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REVIEW

The Forgotten Innate Immune Cells: Unraveling Their Prospective Interactions with Nanomaterials

África González-Fernández[1,2], Immacolata Maietta[1,2]

[1]CINBIO, Universidade de Vigo, Vigo, 36310, Spain; [2]Immunology Group, Galicia Sur Health Research Institute (IIS Galicia Sur). SERGAS-UVIGO, Vigo, Pontevedra, 36312, Spain

Correspondence: África González-Fernández, CINBIO, Universidade de Vigo, Vigo, 36310, Spain, Tel +34-986-130141, Email africa@uvigo.es

Abstract: Nanomaterials, particularly nanoparticles, are revolutionizing various fields, including medicine, due to their distinctive physicochemical properties. Their large surface area, charge and high particle number per unit mass enable enhanced interactions with biological systems, particularly with the immune system. The interaction between nanomaterials and immune cells can influence immune responses in several ways, including modulating cell activation through interactions with pattern recognition receptors (PRRs), internalization, degradation, or accumulation in phagocytic cells, as well as altering the immune microenvironment through the release of granular contents, cytokines, and chemokines. Although many studies have focused primarily on phagocytic (macrophages, dendritic cells, and neutrophils) and Natural killer (NK) cells, less attention has been given to other innate immune cells such as eosinophils, basophils, and mast cells. This review aims to highlight the role of these "forgotten" innate immune cells, providing insights into their function, available cell lines, applicable techniques to understand interactions with nanomaterials, and relevant in vitro and in vivo models.

Keywords: eosinophils, basophils, mast cells, nanotechnology, immunogenicity, interaction

Introduction

Nanomedicine has emerged as a transformative approach in biomedical science, offering novel strategies for diagnosis and therapy. There are several products already on the market, such as liposomes, albumin nanoparticles (NPs), polymeric micelles, polymeric conjugates, and iron oxide NPs-especially for cancer treatment.[1] Some nanomaterials are considered ideal candidates for drug delivery systems due to their unique combination of properties, including their small size (which allows for enhanced cellular uptake), biocompatibility, ability to improve drug stability and solubility, capacity for controlled and sustained drug release, and the possibility of surface modification for targeted delivery, among others.[2] Furthermore, nanoparticles play a crucial role in diagnostics techniques. For instance, gold and silver nanoparticles (Au and AgNPs, respectively) enhance point-of-care testing (POCT) by enabling the rapid detection of infectious diseases.[3] Additionally, they serve as vaccine adjuvants: for example, lipid nanoparticles protect RNA from degradation in vaccines,[4] or polymeric nanoparticles can also significantly boost vaccine effectiveness by promoting antigen uptake in dendritic cells, thereby strengthening immune responses.[5] Additionally, nanomaterials have numerous other therapeutic applications.[6]

Nanomaterials are categorized based on their origin and composition. They can be naturally occurring or artificially engineered, encompassing a wide range of materials such as metals, polymers, lipids, and ceramics, among others. These materials differ in size, composition, surface charge, hydrophobicity, porosity, and texture (rugosity), all of which influence their behavior in biological environments.[2,7] Engineered nanomaterials are further classified into biodegradable and non-biodegradable categories. Biodegradable nanoparticles, including those composed of lipids or polymers, are particularly attractive for medical applications as they can be degraded within the body.[8] In contrast, non-biodegradable

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nanomaterials, such as certain metal nanoparticles, may persist in the body and thus require careful assessment to ensure safe biomedical use.[9] A key challenge in this field is understanding how these materials interact with components of the immune system, which plays a crucial role in determining their biocompatibility, therapeutic efficacy, and potential adverse effects. In addition, we should distinguish between nanoparticles designed for active targeting of specific immune cells and those that passively interact with immune cells due to their physicochemical properties.

While extensive research has focused on the interaction between nanomaterials and some innate cells such as macrophages,[10] dendritic cells,[11–13] neutrophils[14,15] and natural killer (NK) cells[16–18] less attention has been paid to the roles of other innate immune cells, such as eosinophils, basophils, and mast cells. Although less abundant, these latter cells play essential roles in inflammation, allergic responses, and host reaction.[19,20] Their activation by interaction with nanomaterials could have significant implications for both safety and therapeutic outcomes.

This review provides a comprehensive overview of the current state of knowledge regarding these three cell types. We describe their physiological roles, mechanisms of activation, and the potential immunological consequences of their responses to various nanomaterials. Available studies indicate that these cells can recognize and react to nanoparticles in distinct ways. By highlighting the importance of these cells in the context of nanomaterial exposure, we emphasize the need to include them in immunotoxicity assessments and nanomedicine design. Understanding these interactions is crucial for developing safer and more effective nanotherapeutics, especially in applications related to allergy, inflammation, and immunomodulation.

How Do Nanomaterials Interact with Innate Immune Cells?

The interaction of nanomaterials with the immune system is complex and largely depends on their surface properties (such as charge and porosity), composition, size, and shape. For instance, positively charged nanomaterials tend to interact more readily with cellular membranes, which may lead to increase cytotoxic effects.[21] Some nanoparticles are specially designed with characteristics that promote efficient uptake, including variations in size and coating. Regarding size, phagocytosis plays a role in the uptake of larger particles, while smaller particles are mostly captured by endocytosis[22,23] Another example is the coating of the nanomaterial. For example, we demonstrated that nanoparticles coated with different monosaccharides (either galactose or glucose) were differentially recognized by macrophages, significatively affecting cellular uptake, with glucose-coated nanoparticles being favored.[24] Surface roughness (rugosity) is another important factor, as rougher surfaces provide more points of cell contact, potentially enhancing immune recognition, uptake,[25] and cellular attachment.[26]

Another important consideration is the route of entry. Nanomaterials can enter the human body through various pathways, influencing their bioavailability and interaction with immune cells. This diversity in entry routes underscores the need to understand how nanoparticles affect different tissues and immune functions throughout the body. Major entry routes include the bloodstream, inhalation, cutaneous (skin) absorption, mucosal surfaces, oral ingestion, and respiratory pathways.[27] For instance, nanoparticles entering through mucosal surfaces may first interact with macrophages, which act as one of the first sentinels against foreign substances.[28] Upon uptake, these macrophages may either initiate a pro-inflammatory response or, depending on the nanoparticle´s composition and surface characteristics, promote immune tolerance. Platelets, which are among the first responders in the bloodstream, may also interact with nanoparticles, potentially triggering clotting or inflammatory cascades.[29] Oral ingested nanoparticles could pass through the gastrointestinal tract, interacting with gut-associated immune cells, whereas those entering directly into the bloodstream immediately encounter systemic immune cells.[30,31]

The unique properties of nanomaterials hold great promise in biomedicine, but their interactions with the immune system necessitate careful consideration. Variations in size, composition, rugosity, charge, and route of entry can influence immune responses, ranging from beneficial therapeutic effects to potentially harmful immune reactions. A thorough understanding of these interactions is essential for the safe and effective development of nanomaterial-based medical applications.

