative stress and a significant inflammatory response (Ahmad et al., 2012). Although it is believed that the magnetite NPs are not toxic at concentrations under 100 μg/ml (Ahmad et al., 2012), these findings should be treated with caution. For instance, it has been reported (Berry et al., 2003) that magnetite NPs at a concentration of 50 μg/ml significantly reduced cell proliferation. However, coating the surface of magnetite with a layer of an inert metal, such as gold, can significantly reduce the toxicity of magnetic NPs (Chao et al., 2010; Salado et al., 2012). In addition, incubation of mouse fibroblasts with gold-coated magnetite NPs of 35 nm in diameter at concentrations below 1 mg/ml for 24 h showed more than 75% cell survival rate (Li et al., 2011). It was found that the magnetite-gold NPs at the concentration of 100 mg/ml resulted in hemolysis of only 1% of cells when incubated for 1 h with blood, and the median injected lethal dose in mice was found to be 8.39 g/kg body weight.

2.4. Non-metal oxide nanoparticles

Non-metal oxide SiO_2 is widely used as additive to drugs, cosmetics, food, biomedical applications and biosensors. Exposure to SiO_2 NPs results in a dose dependent cytotoxicity in cultured human bronchoalveolar carcinoma-derived cells that is closely correlated to increased oxidative stress. Specifically, increased ROS levels and reduced glutathione levels have been observed as well as increased production of malondialdehyde and lactate dehydrogenase release from the cells indicating lipid peroxidation and membrane damage (Lin et al., 2006). Moreover, these NPs caused an Nrf2-Erk-MAPK-induced expression of oxidative stress responsive transcription factor HO-1, in human bronchial epithelial cells, Beas-2B, while a dysfunction of HUVEC was suggested via JNK, p53 and NF-κB pathways (Eom and Choi, 2009; Liu and Sun, 2010). Incubation with human plasma resulted in the formation of NP-biomolecular coronas enriched with immunoglobulins, complement factors, and coagulation proteins that bind to surface receptors on immune cells and elicit phagocytosis. Protein-coated NPs were protected from uptake by macrophages (Caracciolo et al., 2015). Actually, silica NPs do not aggravate human atopic dermatitis. However, when present in allergen-coated agglomerates, silica NPs lead to a low IgG/IgE ratio, a key risk factor of human atopic allergies (Hirai et al., 2015). Modified silica NPs with alkyne-terminated surfaces resist to agglomeration. Under certain conditions of T-cell activation, modified silica NPs enhance the proportion of antigen-specific CD8+ T cell responses. Various functional groups on modified silica NPs enhance IFN-γ and IL-2 production to different levels (Chen et al., 2014).

Silica NPs may cause immunotoxic effects that depent on their size and charge. The small-sized and negatively charged NPs have the most potent immunotoxicity by decreasing pro-inflammatory cytokine production, thus leading to immunosuppression (Kim et al., 2014b). In contrast, irrespectively of diameter size, silica particles induce caspase-1 activation in macrophages (Kusaka et al., 2014). Other effects of silica NPs include ROS generation, the production of IL-6, IL-8, MCP-1, TNF-α, IL-1β, and the enhanced expression of CD106, CD62E and tissue factor in human endothelial cells and monocytes. These suggest that interactions between particles, endothelial cells and monocytes may trigger or exacerbate cardiovascular dysfunction, atherosclerosis and thrombosis (Liu et al., 2012). Silica NPs affect inflammatory response in dendritic cells by activating p38 and NF-κB. The exposure of dendritic cells to ultrafine silica NPs decreases cell viability by inducing cell death in size- and concentration-dependent manner (Kang and Lim, 2012). The 30 nm and 50 nm silica-coated iron oxide NPs are taken up to a significantly higher degree through an active, actin cytoskeleton-dependent process with irrespective of size. On the other hand, upon administration of particles, macrophage or dendritic cell secretion of pro-inflammatory cytokines could not be detected (Kunzmann et al., 2011).

2.5. Biopolymers

Biopolymers are produced from various natural resources and crude oil. Four categories are recognized: a) biopolymers extracted directly from natural raw materials, such as cellulose, b) biopolymers produced by chemical synthesis from bio-derived monomers, such as polylactic acid (PLA), c) biopolymers produced by microorganisms or genetically modified bacteria, such as polyhydroxyalkanoates (PHAs), and d) biopolymers produced from crude oil, like aliphatic and aromatic polyesters, polyvinyl alcohol and modified polyolefins. Biodegradable PLA polymers are widely used in medical applications as surgical implants (Jain, 2000), tissue cultures and controlled release systems (Kuskov et al., 2010a, 2010b; Luu et al., 2003; Uhrich et al., 1999) as well as in active food packaging as an antimicrobials, because of their useful physical and mechanical characteristics (Jin and Zhang, 2008). In accordance to Regulation (EC) No. 1907/2006 and Regulation (EU) No. 453/2010, short-term exposure to PLA may result in adverse health effects affecting the mucous membranes and respiratory system as well as the kidneys, liver and central nervous system. Long-term exposure to PLA may cause non-allergic contact dermatitis and absorption through the skin. PHAs are a class of naturally occurring polyesters, consisting of over 100 different types of 3-hydroxy fatty acid monomers that are produced by a wide variety of microorganisms (Chen et al., 2015). Although they are derived biologically, the structures of these polymers are very similar to the structures of some synthetic absorbable polymers currently used in medical applications, especially for the development of tissue-engineered cardiovascular products (Li and Loh, 2015; Masood et al., 2014).

The main categories of NPs, according to their dimensions and structural characteristics, are summarized in Table 1. These materials generate a minimal host inflammatory response and degrade into non-cytotoxic components. However high concentrations of the degradation products may have toxic effects.

