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Mini Review

Metal Nanoparticles in Immunotherapy: Applications, Limitations and Pespectives

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Abstract

Metal oxide nanoparticles are becoming essential in various biomedical applications, from diagnostics and imaging to anticancer therapy, bacterial infections, wound healing, and others. The application these nanostructures for immunotherapy is also emerging, particularly because they undergo phagocytosis and transmission by macrophages, and exhibit pro- or anti-inflammatory features depending on the nanoparticle' content and pathological context. However, there is still a number of limitations that have to be addressed before the nanoparticles enter the clinic. First, metal oxide nanoparticle may evoke cytotoxicity in various cell types including immune cells. Second, the immunogenic potential of nanoparticles may affect the immune populations outside the tumours or inflammatory sites. Third, the effects of nanoparticles differ in respect to cell microenvironment and can be hardly predictable and controllable. Nevertheless, most of these limitations can be addressed by combining other approaches such as chemotherapy, antibody-mediated targeted delivery and / or RNA-loaded machines.

Introduction

Metal nanoparticles (NPs) functionalize numerous cell populations critical for combating cancer, bacterial and viral infections, parasites, etc. Essentially, among the target cells that encounter NPs are the immune cells, one of the first responders and transmitters of external signals in the organism. Heterogeneity of the immune cell populations complicate the systemic analysis and NPs adjustment for immunomodulation; also, severe complications should be taken into consideration since the cells can respond unpredictably to the treatment. Nevertheless, the application of NP in medicine is rapidly emerging, therefore the above limitations must be carefully addressed.

Metal nanoparticles and immune cell heterogeneity

Currently, various metal NPs are used for diagnostics and therapy. The metal component can be represented by Ag, Au, Pt, rare earth metals, oxides of iron, nickel, copper, and others. These NPs can interact with the immune cells depending on the delivery root (local or systemic, intravenous or dietary or intranasal) [1,2].

Metal nanoparticles and inborn immunity

Once NPs enter the body, they encounter circulating monocytes or tissue resident macrophages that actively engulf and transfer NPs to different sites. NPs can polarize macrophages towards pro- (M1) or anti-inflammatory (M2) profile with respect to microenvironment and the type of metal [3]. M1 and M2 macrophages release a variety of cytokines which, in turn, recruit other immune cells that suppress (regulatory T cells) or prolong (cytotoxic T cells, T helpers, B lymphocytes) inflammation and the immune reaction triggered by NPs. Simultaneously with macrophages, NPs target neutrophils, the innate immune cells that fight against pathogens via extracellular trap formation and subsequent specific cell death termed netoptosis, for pathogen restriction and killing. A number of metal NPs up-regulate neutrophil extracellular trap activity and stimulate antimicrobial potential [4,5]. In some cases, nanosilver can also cause non-classical activation of neutrophils with IL8 release but not netoptosis, and the effect depends on NP size [6,7].

Metal nanoparticles and adaptive immunity

Following activation of macrophages and neutrophils, metal NPs involve evoke an adaptive immune system response driving the potential of T- and B-lymphocytes [8]. This stage is mediated directly by NPs as well as by the release of pro (TNFa, IL1b, IL6, IL8, chemokines CXCL10, CCL3,7) and anti (IL10, CXCL6) inflammatory cytokines to regulate lymphocyte activity [9,10]. Gold NPs are known to stimulate antibody production by B cells via modulation of Blimp1/Pax5 signaling pathway [11]. Interestingly, aluminum oxide NPs increase neutrophil and monocyte counts together with pro-inflammatory cytokines in systemic circulation; however, lymphocyte activity and antigen presentation are suppressed suggesting complex and indirect effects of NPs [9].

Application of metal NPs, alone or in combination with other approaches, allows to modulate other immune cell populations although these effects are less studied. For example, natural killer cells can be guided with iron NPs and magnetic field to reveal their cytotoxic potential specifically against the tumor [12]. Titanium, silver and gold NPs are known to activate dendritic cells, particularly against viral infections, such as HSV-2 [8,13,14].

Metal nanoparticles within immune microenvironment

Except the direct effect on cells within inflammatory sites, metal NPs can modify immune microenvironment.

1.1. Non-specific interactions with extracellular proteins

Due to their chemical and physical properties metal NPs interact with extracellular molecules. In the body NPs form so-called surface corona consisting of extracellular proteins [15]. Circulating NPs collect immunomodulatory proteins including the components of the complement system, hemoglobin, immunoglobulins, as well as cell growth/differentiation factors [16-18]. The corona changes the immunogenic activity of metal NPs but can also cause an immunosuppressive response in target cells [19].