It is important to consider that the immune system is a complex network of cells, tissues, and signaling molecules (such as cytokines and chemokines),[32] that not only defends the body against infections, but also eliminates senescent and tumor cells, facilitates wound healing, detects incompatible transplants, and responds to internal danger signals. The

innate (comprising many different cell types) and adaptive branches (mediated by T and B lymphocytes) work with remarkable precision to maintain health, continuously evolving to counteract novel microbial threats and internal challenges.[32] The innate immune system serves as the body's primary defense mechanism, employing a diverse array of cellular subsets to detect and respond to pathogens and tissue damage. Key players—monocytes/macrophages, neutrophils, and dendritic cells—identify and eliminate invaders through processes such as phagocytosis.[33] Other innate immune cells, including eosinophils, basophils, mast cells, natural killer (NK) cells, and innate lymphoid cells (ILCs), mediate a wide range of responses, from parasitic and allergic inflammation to antimicrobial defenses.[34]

The immune system's structure and function relies on constant interaction among its components, each reinforcing the other to create a multi-layered defense. This coordination between innate and adaptive cells ensures not only the elimination of pathogens, but also the maintenance of immune memory, providing innate (trained) immunity[35] and adaptive long-term immunity.[32] Several innate immune cells such as neutrophils, monocytes, macrophages, NK cells and dendritic cells have been extensively studied in the field of nanomaterials due to the availability of several cell lines and access to primary cells from both murine and human sources.[36–40]

Examples of consequences of the interaction between nanomaterials and these innate immune cells include cell activation, cytokine release, the production of reactive oxygen species, blocking/increasing routes of uptake (phagocytosis, endocytosis, caveoli- mediated uptake, etc)., induction of inflammation or tolerance, and anti-tumoral or anti-pathogen effects, among others.[11,13,15–18,28,41]

However, other innate immune cells derived from a common myeloid precursor (Figure 1), such as eosinophils, basophils, and mast cells, have not been widely investigated in the context of nanomaterials. This is despite their crucial roles in allergic reactions, inflammation, and the immune response to parasites, and their release of various mediators, including histamine, leukotrienes, and cytokines.[42] There are several reasons that could explain the lack of information on these cells. First, nanobiology is a relatively new field, and research on interactions between nanomaterials and various biological systems[43] is still in its early stages. Second, these cells are less abundant, making them more difficult to work with due to factors such as early apoptosis, short lifespan, tissue location, and the variety of tissues involved. Third, the specific mechanisms of nanomaterial-cell interactions are complex and can vary depending on the type of nanomaterial, its size, shape, and surface chemistry, as well as the specific cell type and its physiological state.[44]

The potential impact of nanomaterials on these cells and their functions could be significant, as nanoparticles can interact with them and potentially affect their cellular processes. Understanding the interaction between the cells and nanomaterials could highlight the importance of nanomaterial development and design. Moreover, there is growing interest in understanding the implications of these interactions in the field of nanotoxicology and nanomedicine. This review will focus on these three types of cells, their characteristics, methods for studying them, and the progress and challenges in understanding nanoparticle-cell interactions.

Eosinophils

Cellular Origin and Differentiation

Eosinophils, described by Dr. Paul Ehrlich in 1879, are the second most abundant granulocytes (1–3% circulating leukocytes and approximately 6% in bone marrow). They are myeloid-derived cells (Figure 1) characterized by their bilobed nuclei and specific granules that can be stained with acid coal tar dyes.[45] Their development from CD34+ hematopoietic stem cells to lineage-committed eosinophil precursor (EoP) expressing CD34+, CD38+, interleukin 5 receptor (IL5-R)α+, IL-3Rα+, and CD45RA[46] (Table 1) is critically dependent on cytokines like IL-5 and further supported by IL-33 and Granulocyte Macrophage-Colony stimulating factor (GM-CSF).[47] Key transcription factors such as GATA-1, Helios, C/EBPε, Aiolos, and XBP-1[48] are essential for this lineage commitment. Mature eosinophils circulate briefly (4,5 to 8 hours) before migrating to tissues,[49] particularly the gastrointestinal tract and sites of high epithelial turnover or inflammation.[50] Isolated blood eosinophils undergo spontaneous apoptosis within two days of culture without specific modulators,[51] and their tissue lifespan under homeostatic conditions is short (under a week), regulated by apoptosis.[47] However, inflammation, particularly through IL-5, can prolong this lifespan. Clearance of