Polymeric biomaterials are selectively degraded by cell-generated ROS (Liu et al., 2011). ROS-induced degradation of biodegradable polymers accelerates *in vivo* release of polymeric drug delivery systems (Knab et al., 2015). These polymeric particulate delivery systems are able to present antigens and induce pro-inflammatory cytokine production by activating both humoral and cellular responses (Nicolete et al., 2011). Nevertheless, poly(lactic-co-glycolic acid) (PLGA) particles have been extensively used as biodegradable delivery systems to achieve efficient uptake of protein-based materials, as well as major histocompatibility complex (MHC) class I cross-presentation and effective T and B cell responses. In this respect, NPs induce a balanced Th1/Th2-type antibody response (Silva et al., 2015). Furthermore, tolerogenic NP therapy is a potential novel approach for the treatment of immune diseases. Treatment with tolerogenic NPs results in inhibition of CD4+ and CD8+ T-cell activation, increase in regulatory cells, and durable B-cell tolerance resistant to multiple immunogenic challenges (Maldonado et al., 2015). A critical mechanism that induces persistent antibody responses is the activation of immune cells through TLRs or Nod-like receptors (NLRs). NLRs ligands encapsulated into poly-Lactic acid (PLA) NPs are efficiently taken up by human dendritic cells and subsequently strongly up-regulate maturation markers and enhance pro-inflammatory cytokine secretion by dendritic cells (Pavot et al., 2013). Furthermore, PLA NPs covalently couple with antibodies. Antibody-labeled NPs efficiently bind to cancer cells and produce ten-fold or higher signal (Nobs et al., 2006). Thus, IL-12 and TNF-α loaded PLA microspheres promote the systemic antitumor immunity and lead to the induction of specific anti-tumor T-cells in the lymph nodes and spleens resulting in memory immune response (Arora et al., 2006).

3. The ADME process

Upon a substance entering the human body, either via external or internal exposure, the processes that follow the infection/intrusion are: absorption, distribution, metabolism and excretion. These are called ADME processes and constitute the subject of toxicokinetics (Fig. 1). A substance may enter the organism via medical intervention or dermal, oral as well as respiratory exposure. Therefore, toxicokinetics deals with the potential toxic effects of substances on the exposed tissues/organs. Although numerous ENMs have been manufactured, only a few studies exist in the field of ADME processes. To date, the majority of toxicokinetic studies deal with metals or metal oxide ENMs and to a lesser degree with polymer ENMs (Balani et al., 2005; Landsiedel et al., 2012).

3.1. Absorption

The nanospecific properties and characteristics of various ENMs are likely to affect their toxicokinetic behavior and toxicity profile. Skin is an important barrier that protects from environmental infection. It consists of two main structural layers: the epidermis and the dermis. The epidermis is the outer layer of the skin which has the role of the physicochemical barrier between the interior body and the environment. The outer layer of the epidermis (*stratum corneum*) covers the outside of the body and contains strongly keratinized dead cells (Bissett, 2009). Percutaneous absorption of substances follows the passing through this layer. On the other hand, the dermis is the deeper layer that provides the structural support of the skin. Several studies have focused on whether different drug formulations could penetrate into the skin after dermal exposure (Tinkle et al., 2003). The most unique particles are: liposomes, poorly soluble materials, such as TiO_2 NPs, and submicron emulsion particles, such as solid lipid NPs (Hoet et al., 2004). As shown from a number of studies, skin absorption is size dependent. Indeed, in the case of TiO_2 NPs that are used in sunscreen to protect skin from the UV light, nanosized particles are

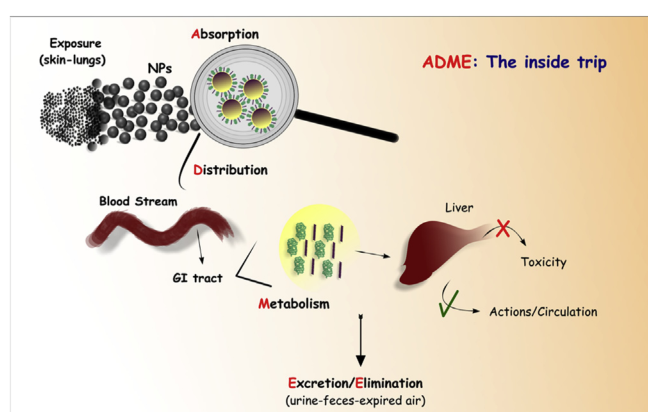


Fig. 1. Schematic presentation of the ADME process. When NPs enter the human body, through various exposure ways (such as skin and inhalation), the following processes include absorption, distribution, metabolism and excretion. When translocated in the gastrointestinal tract, NPs are transformed into their free forms and absorbed through the liver and/or the lymphatic system. Then they are capable to present their different mode of actions, however, their possible health risks must be under case-by-case analysis.

