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Review

Modulating the immune system through nanotechnology

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ABSTRACT

Nowadays, nanotechnology-based modulation of the immune system is presented as a cutting-edge strategy, which may lead to significant improvements in the treatment of severe diseases. In particular, efforts have been focused on the development of nanotechnology-based vaccines, which could be used for immunization or generation of tolerance. In this review, we highlight how different immune responses can be elicited by tuning nanosystems properties. In addition, we discuss specific formulation approaches designed for the development of anti-infectious and anti-autoimmune vaccines, as well as those intended to prevent the formation of antibodies against biologicals.

1. Introduction

The modulation of the immune system is the base of new and promising therapies for some of the most prevalent and/or severe diseases of our time, such as cancer, HIV, and type 1 diabetes. The development of treatments based on this modulation is a field in expansion, where the contribution of nanotechnology is growing exponentially [1–3]. Based mainly on the molecular principles that govern the interaction between pathogens and immune cells, the use of nanotechnology represents a new way of communication with the immune system. Both, the composition and the physicochemical characteristics of nanocarriers, can influence their interaction with immune cells. By mimicking the size of microorganisms (bacteria and viruses) and incorporating key molecules involved in immune processes (TLR agonists, cytokines, etc.), nanocarriers can be taken up by the immune cells and modulate their responses. Besides, the use of nanocarriers decorated with targeting moieties can favor their preferential access to specific immune cell populations [2,4–9]. Importantly, the tunable nature of nanotechnology offers the possibility of reinforcing the desired aspect of immunomodulation, which may be (i) the activation of the immune system in order to generate an immune response against a specific antigen, or (ii) the induction of immunotolerance against antigens and immunoactive drugs. The first option improves the chances of controlling infectious diseases that do not respond well to traditional vaccines, such as HIV or tuberculosis, among others [10–12]. The second, and less explored option, refers to the development of vaccines against autoimmune diseases as well as the targeted administration of immunomodulatory drugs [13–15]. The capacity of nanotechnology to elicit different responses comes from its versatility, gained through the specific combination and meticulous choice of its molecular components, and from the physicochemical properties of the nanosystems.

In this review, we first summarize how nanotechnology may help reaching the desired cell population, and achieving its specific modulation. Then, we offer an overview of the role that nanotechnology has played in the development of new vaccines against infectious diseases, followed by an analysis of its contribution to the treatment of autoimmune diseases. Finally, recent achievements to fight antidrug antibodies are summarized.

2. Access of nanostructures to target cells

For a nanovaccine to be effective, it first needs to access the tissues where the target cells are present. Depending on the administration route, different physiological barriers must be overcome to reach these cells. Thus, nanoparticles (NPs) should be specifically engineered to go preferentially to the target tissue from the site of administration.

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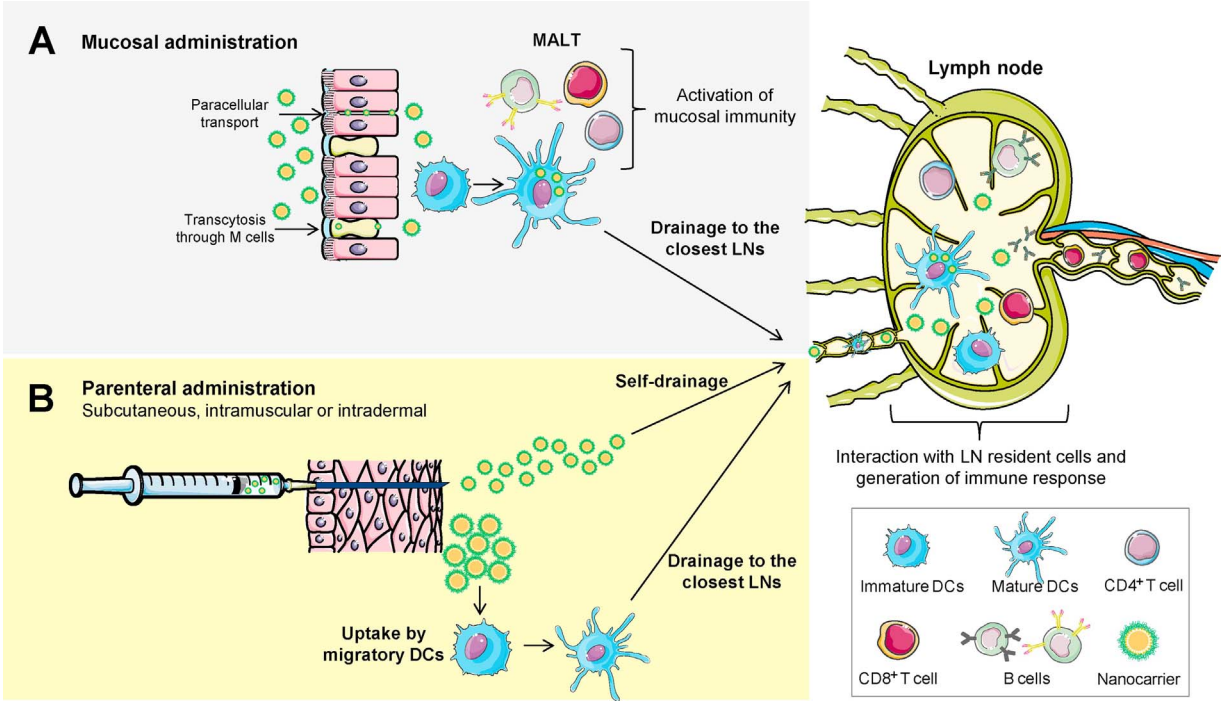