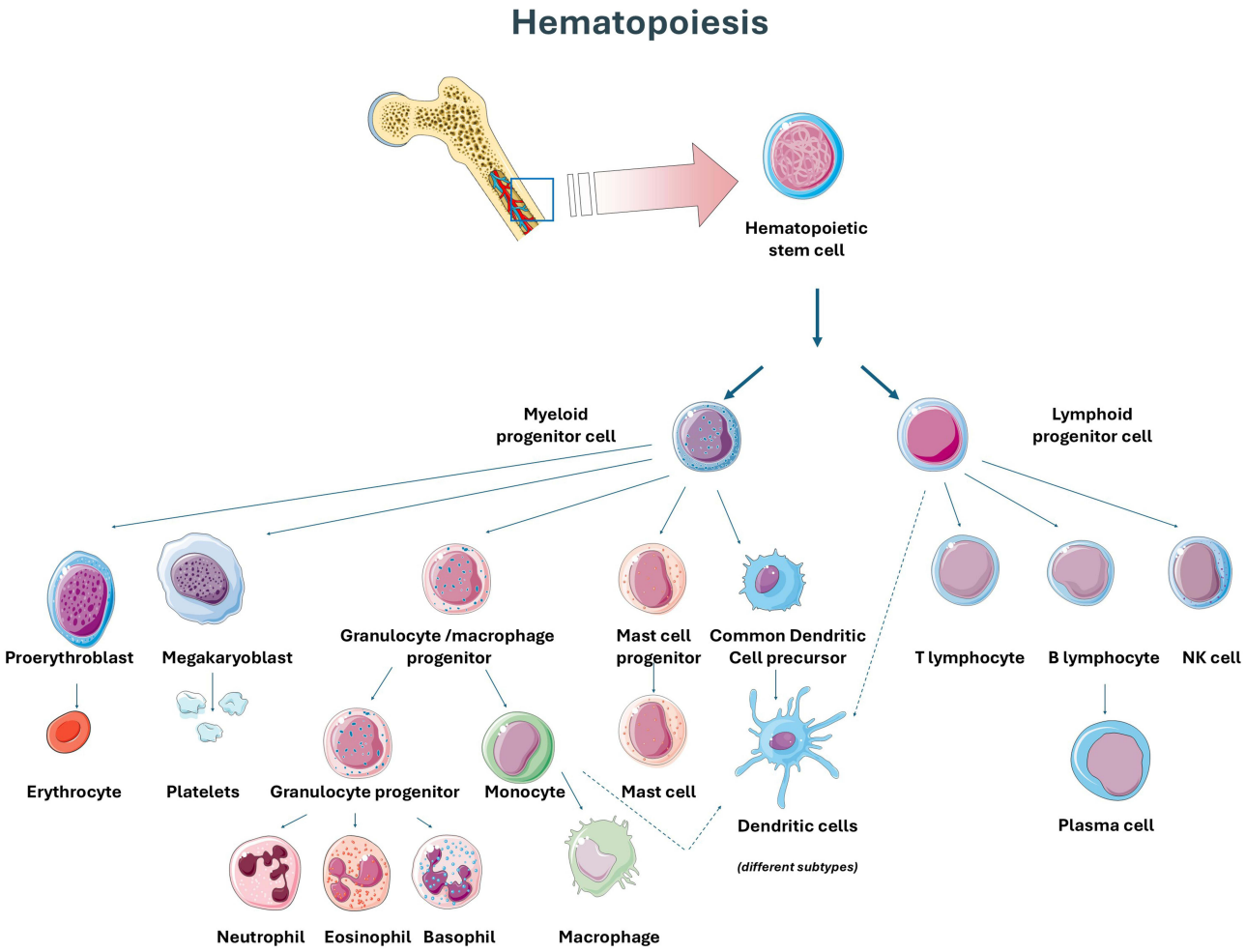

Figure 1 Schematic representation of hematopoiesis showing the differentiation of multipotent hematopoietic stem cells into myeloid and lymphoid lineages.

apoptotic eosinophils occurs via phagocytosis through efferocytosis, and impaired clearance is linked to chronic inflammatory and autoimmune diseases.[52]

Eosinophil recruitment to inflammatory sites is a sequential process initiated by rolling along endothelial cells, followed by loose adhesion via selectin receptors and firmer adhesion through integrin receptors.[32] Subsequent diapedesis into the interstitial space and migration to the inflammation site are driven by chemotaxis in response to eotaxins (CCL-11, CCL-24, CCL-26).[53] Clinically, therapies blocking cell migration molecules, like natalizumab (anti-CD49d), vedolizumab (anti-α4β7), or dupilumab (anti-IL-4 receptor), can induce blood eosinophilia by altering eosinophil trafficking.[54]

Functional Role of Eosinophils

Beyond their classical roles in allergic diseases, inflammation, and parasitic responses, eosinophils are increasingly recognized for their involvement in diverse homeostatic and immunomodulatory processes.[55] Their conserved presence across vertebrates and the lack of reported congenital eosinophil deficiency in humans[56] strongly indicate their importance in fundamental biological functions. During immune responses to pathogens or inflammatory stimuli, eosinophils degranulate, releasing a variety of cationic proteins from their granules, including major basic protein (MBP), eosinophil peroxidase (EPX), eosinophil-derived neurotoxin (EDN), and eosinophil cationic protein (ECP).[57] Moreover, eosinophils modulate immune responses by releasing cytokines such as the immunosuppressive IL-10 and the Th2-driving IL-4 (a key cytokine in Th2 responses)[58] (Figure 2).

Table 1 Comparison Between Eosinophils, Basophils, and Mast Cells

Characteristics	Eosinophils	Basophils	Mast Cells
Origin	Derived from CD34+ bone marrow progenitors → eosinophil progenitors (EoPs); differentiation driven by IL-5, and later by IL-33 / GM-CSF	Derived from CD34+/IL-3Rα+ bone marrow progenitors; regulated mainly by IL-3	Derived from CD34+ progenitors that migrate to tissues; local differentiation supported by stem cell factor (SCF)
Main Surface Markers	• Blood eosinophils: IL-5Rα, CCR3, Siglec-8, EMR1, CD11b • Lung resident: Siglec-F intermediate $^{(int)}$ CD101 low $^{(Low)}$ and CD62 positive $^{(+)}$ • Lung newly recruited eosinophils: SiglecF^{high} CD101^{high} CD62^{neg} • Gut eosinophils: CD11c, Ly6G, CD44	CD9, CD22, CD36, FcεRI, CD203c, IL-3Rα	FcεRI, CD117 (c-Kit), CD203c, tryptase
Key transcription factors	GATA-1, Helios, C/EBPε, Aiolos, and XBP-1	GATA2 and C/EBPα at the earlier stages, and Promoter-derived Runt-related transcription factor (1P1-Runx1) later on GATA-1	GATA2, MITF, AP-1, Ehf, BATF and STAT-5
Lifespan	Homeostatic: < 1 week	Homeostatic: < 60 hours	Homeostatic: in tissues from months to years.
Released Mediators	Major basic protein (MBP), eosinophil peroxidase (EPX), eosinophil cationic protein (ECP), IL-4, IL-10	Histamine, IL-4, IL-13, prostaglandins, Cysteinyl leukotriene 4 (LTC4), heparin	Histamine, tryptase, chymase, prostaglandins, cytokines
Main Functions	Anti-parasitic defence, allergic responses, regulation of inflammation	Allergic responses, parasitic infections (especially helminths), modulating innate and adaptive immunity	Allergic reactions, anaphylaxis, microbial defence, tissue repair
Body Distribution	Blood (1–3% of circulating leukocytes), bone marrow (6%), lungs, gastrointestinal tract, spleen, thymus	Rare in blood (<1%) and bone marrow, migrates to inflammatory/ allergic sites	Resides in vascularized tissues: skin, lungs, mucosa, skeletal muscle.