more likely to penetrate deeply in the skin layers (Andersson et al., 2002; Monteiro-Riviere et al., 2011; Nohynek and Dufour, 2012). Micro-sized liposomes do not easily penetrate into the epidermis, while those with an average diameter of 270 nm can reach the viable epidermis; smaller-sized liposomes can be found in higher concentrations in the dermis. Finally, biodegradable PLA used in transepidermal drug delivery has been found to penetrate into 50% of the dysfunctional hair follicles. Indeed, in 12–15% of the follicles, the PLA particles achieved a maximal penetration depth which corresponds to the position of the sebaceous glands pores. These results suggest that particles based on PLA polymers may be useful carriers for hair follicle and sebaceous gland targeting (Rancan et al., 2009). There are limited data about the absorption of different ENM after dermal exposure and even lesser information on the transportation of the particles from the skin into systemic circulation. The journey of NPs to the targeted site of action is limited by many physiological barriers, one of them being the endothelial cells lining the lumen of blood vessels. The endothelial cells lining the lumen of blood vessels are a physiological barrier that controls the transportation of macromolecules and fluids from the blood to the interstitial space as well as the transfer of the NPs from the vasculature into target tissues. Water soluble particles cross more easily to the interstitium, a process facilitated by endothelial permeability and specific carriers (Mehta and Malik, 2006). However, any disturbance in the endothelial system may lead to inflammation and subsequent loss of this function. Thus, the NPs by escaping from phagocytosis and directly interacting with the endothelial monolayer or getting phagocytized by the macrophages may provoke oxidative stress responses (Zhu et al., 2011). The endothelial lining of blood vessels differs in respect to its morphology and permeability in various organs (Pries and Kuebler, 2006). Most of the non-sinusoidal blood capillary walls permit the entrance of the lipid-insoluble endogenous and non-endogenous macromolecules up to 12 nm. Therefore, particles larger than the physiological upper pore size of the capillary walls limits do not accumulate within the respective tissues' interstitial spaces (Sarin, 2010). The macromolecules are transported through the endothelium via transcellular and paracellular pathways. In healthy, non-inflamed vessels the paracellular permeability of the endothelial cell–cell contacts is limited, while caveolae is responsible for the transcellular transport from the blood to the perivascular interstitium. However, during the inflammation, the endothelial cell-matrix is disturbed and interendothelial cell–cell junction openings are increased, thus paracellular permeability is increased (Sun et al., 2011).

The intestinal uptake of NPs has been more extensively studied and is better understood than pulmonary and skin exposure. For those NPs designed to stabilize food packaging or for drug delivery via intestinal uptake, it is possible to predict their behavior in the gastrointestinal (GI) tract. A substance that entered the human body after ingestion, as for example NPs that persist in the food matrix, may split in the GI tract. There are only a few data about the absorption of ENMs, but it is possible that they may not remain in a free form. Conversely, ENMs can agglomerate, become soluble, aggregate or react with some components of GI system, such as enzymes, intestinal microbiota or acids. Therefore, free form of NPs is going to be fully or partially lost. When NPs spilt in the GI tract there is a possibility for them to translocate through the intestinal wall. Translocation through the epithelium is a multistep process and depends on the properties of each nanomaterial such as surface area and charge, size, presence or absence of ligand and physiology characteristics of the GI tract (Maisel et al., 2015). The translocation of ENMs involves diffusion through the intestinal mucus, cellular or paracellular transport and contact with enterocytes or M-cells (Yun et al., 2013). Particles may pass through the GI lining via transcytosis by enterocytes, as observed in normal digestion, transcytosis by M-cells or by passive diffusion. The GI absorption of ENMs can also be affected by different surface coatings and surface charge, but these have been investigated to a lesser extent (des Rieux et al., 2006). Conclusively, ENMs studied up to date are not absorbed in a great extent in the GI tract. The amount of absorbed nanoparticles will then go through the portal circulation to the liver.

3.2. Distribution

After passing the GI tract, the absorbed ENMs can enter the capillaries and be transported to the liver or the lymphatic system through the portal circulation. The liver and the spleen are known to be the two major organs for systemic distribution of a large number of ENMs. However, certain ENMs may target all organs as demonstrated by their respective detection (Fig. 1). In addition, ENMs can interact with proteins and affect their tertiary structure leading to their dysfunction. This interaction could also lead to membrane expansion and cellular penetration, causing apoptosis in the exposed normal cells (Linse et al., 2007). Generally, it is acknowledged that ENMs of smaller sizes are more abundant in tissues as compared with larger-sized ENMs. The smaller particles are detected in kidney, liver, spleen, lungs and brain, while the larger particles remain inside the GI tract (Bergin et al., 2015). There is limited information about the distribution of injected and inhaled NPs and even fewer data about oral exposure. Irrespective of the uptake route, the distribution of NPs depends on the surface characteristics and the size of particles. Therefore, these are important issues to consider during drug design.

3.3. Metabolism

The metabolism (biotransformation) of ENMs via known routes (oral, inhaled, injected, dermal) depends, among others, on their surface chemical composition. The acidic environment of macrophages enhances dissolution of metal-containing particles as compared to neutral pH conditions (Arvizo et al., 2012; Pereira et al., 2015).

Heavy metal-containing nanomaterials are widely used for clinical purposes. However, the charge of the particle coating as well as the hydrodynamic diameter (HD) play an important role in the adsorption of serum proteins (Choi et al., 2007). Thus, HD is a determinant during the production of clinically applicable nanoagents. Although neutral colloidal semiconductor nanocrystals quantum dots do not bind serum protein, it is not possible to synthesize them with an HD that allows them freely pass through the endothelial barrier (Uyeda et al., 2005). Zwitter ionic-coatings make the NPs more biocompatible. After the entrance of the NPs to the physiological environment, they readily wrapped up with protein corona which is the essential dictator of the fate, transport and toxicity of the nanomaterial in the host system (Ding et al., 2013). This may affect the internalization and clearance of the NPs by the immune cells for modulation of their further actions (Wang et al., 2013). On the other hand, the conformational changes of the proteins that coat the NPs may induce immune response (Nel et al., 2009). When the NPs are coated with antibodies for VCAM-1 and E-selectin in equal proportions, a more uniform vascular distribution is achieved (Hossain et al., 2014).