Fig. 1. Vaccine administration routes. The main administration routes for vaccines are mucosal and parenteral. (A) Mucosal administration refers to the administration mainly through the nasal, oral or vaginal routes. In all these cases, nanocarriers need to reach the mucosal-associated lymphoid tissues (MALT). This can be principally achieved either by a paracellular or transcellular across the microfold (M) cells. At the level of M cells or underneath the epithelium, nanocarriers will encounter the resident dendritic cells and activate them, generating a mucosal immunity while, at the same time, some dendritic cells will drain to the closest lymph node and activate a systemic immune response. (B) Parenteral administration includes subcutaneous, intramuscular or intradermal injection of the nanosystems. The nanocarriers are deposited in the interstitium, where they can have two different fates: self-drain to the closest lymph node or be taken up by migratory dendritic cells, which then will migrate to the closest lymph node.

2.1. Routes of administration of nanocarriers intended for immunomodulation

Although immune cells are distributed throughout the body, the key cells involved in immunity are concentrated in the lymphoid tissues. Hence, targeting these tissues facilitates the access to immune cells and, consequently, increases the efficacy of administered nanovaccines. Lymphoid tissues are directly accessible through the mucosal surfaces, such as airways, the intestinal tract, or the vagina, although a more straight way to target them is by parenteral injection. The way antigens reach the lymph nodes (LN), following different modalities of administration, is illustrated in Fig. 1.

2.1.1. Mucosal administration

Following mucosal administration, a needle-free and appealing route for vaccination, it is possible to induce both, mucosal and systemic, immune responses [16]. The mucosa-associated lymphoid tissues (MALT) are connected to the mucosal environment through the M cells, which are specialized in the transcytosis of microorganisms and particulate components [3,16]. The activation of mucosal resident T and B cells can be of great importance for an efficient mucosal vaccination [17,18]. This is the reason our group and many others have explored the potential of nanocarriers for the transport of antigens across different mucosae in order to reach a proper stimulation of the immune system. Moreover, the administration of nanocarriers through mucosal routes has also been investigated for tolerance generation [19].

In order to elicit an adequate response, NPs need, first, to overcome the mucus layer that covers the mucosal surfaces. Then, once in contact with the epithelium, nanocarriers are transported either by M cells or by regular epithelial cells [20–22]. NPs can also be internalized by paracellular transport if their composition includes components that can open tight junctions [23]. Moreover, it has also been described that dendritic cells can take up NPs by extending their dendrites into the lumen [24,25].

The specific physiology of the mucosal surfaces is different throughout the body and, hence, the optimal properties for the nanocarriers to cross them may also be different. Initially, bioadhesive nanosystems were thought to be a promising strategy to facilitate the interaction of nanocarriers with the mucus layer and a number of strategies have been described for that purpose [26,27]. For example, Nochi *et al.* developed adhesive cationic nanogels made of cholesterol-modified pullulan that were able to increase the survival rate of mice after intranasal vaccination against tetanus and the botulin neurotoxin [28]. However, it was also observed that if the systems were retained in the mucus by high adhesive forces, they could be soon eliminated by the clearance mechanisms. This disadvantage led to the engineering of nanocarriers with mucodiffusive properties that would allow them to cross the mucus layer and reach the epithelium. Nowadays, a precise balance between mucoadhesive and mucodiffusive properties is believed to be critical for the effectiveness of nanocarriers delivered through mucosal routes. For good mucodiffusion properties, it has been reported that particle size should be smaller than the mucus mesh size [29]. Although there are studies where microparticles (MPs) showed better results than NPs after oral administration [30,31], in general, the recent trend has been to consider that NPs perform better than MPs [32–37]. In this regard, our group reported that the transport of pegylated polylactic acid (PEG-PLA) NPs across the nasal mucosa was higher than that of MPs. Furthermore, the smaller micrometric sizes (1 and 5 μm) also crossed the epithelium more efficiently than 10 μm particles, with no significant differences between 1 and 5 μm [38]. Interestingly, based on recent *in vivo* data, very small nanometric sizes (30 nm) may not be as effective as larger ones (200 nm) [39].

Besides the particle size, other nanocarrier's features may also have important consequences for mucopermeation. For example, in 1998, our group described for the first time that the presence of a PEG coating in NPs made of PEG-PLA had an important role in increasing their transport rate through the nasal [40] and intestinal epithelia [41].