Abbreviations: ECP, Eosinophil cationic protein; EoPs, Eosinophil progenitors; EPX, eosinophil peroxidase; GM-CSF, granulocyte-monocyte colony stimulating factor; MBP, Major basic protein; 1P1-Runx1, promoter-derived Runt-related transcription factor.

Molecular Markers and Phenotypic Heterogeneity

Human eosinophils are identifiable by high side scatter (SSC) in flow cytometry[46] and the expression of surface markers such as IL-5Rα, CCR3 (a major eotaxin receptor involved in eosinophil recruitment), Siglec-8 (an inhibitory receptor specific to eosinophils and mast cells), EMR1 (EGF-like module-containing mucin-like hormone receptor 1, involved in adhesion and migration), and CD11b (an integrin subunit involved in adhesion and phagocytosis).[59] A wide array of other membrane receptors, including various adhesion molecules and chemokine/cytokine receptors, contribute to their complex microenvironment interactions. While human eosinophils exhibit phenotypic heterogeneity based on location, the existence of distinct regulatory subsets, as seen in mice,[60] is still under investigation. For example, lung-resident mouse eosinophils display a marker profile that suggests a regulatory role in the absence of inflammation, unlike newly recruited eosinophils. In other locations like the intestine, where epithelial turnover is constant, mouse eosinophils express CD11c, Ly6G and CD44. This suggests that eosinophil heterogeneity is influenced by both maturation state and the specific tissue location and activity.

Tissue Distribution and Isolation Methods

The most accessible source of eosinophils in humans is blood, while the bone marrow contains the highest number. Peripheral blood eosinophils can be measured and identified in a complete blood count (CBC) via conventional

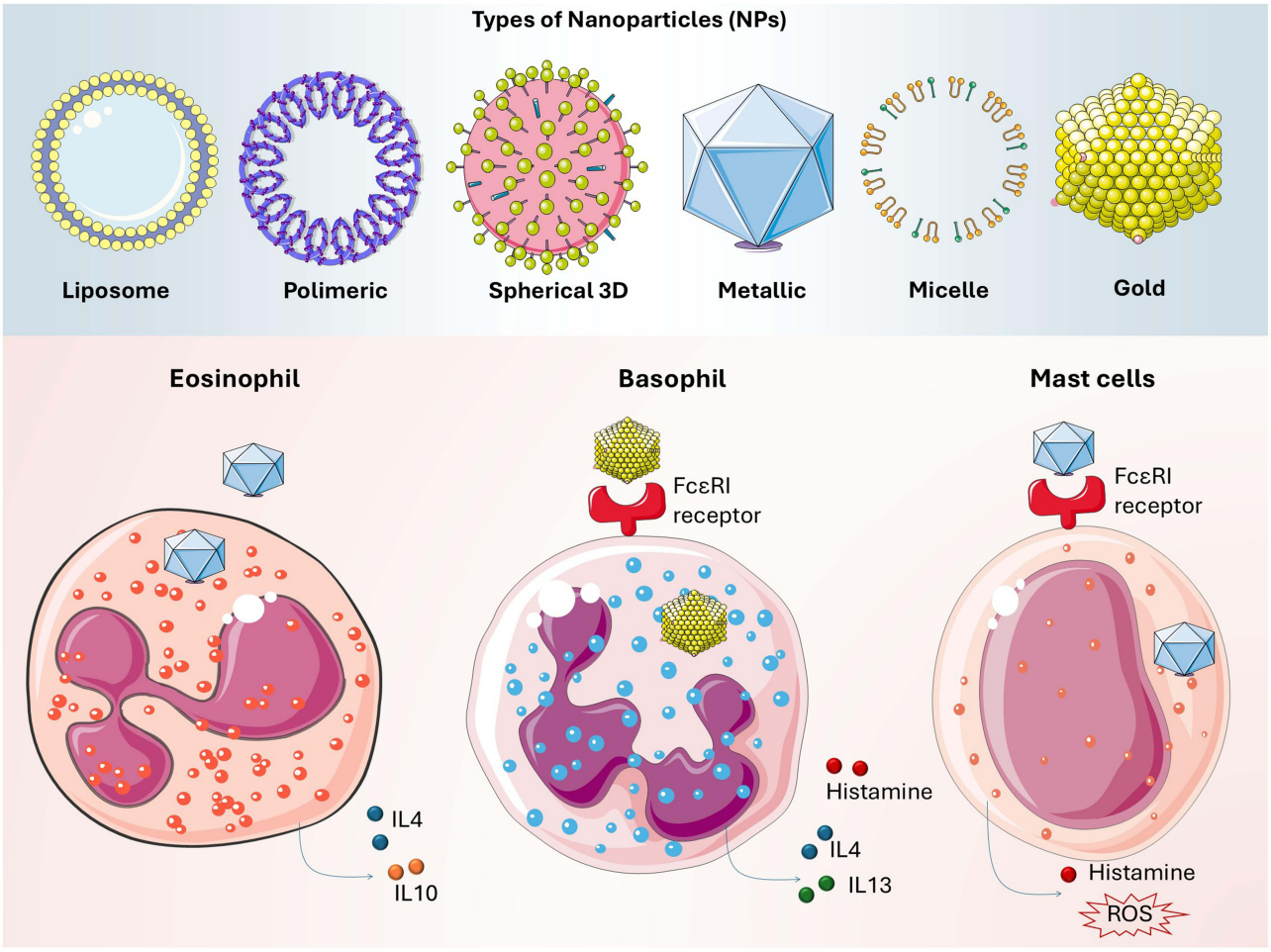

Figure 2 Schematic illustration of the interaction between different types of nanoparticles (NPs) — including liposomes, polymeric, spherical, metallic, micellar, and gold nanoparticles — and innate immune cells: eosinophils, basophils, and mast cells. These cells can internalize or respond to NPs, leading to the release of various mediators such as interleukins (IL-4, IL-10, IL-13), histamine, and reactive oxygen species (ROS). FcεRI receptor-mediated activation is particularly relevant for basophils and mast cells, highlighting their role in allergic responses and inflammation.