SWCNTs were shown to be catalytically biodegraded over several weeks by the plant-derived enzyme, horseradish peroxidase. However, it has not been investigated yet whether peroxidase intermediates that are generated into the human cells or biofluids are involved in the biodegradation of CNTs. It has been shown that hypochlorite and reactive radical intermediates of the human neutrophil enzyme myeloperoxidase catalyze the biodegradation of SWCNTs *in vitro*, in neutrophils and to a lesser degree in macrophages. Importantly, the biodegraded nanotubes do not generate an inflammatory response when aspirated into the lungs of mice (Kagan et al., 2010).

3.4. Excretion

Up to date there is limited information about the excretion of NPs. The limited data available indicate that insoluble ENMs may remain in the tissues after exposure for long periods and accumulate. No evidence exists on the presence of ENMs in the milk (The EFSA Journal, 2009).

4. Nanoparticles and their applications

Like other major technological advances, nanotechnology offers novel advantages and challenges, especially when applied to the medical and food-related products regulated by the Food and Drug Administration (FDA). The unique chemical and biological properties of nanomaterials make them useful in many products for human uses, including those in industry, agriculture, business, medicine, clothing, cosmetics and food (Oberdorster et al., 2005a, 2005b) (Fig. 2).

4.1. Therapeutic delivery systems

Drug or gene delivery is a very promising application for NPs. The primary research goal of therapeutic delivery includes high specificity for both drug targeting and delivery. The second goal is the reduced toxicity, while therapeutic efficacy is maintained. Therefore, the utilized NPs have to be well characterized in terms of their toxicity before their clinical use. NP carrier systems must be biologically safe and biocompatible in order to avoid the adverse effects derived from the interactions among NPs and living cells (Hossain et al., 2011). Indeed, there are many advantages arising from the use of nanobased drug delivery systems (Emerich and Thanos, 2007; Groneberg et al., 2006; Petrochenko et al., 2015).

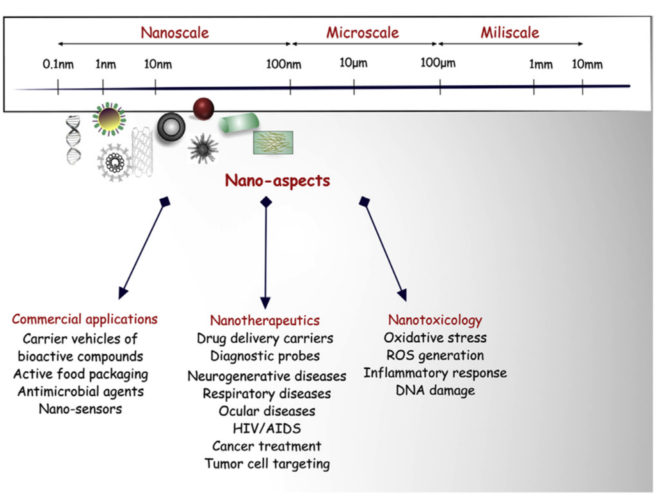


Fig. 2. Schematic representation summarizing the emerging aspects of nanomaterials in health and disease. According to the European Commission Recommendation, nanomaterial contains particles with one or more external dimensions in the size range 1–100 nm. NPs offer new benefits and challenges with their applications in consumer, food-related and medical products. Nanomedicine specializes in fields including therapeutic targeting, drug delivery systems and cancer focused therapeutic approaches. However, at all costs, NPs toxicological effects must be evaluated in order to serve as beneficiary and safe agent in commercial applications.

These include improved solubility, prolonged drug circulation lifetime, reduced immunogenicity and specific and selective drug delivery with minimum side effects. Moreover, drug delivery systems are characterized by the ability of combined therapy and drug resistance suppression, applying two or more drugs during drug release. Therefore, it is clear that the NPs-based drug delivery is a promising approach with a number of compositions under clinical trials (Zhang et al., 2008). The novel properties of nanomaterials offer them the opportunity to be used as drug delivery carriers as well as diagnostic probes. The utilization of NPs in this sector gives the opportunity for targeted drug delivery with the minimum toxic effect, in order to deal with several diseases (Bawarski et al., 2008).

4.2. Applications in chronic diseases

NPs have made a tremendous impact in the treatment of ocular, neurodegenerative and respiratory diseases, as well as HIV/AIDS and cancer, as shown by the numerous NP-based drugs and therapeutic delivery systems that are already in clinical use (Fig. 2). Indeed, the utilization of molecules such as DNA, RNA and proteins in drug development is restricted as they do not have the ability to enter the cells through passive diffusion. Therefore, their interaction with NPs is required to enable effective delivery. Manipulating polymer- (Kuskov et al., 2010b) and liposome-based drug delivery nanodevices, gives scientists the opportunity to focus on their properties and use them for the benefit of clinical medicine (Hossain et al., 2011; Kuskov et al., 2010a, 2010b).