Extracellular matrix

Metal NPs also interact with Extracellular Matrix (ECM). ECM is a non-cellular scaffold presented of all tissues and organs that provides an essential signalling for initiation of biochemical and biomechanical cues for morphogenesis, differentiation and homeostasis of all cells, including immune. Although, fundamentally, ECM is composed of proteins and polysaccharides, each tissue has the unique ECM composition and topology that can be associated with certain pathological events as inflammation or tumor growth and metastasis [20]. ECM variations also lead to heterogeneity of NP effects in various contexts. Importantly, ECM is an indispensable part of biological barriers and modulates NP delivery to the required therapeutic sites. NPs, including metal NPs, are influenced by ECM components via three directions: (i) physical localization of along ECM fibers; (ii) NPs restrict thermal motion of water molecules due to the proximity to the fibers (which also influences hydrodynamic interactions and slow NP diffusion (hydrodynamic interactions), and (iii) charged particles interact with polarized ECM components via electrostatic interactions to stabilize the system [21].

The predominant components of ECM are collagen and laminin produced by fibroblasts. Metal NPs change the cell - matrix interaction. Flow cytometry analysis showed that treatment with metal NPs reduced the percentage of cells expressing the collagen receptor, $\alpha_2\beta_1$ integrin (VLA-2) and the laminin receptor $\alpha_6\beta_1$ integrin (VLA-6). In contrast, NPs can increase and decrease the percentages of VLA-2- and VLA-6-positive cells, respectively. Besides, metal NPs can cause cytoskeletal reorganization, namely, increase the formation of stress fibers and cell protrusions, thereby impairing cell polarity [22].

Matrix metalloproteinases

ECM matrix metalloproteinases (MMPs) are a family of zinc-dependent neutral endopeptidases. Partially, MMPs are produced and controlled by macrophages and neutrophils [23-25]. MMPs are designated to modulate ECM and are thereby involved in important physiological and pathological events such as wound healing, cancer progression, inflammation, and drug / NP delivery [21]. With that, the immune cells activated by NPs interfere the ECM structure and function, cause tissue remodeling and change the delivery routes of drugs, tumor metastatic potential and CO_2/oxygen exchange in tissues [26].

Limitations of nano therapy for immunomodulation

A plethora of biological stimuli induce reactive oxygen and nitrogen species (ROS and RNS) generation by immune cells, particularly macrophages and neutrophils, as ROS production is considered as a part of inborn immune response. ROS/RNS promote inflammation and increase death of pathogens or tumor cells [27-29]. Similarly, NP exposure often leads to ROS delivery from various cells, which, in this case, may also serve as a hallmark of cytotoxicity. Indeed, a number of studies have shown that NPs induce endoplasmic reticulum stress, mitochondrial damage and cell death in macrophages, neutrophils and lymphocytes [30-35]. This suggests that metal NPs may suppress immune cell function, and this factor is difficult to detect and control. On the contrary, in some cases metal NPs can induce strong inflammation and be harmful for normal tissues [36,37]. This may arise from systemic effects of NPs, e.g., i.v. delivery and accumulation in non-specific sites [38].

Combination approaches to improve efficiency of metal NPs

Considering the diversity of immune cell populations and the complexity of NP-mediated effects, it is recommended to use NPs in combination with other therapeutic approaches keeping in mind biological, physical or chemical properties of metal NPs [39]. This will provide the specificity of action and allow to modulate immunity in a more precise mode. Metal NPs can be combined with antigens or DNA vaccines for targeted delivery to the pathological site or specific cancer cell/pathogen elimination [13,39,40]. Zinc, aluminum, gold NPs act as adjuvants for therapy and result in increased number of antigen-specific T cells and more efficient antibody production, so that the immune response can be driven against tumor or bacteria without any self-toxicity [41-45] antigen.

In allergic conditions iron oxide NPs can eliminate the reactive T lymphocytes [46,47]. Iron magnetic NPs combined with antigens can be used for control delivery of immune cells to the damage/infection site or any other specific location by external magnetic field [48,12]. Magnetic and antigen-specific nanoparticles allow to isolate specific lymphocyte clones in a fast and reproducible way suitable for experimental and therapeutic applications, such as delivery tumor antigen engineered T cells to the patient [14,49].

For immunomodulatory purposes metal NPs can be used together with pro- or anti-inflammatory cytokines that can guide macrophage polarization and T lymphocyte differentiation towards the cytotoxic or regulatory profiles. For modulation of macrophage polarization metal NPs loaded with pro- or anti-inflammatory cytokines can be used [50]. Metal NPs can be modified with other nanostructures such as hyaluronic or tannic acids for modulation of the immune cell survival and activity within the tumor [51,52]. Finally, it is possible to use the combinations of metals to achieve the controllable systemic immune activity at different stages of the disease. For example, titanium stimulates pro-inflammatory activity of macrophages that can be used against bacterial infection in the wound, while lithium exhibits an opposite effect attenuating inflammation and can be used to accelerate regeneration process [53].

Conclusion and Future Directions

Biomedical and therapeutic application of metal NPs in immunotherapy remain a challenge due to (i) risk of cytotoxicity and (ii) non-specific activation of immune subpopulations and redundant inflammatory outbreak. However, all these limitations can be minimized or even avoided if NPs are used together with other medical strategies. Overall, metal NPs represent a promising tool for controllable immunomodulation.

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