hemogram and can also be stained with the acidic red dye eosin for further analysis. Studying eosinophils with conventional flow cytometry is challenging due to their low blood numbers, short lifespan, and high autofluorescence. Furthermore, their cationic proteins interfere with specific antibody binding to low abundance proteins, leading to high fluorescent backgrounds.[61] Due to fluorescence interference, researchers avoid flow cytometry and prefer optimized in vitro protocols to isolate blood eosinophils (by immunomagnetic separation) or tissue-resident eosinophils (using proteases) for subsequent fixation and staining. Many studies identify eosinophils in different tissues using immunohistochemistry rather than isolation. Bronchoalveolar-lavage fluid is another source, particularly in allergic asthma mouse models.[62]

Eosinophil Activation (in vitro and in vivo)

Eosinophils can be activated in vitro by various agonists, including immunoglobulins, lipid mediators, and cytokines. For instance, LIR7 cross-linking with plate-bound antibodies induces a dose- and time-dependent release of eosinophil-derived neurotoxin and leukotriene C_4.[63]

In vivo, eosinophils are activated by parasitic infections, allergens, IL-5, IL-3, and GM-CSF, certain drugs (cytokine therapies, tetracyclines, cephalosporins, check point inhibitors), and even some nutritional supplements and herbs. Drug hypersensitivity can manifest from asymptomatic eosinophilia to severe, life-threatening complications, with eosinophilia

potentially persisting for months after drug cessation or requiring treatment with glucocorticoids or other immunosuppressants.[64]

Eosinophil-related disorders affect multiple organs, causing diverse symptoms[65] from common allergies (urticaria, angioedema, anaphylaxis) to lung (asthma, pneumonia, hypereosinophilic syndrome), gut (esophagitis, gastroenteritis, colitis), heart (myocarditis, endomyocardial fibrosis), and kidney (nephritis) issues, and rarely, associations with malignancies.

Interactions of Eosinophils with Nanomaterials

The in vitro interaction between nanoparticles (NPs) and eosinophils is relatively underexplored, although in vivo studies have increasingly focused on the context of allergies, inflammation or cancer.[66] In vitro models, such as the use of AML14 and AML14.3D10 cell lines (reviewed by Baumann et al[67]) have served as valuable tools for analyzing the effects of various nanomaterials, including metal nanoparticles.[68,69] Furthermore, progenitor cell lines such as HL60 clone 15 and EoL-1 can be differentiated into eosinophils through continuous histone acetylation. This characteristic allows researchers to investigate the mechanisms of eosinophil differentiation by employing histone deacetylase inhibitors.[70]

Cho et al[71] analyzed the effect of metal oxide Nps and their soluble ions in both in vitro and in vivo, observing the recruitment of eosinophils to the lungs. More recently, studies have focused on the interaction of nanoparticles with eosinophils in the context of allergies and inflammation. In vivo experiments showed that these nanoparticles effectively reduced inflammation by modulating the Toll-like receptor 4 (TLR4)/MyD88/NF-κB signaling pathway. Additionally, they positively impacted the gut microbiota composition and increased the production of short-chain fatty acids, suggesting a multifaceted approach to alleviate allergic responses and highlighting the therapeutic potential of nanoparticle-based strategies for eosinophil-associated conditions.[72]

In a mouse model of allergic asthma, Wang et al[73] showed that immunization with a tolerogenic lipid nanoparticles (LNPs)-based mRNA vaccine was able to significantly decrease asthma symptoms by reducing the accumulation of eosinophilic granulocytes and mucus secretion.

Understanding the diverse functions of eosinophils, including their cytotoxic potential through granule protein release to their immunomodulatory capacity via cytokine production, is essential for considering their interactions with nanomaterials. Nanoparticles could potentially trigger or inhibit eosinophil degranulation, interfere with cytokine signaling at their receptors, affect adhesion molecule interactions, or influence eosinophil lifespan and clearance mechanisms. Furthermore, they could modulate the production and release of regulatory cytokines like IL-10 and IL-4 (Figure 2), thereby impacting the overall immune response to the nanomaterial itself or within other biological processes.

Basophils

Cellular Origin and Differentiation

Basophils, also first described by Paul Ehrlich,[74] are the rarest granulocytes, characterized by their basophilic-staining granules. They constitute less than 1% of circulating white cells and a minor component of bone marrow.[20,75,76] While initially considered redundant circulating mast cells, basophils differ in size, maturation site, lifespan, nucleus shape, and granule content, and have distinct functions in allergic and immune responses (Table 1).

Basophils originate from pluripotent CD34+ hematopoietic stem cells in the bone marrow (Figure 1) likely evolving from $CD34^{+}$/IL-3Rα^{+}/IL-5^{+}eosinophil/basophil progenitors. While it was previously thought that basophils and mast cells have distinct bone marrow precursor,[77,78] remains unknown whether an ancestor with this unique differentiation potential exists or whether basophils derive from hybrid progenitors, which share mast cells, eosinophil, and/or megakaryocyte differentiation potential. In fact, Siracusa et al[79] identified a multipotent granulocyte-monocyte progenitor (GMP)-like Lin− CD34+ c-Kit+ FcεRIα− cell population in the spleen that can give rise to both basophils and mast cells, as well as other cell lineages, highlighting the significant role of thymic stromal lymphopoietin (TSLP) in this extramedullary hematopoiesis. Key transcription factors contributing to early basophil development are GATA2 and C/EBPα (Table 1). However, the distal promoter-derived Runt-related transcription factor (1P1-Runx1) appears necessary

for a later stage of basophil development. GATA-1 seems also to play a role,[80] because mice lacking GATA 1 (ΔdblGATA) exhibit lower number of basophils in addition to eosinophil deficiency.[80]