4.3. Improving cancer treatment strategies

Currently, the use of NPs in cancer treatment includes dendrimers, liposomes, polymeric NPs, polymeric micelles, protein NPs, nanocrystals, viral NPs, metallic NPs as well as CNTs. These systems have been evaluated for their suitability of their application for *in vivo* cancer imaging and treatment (Byrne et al., 2008; Cho et al., 2008; Hahn et al., 2011). Recent advances have led to the development of bioaffinity NP probes for molecular and cellular imaging, intracellular targeting, targeted NP drugs for cancer therapy and integrated nanodevices for early screening and cancer diagnosis (Jabir et al., 2012; Ruan et al., 2015; Yang et al., 2015a; Zhu et al., 2015). Cancer nanotechnology is a rapidly growing field that has made a remarkable contribution to treatment strategies by enabling selective and specific release of chemotherapeutic agents based on their physicochemical and biological properties (Cho et al., 2008; Ranganathan et al., 2012). Various approaches have been applied for the use of nanomaterials in cancer treatment. Targeted drug delivery system via nanocarriers reduces tumor growth and related tumor events, such as angiogenesis and metastasis without damaging healthy tissues (Byrne et al., 2008; Ranganathan et al., 2012). An alternative approach is the targeting of the tumor cell via ligand-mediated specific interactions between NPs and cancer cell surface. The respective ligands may be growth factors, cytokines and antibodies (monoclonal and artificially engineered antibodies or antibody fragments) that facilitate the uptake of carriers into target cells (Alexis et al., 2008; Kontermann, 2006; Puri et al., 2008). Nanotherapeutics is effective in the targeting of the tumor microenvironment, which is characterized by enhanced permeability and retention (Fang et al., 2011). Finally, progress has been accomplished in the targeting of recurrent and drug resistant cancers, even though this approach is often limited by the lack of specific ligands. It has been reported that targeting of metastatic colon cancer cells is possible using a PEGylated liposome modified with a fibronectin-mimetic peptide (Garg et al., 2009). Moreover, PEG has been demonstrated to be a safe carrier for inhalational agents (Zarogoulidis et al., 2012a).

Indeed, directed cell targeting has been the focus of several scientific groups. Alveolar macrophages are found to be the vehicle to deliver a chemotherapeutic agent to the lymph nodes through the lymphatic circulation. Moreover, intracellular targeting is used to improve drug efficiency, while focusing on specific cellular parameters (Ranganathan et al., 2012; Tarhini et al., 2013), including intracellular trafficking, endosomal release and nuclear localization (Goren et al., 2000; Lundberg et al., 2003; Zarogoulidis et al., 2012a, 2012c).

It has been reported that certain delivery systems have the ability to deliver their entire drug cargo to patients without any loss to the environment, such as toxins release (Wittgen et al., 2006; Zarogoulidis et al., 2012b). However, further evaluation is needed regarding the use of these investigational strategies. Clinical trials have shown that the lipophilic diterpenoid paclitaxel has antineoplastic activity, particularly against primary ovarian epithelial carcinoma, breast, colon, head and neck cancers and non-small cell lung cancer (Cai et al., 2012). Nanodevices offer the opportunity to achieve targeted delivery of paclitaxel, a commonly used chemotherapeutic agent in cancer treatment, to tumor sites. PEGylated liposomes conjugated with truncated fibroblast growth factor receptor, a receptor found in many tumor types, are designed to achieve prolonged circulation time in the bloodstream and enhanced accumulation of paclitaxel in tumor tissues. These benefits may improve the therapeutic efficacy of paclitaxel as well as the promising potential as a long-circulating and selective tumor-targeting delivery system (Cai et al., 2012; Guo et al., 2015).

Nab-paclitaxel is a novel albumin-bound nano-formulation of paclitaxel that enables higher intra-tumoral drug concentrations to be achieved (Desai et al., 2006). Antitumor activity of nab-paclitaxel is enhanced over solvent-based paclitaxel, whereas its toxicity profile is distinct to paclitaxel. Nab-paclitaxel has proven clinical benefit and is currently approved in both the US and Europe as monotherapy in metastatic breast cancer, in combination with gemcitabine in advanced pancreatic cancer, and in combination with carboplatin in the first-line treatment of advanced non-small cell lung cancer (Gradishar et al., 2005; Socinski et al., 2012).

The delivery of DNA or RNA to cells represents a limiting step in the development of cancer gene therapy and RNA interference protocols for intracellular targeting. SWCNTs are of interest as carriers of biologically active molecules because of their ability to cross cell membranes. In a recent study, a novel strategy has been reported for chemical functionalization of SWNTs in order to bind small interfering RNA (siRNA) by disulfide bonds when applying to siRNA-mediated gene silencing in breast cancer cells. This approach has led to the efficient inhibition of breast cancer cells' proliferation (Chen et al., 2012). Moreover, intracellular targeting via siRNA delivery through endocytosis is of great importance. Thus, applying biocompatible siRNA-carbonate apatite NPs complexes, in a pH-sensitive environment, leads to an efficient gene transfection, intracellular targeting and an effective knockdown of functional cancer genes resulting ultimately in cancer cell death (Hossain et al., 2010, 2011).

4.4. *Synthetic extracellular matrices: multipurpose nanoscaffolds*

The natural extracellular matrices (ECMs), which support cells in tissues, are mostly composed of proteoglycans, glycosaminoglycans, adhesion molecules, collagen fibers as well as various signaling molecules (Barbouri et al., 2014; Theocharis et al., 2014; Tzanakakis et al., 2014). Synthetic ECMs must be capable of mimicking endogenous human tissue ECMs in order to support tissue regeneration or replacing (Lee et al., 2014a; Wang et al., 2014). Thus, synthetic ECMs must exhibit mechanical and tensile characteristics, identical to those of natural ECMs and simultaneously be nontoxic and non-immunogenic (Tonelli et al., 2012). Indeed, there is a focused effort to use nanostructured biomimetics as nanoscaffolds modulated at the molecular level. Thus, scaffold topography mimics the native ECMs in terms of framing, porosity and bio-functionality (Singh et al., 2014). In recent years, CNTs and their applications became attractive as materials for artificial bone development and bone regeneration due to their biocompatibility, biodegradability, physicochemical stability, mechanical strength as well as low immunogenicity (Karahaliloglu et al., 2015; Silva et al., 2009). The nanotubes are chemically inert, but upon chemical modification, they can be conjugated with collagen, bestowing them the ability to form efficient scaffolds for cell growth in 3D arrays (Hopley et al., 2014). High degree of flexibility and porosity (Shokrgozar et al., 2011), interaction with proteins and DNA (Li et al., 2012) and large contact surface area, are some of the CNTs features that are common with the natural ECM components.

Successful tissue engineering requires several obligatory components: a biocompatible ECM, suitable cells, a medium containing cytokines and a bioreactor (Padmanabhan and Kyriakides, 2015; Raftery et al., 2015; Sikavitsas et al., 2002). A synthetic scaffold, composed of variously functionalized CNTs and collagen fibers was found to be a promising substitute for natural ECM. CNTs increase the strength and regulate the orientation of collagen fibers, which results in scaffolds' increased stability and bioactivity. Subsequently, the artificial scaffold is combined with suitable progenitor cells in order to support their growth and specific differentiation to mature cell types e.g. osteoblasts, osteoclasts and muscle cells (Silva et al., 2009). In vivo, the scaffold is gradually biodegraded, as proliferation and differentiation of implanted cells continue, allowing contact of implanted cells with host blood vessels. The desired end-result is the normal function of the regenerated tissue (Suck et al., 2010).

In a different approach, gold (Au) NP embedded nanofibrous scaffold of FDA approved polycaprolactone (PCL), Vitamin B12, Aloe Vera and Silk fibroin (SF) was constructed to induce the differentiation of mesenchymal stem cells into cardiac lineage cells in order to obtain the regeneration of infarcted myocardium. The gold NP blended PCL scaffolds were found to support MSCs proliferation and differentiation into cardiomyocytes. The appropriate mechanical strength provided by the functionalized nanofibrous scaffolds supported the MSCs to produce contractile proteins and achieve typical cardiac phenotype (Sridhar et al., 2015). Importantly, silk fibroin due to its excellent biocompatibility is a candidate material to replace collagen. Indeed, membrane-reinforced three-dimensional electrospun silk fibroin scaffolds were shown to support the growth of human osteoblasts in a manner superior to collagen scaffolds and to increase the bone tissue formation in rat calvarial defect models (Yang et al., 2015b). Hydrogels are known to possess high water content and to resemble the microenvironment of extracellular matrix. Magnetic NPs were incorporated into a hybrid hydrogel containing type II collagen, hyaluronic acid (HA), and polyethylene glycol (PEG) to produce a magnetic nanocomposite hydrogel (MagGel) for cartilage tissue engineering. The MagGel could travel to the tissue defect sites in physiological fluids under remote magnetic guidance and support bone marrow derived mesenchymal stem cells adhesion and survival exhibiting potential for cartilage tissue engineering application (Zhang et al., 2015). Moreover, natural polysaccharides were found to enhance chondrocyte adhesion and proliferation on magnetic NP/PVA composite hydrogels suggesting that magnetic composite NPs and polysaccharides provide synergistic facilitation of cell adhesion and growth (Hou et al., 2015). The participation of natural polysaccharides (HA and CS) in the creating of nanostructured biomimetic scaffold system in the form of micro-porous polycaprolactone (PCL) spiral structure decorated with sparsely spaced bioactive PCL nanofibers, was reported to enhance the differentiation of the rat bone marrow stem cells (rBMSCs) into chondrogenic lineage *in vitro* (Lee et al., 2014b). The formation of a bi-layer scaffold of chitosan/PCL-nanofibrous mat and PLLA-microporous disc for keratinocyte and fibroblast co-culture provided a microenvironment similar to those present in the native ECM during initial wound healing (Lou et al., 2014). Moreover, layer by layer self-assembling of polysaccharide-coated BSA NPs on Ti surfaces resulted in nanostructured architectures which created cellular microenvironments mimicking natural ECMs (Wang et al., 2015).

4.5. Nanotechnology in stem cell research

The incorporation of stem cells into CNTs gives them the ability to proliferate and differentiate into various cell types. Cells utilized in tissue engineering are progenitor cells arising from bone marrow that can be directly injected to injured tissues cultured *in vitro*, or be conjugated with the scaffold and then used to regenerate tissues (Bianco and Robey, 2001). However, further investigation is needed to elucidate the biological impact of CNTs on stem cells. The improvement of cellular responses by creating an appropriate nano-biointerface, the enhancement of scaffolds bioactivity as well as the improvement in delivery of bioactive molecules, could lead to optimization of nanofibrous materials for tissue engineering and other clinical applications (Ilie et al., 2012).