Basophils mature in the bone marrow (taking approximately 7 days) before being released into the bloodstream. Their lifespan is short (1–2 days)[81] and are not typically found in healthy connective tissues. Basophils migrate to sites of parasitic infection and inflammation, notably the nose and lungs during allergic reactions, where they participate in the late phase response.[82]

Studying basophils is challenging due to their rarity, lack of homogenous cell lines, limited animal models, and difficult isolation with poor purification. Consequently, they have been a largely unexplored subpopulation. However, recent advances, including specific monoclonal antibodies and more sensitive techniques, have increased interest in basophils and their emerging roles in the immune system, leading to a better understanding of their functions beyond allergy.[75]

Functional Role of Basophils

Basophils play essential roles in defense against parasites, such as helminths, and participate in allergic disorders, autoimmune diseases, and certain cancers. Like mast cells, they secrete cysteinyl leukotrienes, heparin and histamine upon IgE receptor (FcεRI)/IgE complex activation in allergic reactions, and mediate innate and adaptive immune responses.[83] Basophils produce prostaglandin D2 (PGD2) albeit at lower levels than mast cells.[84] In vivo, IgE-triggered basophil activation is modulated by IL-3, IL-5, GM-CSF, neurotrophic cytokines, complement factors, and histamine-releasing factors.

In response to parasitic infections, basophils can be activated directly by parasite-derived factors or indirectly by recognizing parasite antigens. For example, exposure to proteases from helminths and house dust mites induces a type 2 cytokine profile in basophils.[85] Once primed, basophils are a significant source of IL-4 and IL-13, which activate other cells to facilitate worm expulsion and provide protection against parasitic infections.[86,87]

Basophils and eosinophils share some functions, such as releasing inflammatory cytokines (IL-4, IL-13) in allergic inflammation and expressing several common surface markers. However, basophils primarily initiate inflammatory responses by releasing histamine and other mediators, whereas eosinophils are mainly involved in combating parasitic infections by releasing toxic granule proteins and regulating inflammation and immune reactions.[88,89]

Molecular Markers and Phenotypic Heterogeneity

Basophils express surface markers, including CD9, CD22, CD36, CD40LG, FcgR2B, and CD38, which can be used to differentiate them from eosinophils, neutrophils, and mast cells (Table 1). They share molecules such as FcεR1A and CD203c with mast cells.[90] Because markers like CCR3, CD33, and IL5RA are also expressed on other white blood cells, specific basophil identification requires a combination of antibodies. For instance, studying CD18, CD31, CD116, IL-2R, IL-18R, and CD123 can distinguish basophils from mast cells.

While IL-3 and allergen-IgE were long considered primary basophil activators, thymic stromal lymphopoietin (TSLP) is now recognized as a key initiator of type 2 immune responses.[91] At least two basophil populations exist, differing in their activation by IL-3 or by TSLP[92] and tissue-resident basophils may develop through extramedullary hematopoiesis.[74] Clinical studies support this heterogeneity, as polymorphisms in TSLP genes are associated with human allergic disorders (asthma, rhinitis, atopic dermatitis, and oesophageal eosinophilia). Therefore, anti-IgE therapies show limited efficacy in these patients,[92] and the better therapeutic options could involve anti-TSLP drugs alone or in combination with anti-IgE.

Tissue Distribution and Isolation Methods

The most accessible source of basophils is blood. They can be measured and quantified as a percentage in a complete blood count (CBC) test but also stained to identify the basic granules. In recent years, monoclonal antibodies have enabled the development of techniques to assess human basophil activation using flow cytometry, without the need for basophil isolation from whole blood or peripheral blood mononuclear cells (PBMCs). Furthermore, several protocols for basophil purification have been described.[93,94] Generally, a density gradient centrifugation step (often using Percoll for initial enrichment) followed by immunomagnetic negative selection is the most common approach, yielding high purity (99%). Other methods, such as cell sorting by flow cytometry, are disfavored by some authors due to the time required and potential degranulation of cells during the sorting process.[93]

Basophil Activation (in vitro and in vivo)

It is possible to study basophil activation by using basophil cell lines or blood basophils. There are several basophil cell lines well characterized[95] such as: KU812[96] and LAMA-84.[97] Moreover, the activation of human basophils mediated by allergen-IgE bound to FceRI on their surfaces, lead to increase the expression of some markers (CD63, CD123, CD203c, CCR3 and LAMP1), that can also be analyzed.

The basophil activation test (BAT) measures by flow cytometry the activation of basophils, based on the expression of CD63 and CD203c markers after an allergen-IgE complex bind to FceRI. While at the beginning only the marker CD63 was used, new protocols suggested that other markers like CD203c, CD123 or CCR3 (CD193) should also be studied.[98,99] The advantage of this technique is that does not require the previous isolation of basophils from blood, can be used for the detection of acute allergy-hypersensitivity, but also for the monitoring after allergy vaccination of the hyposensitized stage. Moreover, it is possible to analyze the release of several basophil mediators after in vitro activation. A short preincubation or coculture of basophils with IL-3 causes significant release of histamine and LTC_4 to different immune and nonimmune stimuli such as anti-IgE, C5a and C3a (complement-derived anaphylotoxins), the eosinophil product major basic protein, or platelet-activating factor.[100] In addition to IgE, cytokines or drugs, basophils can respond directly to proteases, leading to the production of cytokines (IL-4, IL-5, IL-13), that can also be measured.[85]

New studies have advanced our understanding of basophil activation in allergic inflammation. Some authors investigated the role of signal-transducing adaptor protein-2 (STAP-2) in basophil activation.[101] Using STAP-2-deficient mice, researchers observed that the absence of STAP-2 led to reduced degranulation and cytokine production in basophils upon IgE-mediated stimulation. Furthermore, STAP-2-deficient mice exhibited significantly diminished IgE-dependent chronic allergic inflammation compared to wild-type controls. These findings suggest that STAP-2 positively regulates FcεRI-mediated basophil activation and could serve as a potential therapeutic target for allergic diseases.