4.6. Applications in food industry and related areas

Nanotechnology can also be applied to all phases of the food cycle. Food packaging is one sector of the industry where nanotechnology applications and synthesis of nanomaterials are rapidly expanding (Fig. 2). Modern food packaging started in the 19th century with the invention of canning by Nicholas Appert. The introduction of plastics as food packaging materials started one century later and its application is under continuous development. Indeed, during the last decades, the innovations are correlated with polymer nanotechnology and they are characterized by novel properties. Even though the novel properties of ENMs make them attractive in food packaging applications, safety issues may occur, different from those raised by conventional-scale version of the same material (Fubini et al., 2010). The basic categories of nanotechnology applications in the development of food packaging include: the manipulation of polymer barriers, the improvement of active components that can protect food and/or deliver functional attributes and the design of smart packaging materials that can facilitate the transduction of relevant information. As regarding improved food packaging, NPs improve the packaging properties of the polymer. Barrier properties are perhaps one of the most important and challenging components of food packaging. The penetration of light, moisture or gases can alter the sensory characteristics of food products, as well as induce possible dangerous spoilage (Marsh and Bugusu, 2007; Sekhon, 2010). Whereas many other applications of nanotechnology are still destined for the future, nanocomposites that enhance barrier properties are already commercially available. Nanoclays and CNTs demonstrate improvements in the structural, thermal, barrier and flame-retardant properties of plastics, while CNTs also enhance electrical conductivity. In active food-packaging, the presence of NPs allows package materials to interact with food and environment, which is important for food preservation. Antioxidants, O_2 scavengers, antimicrobial agents and humidity regulators are some of the including characteristics of the active packaging, that give the characterization of antimicrobial activity of nanocomposites included in food packaging (Sondi and Salopek-Sondi, 2004). Another important application of nanomaterials in this type of food packaging is the degradation of ripening gas, such as ethylene (Maneerat and Hayata, 2006). The presence of nanocomposites in smart food packaging can monitor the condition of packaged food or the environment surrounding. These novel materials are called nanosensors and they are able to respond both to environmental changes, such as temperature, humidity and oxygen levels in storage rooms, and to indicate degradation products or microbial contamination via oxygen indicators and pathogen sensors. Nanosensors are also designed to give information about the enzymes produced in the breakdown of food substances, making them unsafe for human consumption. There are also some devices, offered for the consumer's services on the basis of intelligent preservative-packaging technology, which will be capable of releasing a preservative if contained food begins to spoil (Duncan, 2011; Sekhon, 2010). Different types of functional nanostructures can be used to create materials with novel properties and introduce new functionalities in the food industry. They include nanoclays, carbon NPs, nanoscale metals and oxides and polymeric resins. These manufactured substances provide improved strength, temperature and moisture stability, reduce weight and can be used as barriers against O_2, CO_2, moisture, UV radiation and volatiles of packaging materials. For example, CNTs can be used in food packaging to improve its mechanical properties. It has been recently reported that CNTs exhibited powerful antimicrobial effects when applied directly or through aggregates of CNTs. Chitosan-based films, have been shown a promising range of antimicrobial activity (Rhim et al., 2006). Another important field of food packaging nanotechnology is the protection of some nutrients such as vitamins, antioxidants, proteins, carbohydrates and lipids. This can be achieved using the techniques of nanoencapsulation, where the final product will be characterized by improved functionality and stability. Scientists have designed some lipid-based nanoencapsulation systems that enhance the antioxidant activity by improving their solubility and bioavailability, while preventing undesirable interactions with other food components. The main system in this category is nanoliposome technology where nanoliposomes can be used as carrier vehicles of bioactive compounds, nutraceuticals, enzymes, food additives and food antimicrobials (Mozafari et al., 2008).

5. Nanoparticles: cytotoxic aspects

Although NPs primarily target the respiratory system, other organs, such as the GI tract, can also be affected. NPs can enter GI tract via different routes, e.g. indirectly via mucociliary movement or directly via oral intake of water, food, cosmetics and drug delivery systems in nanoscale. Nanotoxicology is the science that studies the nature and the toxic effects of nanoscale particles and composites on humans and other biological systems (Donaldson et al., 2004; Feron and Groten, 2002; Xu et al., 2011). So far, there is limited knowledge concerning the toxicological effects of NPs. However, several authors confirmed that the toxic behavior of NPs differs from their bulk counterparts. Even if NPs have the same chemical composition, they differ in their toxicological properties, while the difference in toxicity depends on size, shape, reactivity, surface charges and types of coating. Therefore, before NPs are commercially used, a toxicity evaluation is important (Kumar et al., 2012). When a nanostructure enters the human body, via external or internal exposure, the processes that follow the infection are: absorption, distribution, metabolism and excretion, known as the ADME processes (Fig. 1). During ADME, any interaction with biological systems can give rise to various cytotoxic effects, including chemical allergy, fibrosis, organ failure, cytotoxicity, tissue damage, ROS generation and DNA damage (Corsini et al., 2013; Golokhvast et al., 2015a; Nel et al., 2006; Singh et al., 2009). These data are summarized in Table 2.

5.1. Nanoparticle interactions with extracellular matrix biomolecules

The complex ECM networks not only provide essential physical scaffolding to the cells in tissues, but also initiate crucial biochemical and biomechanical signals that are required for tissue morphogenesis, differentiation and homeostasis (Karamanos, 2014; Skandalis et al., 2014b; Theocharis et al., 2015). Thus, the cell-ECM interface modulates signaling cascades which regulate almost all aspects of cell behavior (Afratis et al., 2012; Bouris et al., 2015; Gialeli et al., 2011, 2013; Theocharis et al., 2014). Importantly, the ECM is remodeled during the onset and development of different pathologies and these alterations contribute to disease progression (Gialeli et al., 2014; Nikitovic et al., 2013, 2015). Thus, the interactions of NPs at the ECM-cell interface need to be examined to cover safety concerns and health issues. It has been demonstrated that many NPs, such as CNTs, have the ability, by engaging various mechanisms, to interact with and penetrate cell membranes and consecutively locate to the cytoplasm, sub-cell organelles as well as to the nucleus. At these locations the NPs may interfere with various signaling pathways and therefore affect cell behavior (Zhao and Liu, 2012). An important possible consequence of NPs and ECM interactions is the production of ROS and the resulting oxidative stress. It has been reported that the ROS dependent modulations of ECM critically affect human cells' biological functions, while imbalances in ROS levels are strongly correlated with the complex process of tumor progression (Nikitovic et al., 2013, 2014). Moreover, a recent study revealed that nanoformulations of the glycosaminoglycan heparin, apart from their anticoagulant action, exhibit anticancer activity as well. Importantly, nano-heparin derivatives are capable to significantly reduce breast cancer cell proliferation and to regulate the expression profile of major ECM macromolecules, providing strong evidence for therapeutic targeting (Belmiro et al., 2009; Cardilo-Reis et al., 2006; Piperigkou et al., 2016). An example of the deleterious ECM-NP interactions was the finding that the titanium-wear particles, formed at the bone-implant interface, induce osteoblast –dependent ECM remodeling that is responsible for aseptic loosening, which is a main cause of total joint replacement failure (Xie et al., 2015).

The ability of living cells to recognize and respond to chemical and physical stimuli in their surrounding is fundamental for cell survival. Signal transduction, typically driven by growth factors or cytokines, is the main mechanism that cells use to convert an external signal to cellular outcome. The bioavailability of growth factors is largely determined through their interactions with ECM molecules and cell membrane receptors (Moskowitz et al., 2012; Skandalis et al., 2014a). It has been shown that epidermal growth factor and its specific receptor, EGFR, control the activation of numerous signaling pathways, including the phosphoinositide 3-kinase/Akt pathway and the Ras/Erk cascade, which results in an up-regulation of the gene transcription necessary for cell proliferation, survival and migration (Riese and Stern, 1998). A recent study has shown that metallic NPs altered EGF-dependent signal transduction in the human epithelial cell line A-431, through downstream PI3K/Akt and Ras/Erk cascades and thus, affected these cells' immune and inflammatory responses and cell proliferation. Specifically, after internalization, Ag-NPs drastically increased ROS production, followed by attenuation of Akt and Erk signaling. Au-NPs significantly diminished p-Akt and p-Erk levels whereas Fe-NPs strongly modulated EGF-dependent gene transcription (Comfort et al., 2011). PI3K and Akt signaling cascades in addition to EGF effects are triggered via integrin-dependent mechanisms in order to respond to extracellular stress (Abraham, 2005; Alenghat and Ingber, 2002; Attwell et al., 2000). The activation of Akt by EGF-R and β1-integrins is an important component of adhesion-dependent signaling. A recent study has shown that CNT-induced epithelial cell proliferation is mediated by the activation of PI3K and Akt, indicating a specific signaling mechanism (Unfried et al., 2008). An *in vitro* study demonstrated that when the widely used in biomedical applications, gold nanorods, AuNRs, are modified with polyelectrolyte multilayers they interact directly with collagen type I, altering the polymerization and mechanical properties of this important ECM component, which lead to a diminished ability of cardiac fibroblasts to contract collagen gels (Wilson et al., 2009).

6. Conclusions

Nanotechnology has a wide spectrum of applications to medicine (“nanomedicine”) that include screening of early disease, treatment for advanced disease and assessment of therapeutic outcomes. In this context drug delivery carriers as well as NP-based imaging probes in the treatment of cardiovascular disorders, ocular, neurodegenerative, respiratory diseases and AIDS, enhancement of wound healing, selective and specific release of chemotherapeutic agents for cancer, artificial bone development and bone regeneration, cellular microenvironments mimicking natural ECMs are very promising applications for NPs.

Although the NPs are roughly categorized by their material and shape, physicochemical diversities should be considered. Therefore, further studies on nanotoxicity as well as toxicological assessments are necessary in order to determine the effects of NPs in biological systems. Initially, physiological barriers control the translocation of the nano-sized particles between the blood and interstitial space. Later, despite of the differences in their material compositions, NPs provoke oxidative stress in tissues. Thus in CNTs-exposed cells, a higher level of oxidative stress leads to inflammation and

Table 2
Possible toxic effects of nanomaterials as pathophysiological outcomes. Adapted from (Nel et al., 2006).

In vitro NP toxic effects	Pathophysiological outcomes
ROS generation	Protein, DNA and membrane injury, oxidative stress
Oxidative stress	Phase II enzyme induction, inflammation, mitochondrial perturbation
Mitochondrial perturbation	Inner membrane damage, permeability transition, pore opening, energy failure, apoptosis, apo-necrosis, cytotoxicity
Inflammatory response	Tissue infiltration with inflammatory cells, fibrosis, acute phase protein expression (CRP)
Uptake by reticulo-endothelial system	Asymptomatic sequestration and storage in liver, spleen, lymph nodes, possible organ enlargement and dysfunction
Protein denaturation	Loss of enzyme activity, auto-antigenicity
Nuclear uptake	DNA damage, nucleoprotein clumping, autoantigens
Uptake in neuronal tissue	Brain and peripheral nervous system injury
Endothelial dysfunction	Atherosclerosis, thrombosis, myocardial infraction
Altered cell cycle regulation	Proliferation, cell cycle arrest, senescence
DNA damage	Mutagenesis, metaplasia, carcinogenesis

cytotoxicity, while metal oxide NPs exert their genotoxic effects through lipid peroxidation. However, they rapidly interact with the proteins in the biological fluids to form protein corona leading to the alteration in their behavior. Furthermore, metal NPs have biphasic dose–response relationship. Their oxidative damage causes disruption of cell membranes and mitochondrial dysfunction. On the other hand, non-metal oxide NPs cause ROS generation, whereas biopolymers generate a minimal host inflammatory response and degrade into non-cytotoxic components.

European Commission reports included the information considering current regulatory requirements under environmental legislation and provided a series of recommendations to improve the knowledge base on exposure, required for adequate risk assessment of nanomaterials. In this context, introducing innate and adaptive immune responses induced by nanomaterials will clarify desirable or undesirable immunological effects of ENMs and will be guidance for thematic studies. This is considered to be a growing and promising research area which is going to deepen our understanding of the cellular mechanisms of NP actions and their effect on functional cell properties related with human disease. Thus, further investigations are needed to explore the nano-bio interface, immune responses, optimization of nanomaterial utilization for tissue engineering, clinical applications, and the food industry.

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