A 2023 study systematically compared the efficacies of various IgE-mediated and non-IgE-mediated inducers of degranulation using RBL-2H3 cells (derived from a basophilic leukemia).[102] The research evaluated intracellular calcium levels, β-hexosaminidase release, tryptase expression, and CD63 expression as markers of degranulation. Findings indicated that all tested inducers effectively triggered cell degranulation, with the calcium ionophore A23187 showing the highest efficacy across multiple markers. This study provides valuable insights into the relative potencies of different cell activators, enhancing our understanding of allergies and inflammatory responses.

Activation of Basophils by Nanomaterials

Nanomaterials could potentially activate basophils, which express the FcεRI receptor and have overlapping properties and functions with mast cells. However, there is limited knowledge regarding the interaction of nanomaterials with basophils. Some authors have used AuNPs conjugated with anti-CD203c and ascomycin to block IgE-dependent degranulation of both purified human basophils and those present in mixed leukocyte preparations, suggesting specific targeting of these cells, because a mast cell line (LAD2) was not inhibited.[103]

In other studies of human blood cells in the presence of CeO_2, ZnO, Al_2O_3, or TiO_2 NPs, we did not find any basophil activation by flow cytometry.[104] In contrast, other authors using titanium oxide NPs reported histamine release and reactive oxygen species (ROS) production in the rat mast cell line RBL-2H3[105] via a Ca^{2+} dependent pathway.

There is a growing interest in the use of engineered NPs to understand the allergy processes[106] and to develop NP-based immunotherapies to inhibit allergies,[107] such as food allergy[108] or inflammatory processes, such as ulcerative colitis.[109] One potential target is Siglec-8, which is expressed on basophils, mast cells and eosinophils. Ligands to this molecule can induce cell death in eosinophils and to decrease the secretion of several mediators.[110]

In the in vivo studies, not only basophils are implicated in the activation process, but also eosinophils and mast cells. An increase in serum histamine without high levels of tryptase can indicate a hypersensitivity reaction (either allergenic or non-allergenic) caused by activated basophils (Figure 2). However, the lifespan of histamine is very low (20 minutes), compared with that of tryptase (3 hours). This is why, in anaphylactic cases, it is preferred to monitor tryptase alone or combined with histamine levels. As an alternative, biosensors are being developed to monitor histamine levels in the basophil activation test, using colorimetric visualization.[111] In patients with PEG allergy, the basophil activation test can

be used to analyze basophil reactivity to the Covid vaccine[112] or identify those patients at risk, before receiving further treatment or vaccines containing PEG.[113] Thus, testing basophils are now being included in the nanotoxicology studies, together with other toxicological studies.[114]

Mast Cells

Cellular Origin and Differentiation

Although there are several models of development, it is generally accepted that, following differentiation in the bone marrow from a multipotent common myeloid progenitor (Figure 1), a mast cell-committed progenitor ($CD34^+$ $CD117^+$ $CD13^+$) exits the bone marrow into the circulation[115] and migrates- guided by chemokines and adhesion molecules- to various vascularized tissues, where it can persist for extended periods. In these locations, the cells can become activated and undergo further differentiation and maturation. The mast cell progenitor expresses several chemokine receptors - some involved in its retention within the bone marrow (such as CCR1 and CCR5), and others that facilitate its migration to the gut (such as CXCR2).[116,117]

Functional Role of Mast Cells

Mast cells (MCs) play an important role in both innate and adaptive immune responses, acting at the environmental interface between pathogens and the immune system. Under healthy conditions, mast cells are present in various tissues and maintained at stable levels. In cases of allergy or in response to certain inflammatory triggers, mast cells contribute to immune defense, tissue repair, and the neutralization of harmful components including venom.[118]

In terms of host defense, mast cells express several pattern recognition receptors for pathogen- and danger-associated molecular patterns (PAMPs and DAMPs, respectively) as well as complement receptors. They can eliminate microbes by releasing bactericidal peptides (such as defensins and cathelicidins), internalizing pathogens, and producing reactive oxygen species. Additionally, they can generate extracellular traps, releasing proteases that degrade venom and other peptides, and secreting cytokines (eg, IL-4 and IL-13) that promote IgE production. Mast cells also recruit other immune cells and facilitate parasite expulsion at the intestinal level. Furthermore, they assist cytotoxic T cells in combating viral infections through the production of type I interferons.[119]

In certain situations, mast cells behave as antigen-presenting cells, capable of activating T cells, and they can regulate the magnitude of the immune response through the production of anti-inflammatory cytokines. Moreover, mast cells produce growth factors that promote tissue repair.[120]

They are primarily implicated in allergic responses - such as asthma and rhinitis- through allergen recognition and activation of the IgE bound FcεR1 receptor in allergic patients. Their numbers increase in various diseases (asthma, psoriasis, esophagitis, inflammatory bowel diseases, parasitic infection, etc) although their role in these conditions is not yet fully understood. In the case of anaphylaxis, an acute and severe allergic reaction, basophils and mast cells are activated, releasing mediators such as histamine and β-tryptase. Because histamine has a very short half-life, β-tryptase is considered the most reliable marker of mast degranulation in anaphylaxis.[118] Additionally, eosinophils promote mast cell survival and stimulate histamine release by these cells.[121]

Molecular Markers and Phenotypic Heterogeneity

Mast cells can be identified by the expression of the high affinity receptor for IgE (FcεRI), CD117 (c-Kit), CD33, CD203c, and CD300a (Table 1). Considerable heterogeneity has been observed in mast cells regarding protease content, surface markers, and functional responses to allergic and non-allergic stimuli. This variability is evident both within the same tissue and across different tissues. Two main mast cell subsets have been described based on tissue location and granule composition: 1) MCt, found on mucosal surfaces and primarily producing tryptase, and 2) MCtc, located in submucosal and connective tissues, containing tryptase, chymase, and carboxypeptidase A3. Recent transcriptomic studies have revealed even greater heterogeneity than previously recognized, with notable differences in the expression of proteases, adhesion molecules, mediators, and cytokines.[122]

Tissue Distribution and Isolation Methods

Due to their presence in tissues such as skin, gut mucosa, submucosa, pulmonary alveoli, and skeletal muscle, mast cells can be identified in situ by toluidine blue staining or immunohistochemistry in fixed or frozen tissues, using monoclonal or polyclonal antibodies against surface markers like the c-Kit (CD117) and FcεRI, or against granule contents such as tryptase, and chymase.

For mast cell isolation from tissues (eg, skin, lung), enzymatic digestion is required. The yield improves when followed by mechanical disruption and density gradient centrifugation[123] or by positive selection techniques.[124] In some cases, rare circulating mast cell progenitors have been detected in patients with asthma.[125]

Mast Cell Activation (in vitro and in vivo)

There are few human cell lines available for studying mast cells, such as LAD2 (laboratory of allergic diseases 2) and LADR, both derived from a patient with aggressive mastocytosis.[126] Another cell line was developed from a mast cell leukemia (HMC-1 and subclones), and others from CD34+ cells of non-mastocytosis donors: LUVA, ROSA, and MCPV-1.[127] In addition to being used to analyze the effect of several anti-neoplastic drugs, the ROSA cell line can efficiently engraft in NOD/SCID IL2Rg (NSG) mice, making it a good model for both in vitro and in vivo studies.[128]

Several cytokines influence MC growth and development, with stem cell factor (SCF) being the most important for mast cell survival.[129] MCs produce a wide variety of potent mediators in vivo including histamine, tryptases, chymases, heparin, granzyme B, cathepsins, metalloproteinase-9, among others. Most of these mediators are preformed and stored in cytoplasmic secretory granules, but others are synthesized de novo. In the latter case, prostaglandins, leukotrienes, platelet activating factor, cytokines (such as SCF, IL-4, IL-6, IL-10, TSLP, tumor growth factor beta (TGF-β), and IL-33), and growth factors are newly produced upon MC activation.[118,130]

Activation of Mast Cells by Nanomaterials

Nanomaterials can interact with mast cells, either activating or inhibiting them, or modifying their behavior using special therapeutic reagents. The effect can be mediated either by the IgE Fc receptor on the surface of mast cells[131] or by other non-IgE mechanisms.[132] Their activations can lead to the release of histamine, leukotrienes, and other mediators that contribute to allergic reactions and inflammation (Figure 2).

It has been shown that silver nanoparticles can activate bone marrow-derived mast cells (cultured from CD34+ progenitors) throughout the high affinity IgE receptor (high affinity).[131] The effect is mediated by the phosphorylation of FceR1 linked tyrosine kinases, with the potential to exacerbate allergic immune responses.

Mouse models are commonly used for in vivo studies, including both mast cell-containing strains (like C57BL/6), and mast cell-deficient strains (like B6.Cg-Kit$^{W\text{-}sh}$ mice). For example, silver nanoparticles have been shown to exacerbate atopic dermatitis in mice, mediated by mast cells.[133] Exposure to multi-walled carbon nanotubes (MWCNT) induces toxicity through mast cell-mediate mechanism, with the IL-33/ST2 axis involved in pulmonary and cardiovascular responses.[134] Mice lacking mast cells, or unable to respond to IL-33, showed reduced toxic effects.

Instillation of cerium oxide nanoparticle caused pulmonary inflammation in wild-type mice, which was significatively lower in mast cell- deficient mice. Mast cells and their secretory factors also influence vascular responses.[135] Additionally, intravenous injection of amorphous silica NPs in rats (7 mg/kg) induced granulomas, primarily in the liver, with mast cells accumulating in the lungs and heart. Mast cells were recruited early in the liver, even before fibrosis developed, suggesting their role in tissue remodeling.[136] Nanoparticles may also be used for desensitization. Duan et al demonstrated that nanoparticles carrying allergens and siglec-8 ligands can reduce IgE-mediated anaphylaxis by affecting mast cells.[137]

Recently, Newton et al[138] studied four clinical-grade nanomedicines (Abraxane, Doxil, AmBisome, and Feraheme) and three commercial research-grade nanomaterials (PAMAM dendrimers (generation 5) with carboxy-, hydroxy-, or amine- surface functionalities) in the presence of mast cells. The researchers found differences in gene expression profiles – suggesting potential alterations in cellular processes – without affecting the degranulation function. These

results highlight the need for more in vitro and in vivo studies to fully understand the effects of nanostructures on these cells and their potential risks.

The Future Prospective

Nanomaterials hold great promises for revolutionizing medicine, but their interactions with the immune system require careful consideration. While the interactions between nanomaterials and some innate immune cells, such as macrophages, dendritic cells, and neutrophils, have been extensively studied, the roles of eosinophils, basophils, and mast cells have been relatively overlooked. However, these cells play critical roles in the immune system, particularly in inflammation, allergy, and host defense. These cells can be activated or modulated by nanomaterials, which has significant implications for the design of nanomedicines and their potential applications.

Eosinophils, for instance, are involved in the response to parasitic infections and can modulate immune responses through the release of cytokines and cationic proteins. Basophils are key players in allergic reactions and inflammation, and their activation can influence vascular permeability and immune cell recruitment. Mast cells, strategically located at the interface between the host and the external environment, are crucial in initiating inflammatory responses and allergic reactions. The activation of these three cell types by nanomaterials can trigger the release of various mediators, including histamine, leukotrienes, and cytokines, which can influence both the therapeutic efficacy and potential adverse effects of nanomedicines.

Interestingly, the interaction of nanomaterials with these cells could lead to novel therapeutic strategies, where the modulation of their activity is harnessed for specific therapeutic outcomes, such as enhancing anti-inflammatory responses or promoting tissue regeneration. However, these interactions also raise the potential for unintended consequences, such as exacerbated allergic reactions or chronic inflammation. Therefore, a comprehensive understanding of the interactions between nanomaterials and these "forgotten" innate immune cells is crucial for the safe and effective development of nanotherapeutics, especially in applications related to allergy, inflammation, and immunomodulation.

By highlighting the importance of these cells in the context of nanomaterial exposure, this review emphasizes the need to include them in immunogenicity and nanotoxicology assessments. This will allow for a more thorough evaluation of the risks and benefits of nanomaterial-based therapies, ensuring that their development is both safe and aligned with therapeutic goals.

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Disclosure

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