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Review

Nasal nanovaccines

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ABSTRACT

Nasal administration of vaccines is convenient for the potential stimulation of mucosal and systemic immune protection. Moreover the easy accessibility of the intranasal route renders it optimal for pandemic vaccination. Nanoparticles have been identified as ideal delivery systems and adjuvants for vaccine application. Heterogeneous protocols have been used for animal studies. This complicates the understanding of the formulation influence on the immune response and the comparison of the different nanoparticles approaches developed. Moreover anatomical and immunological differences between rodents and humans provide an additional hurdle in the rational development of nasal nanovaccines. This review will give a comprehensive expertise of the state of the art in nasal nanovaccines in animals and humans focusing on the nanomaterial used.

Contents

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1. Introduction

Several recent studies have focused on the use of nanoparticles for nasal vaccine delivery. Nasal administration is convenient to avoid the parenteral route and increase the patient compliance. Targeting the nose-associated lymphoid tissue (NALT) with nanoparticles and, as a consequence, stimulating the mucosal immune response via the production of a persistent immunological memory, has been investigated and seems to be successful (Csaba et al., 2009; Dimier-Poisson et al., 2015; Koping-Hoggard et al., 2005). Nevertheless, few such products have reached the market, even if they are safe, easy to produce and cost effective.

Preclinical studies are mostly performed in rodents. However problems concerning translational medicine highlight the limitations of available research, which are primarily anatomical and immunological differences between mice and humans that make it difficult to foresee the clinical efficacy and safety of nanovaccines. Furthermore the protocols used in terms of number of vaccination doses, volumes, anesthesia and experimental controls have a strong influence on the immunogenicity of the nanovaccines and it is laborious to compare the different nanosystems developed. Standardization of such experiments is necessary. This review aims at giving an overview of the state of the art of the use of nanoparticles for nasal vaccine application in animals and humans.

2. Nasal vaccination: why nanoparticles?

The nasal route is receiving growing interest and some low molecular weight drugs have already been approved and reached the market (Antosova et al., 2009). Examples of molecules delivered via the nasal route are butorphanol for pain relief (previously Stadol NS®, Bristol Myers, now sold as a generic), luteinizing hormone-releasing hormone (LHRH, Kryptocur®, Sanofi-Aventis) for cryptorchidism, LHRH agonists used in some fertility treatments (e.g. Buserelin, Supercur®, Sanofi-Aventis), and desmopressin for diabetes insipidus (Minirin® by Ferring or DDAVP® Nasal Spray by Sanofi-Aventis) (Antosova et al., 2009; Illum, 2003; Marmura et al., 2015).

However for larger molecules, such as proteins, the nasal uptake is very low and it is consequently necessary to develop strategies to improve drug absorption (Dombu and Betbeder, 2013). The mass cut-off for permeation of molecules in the nasal epithelium is approximately 1000 Da (Antosova et al., 2009; Ugwoke et al., 2005) and absorption enhancers are required to ameliorate the mucosal delivery of larger molecules (Davis and Illum, 2003; Subbiah et al., 2012).

Nanoparticles have been identified as successful adjuvants since they act as delivery systems and/or immune-modulators for vaccine applications (Fifis et al., 2004; Ilinskaya and Dobrovolskaia, 2016; Reddy et al., 2007; Schellekens et al., 2013). The main rationale of using nanoparticles to deliver vaccines is their ability to protect antigens against proteolytic degradation and to improve cellular delivery of drugs (Pachioni-Vasconcelos Jde et al., 2016; Peek et al., 2008). Interestingly, via the nasal route, nanoparticles are also able to by-pass the mucus and interact directly with mucosal cells, triggering the immune system (Noh et al., 2013; Suk et al., 2014). It is also possible to modify the physicochemical properties of particles (such as charge, shape and composition), thus increasing the choice for their use as potential protein carriers (Anselmo and Mitragotri, 2017; Decuzzi et al., 2010; Mitragotri, 2009). Thanks to their size, nanoparticles can also mimic viruses, given that the diameter of viruses is generally below 100 nm (Woodrow et al., 2012). Like viruses, their nanometer size allows nanoparticles to by-pass mucus barrier therefore increasing nanoparticle-cell interaction (Pearson et al., 2016). The current paradigm claims that the size of particle is critical for triggering efficient immune response (Gregory et al., 2013; Shah et al., 2014). The optimal size seems to be between 20 and 80 nm, as confirmed for nasal vaccine (Ghaffar et al., 2016; Zaman et al., 2014), but two additional parameters have to be taken into account. Firstly, the particles are usually not monodisperse and photometric analyses like dynamic light scattering inform about a size range even if researchers commonly report the mean size only. Thus the idea of using particle of different sizes in the same administration might be of interest (Oyewumi et al., 2010; Skwarczynski and Toth, 2014). Secondly, the ability of nanoparticles to be mucus-penetrating or muco-adhesive is obviously size-dependent but also and above all relies on the surface charge and hydrophobicity (Ensign et al., 2012; Garg et al., 2010; Schneider et al., 2017) and both these criteria have to be thoroughly controlled for an optimal nasal nanoparticle-based vaccine.

Furthermore, nanoparticles may establish a sustained release of the antigen in the mucosa, in order to improve the chances of antigen uptake by the cells.

All these considerations make nanoparticles good candidates for mucosal route delivery systems for proteins (Marasini et al., 2017).

3. Nose features for vaccine delivery

3.1. Comparison of mouse and human NALT

It is instructive to compare key anatomical elements of rodent and human noses in order to understand how the immune system is triggered by this route.

In rodents, the lymphoid tissue is known as nose-associated lymphoid tissue (NALT) and it is concentrated at the bottom of the dorsal nose duct (Pabst, 2015). It is a paired, bell-shaped tissue that is characterized by an accumulation of lymphoid cells and its complete formation is observed around 5–8 weeks after birth (Kiyono and Fukuyama, 2004).

Human adenoids and tonsils are the principal components of NALT and are an important feature of the human mucosal immune system (Kiyono and Fukuyama, 2004). A ring-shaped formation was recognized in 1884 by Waldeyer, and this structure is nowadays named “Waldeyer’s ring”. It is made of the adenoid, or nasopharyngeal tonsil, the paired tubal tonsils, the paired palatine tonsils and the lingual tonsil (Perry and Whyte, 1998). The tonsils are secondary lymphoid organs situated in the lamina propria of the pharyngeal wall. Macroscopically, the tonsillar surface is characterized by various narrow epithelial channels, called crypts, which penetrate deep into the underlying lymphoid tissue. These crypts considerably increase the tonsillar surface area and play an important role in the respiratory immune defense, since they are designed to trap foreign material (Csaba et al., 2009; van Kempen et al., 2000).

The nasal cavity differs both anatomically and histologically between mice and humans. Murine respiratory epithelium consists of a typical single-layer epithelium with columnar epithelial cells in the turbinate portion of the nasal cavity, whereas pseudostratified columnar epithelium covers the olfactory epithelium in mice (Mery et al., 1994). In contrast, a single-layer epithelium is not observed in the human nasal cavity, and both the upper respiratory and olfactory surfaces are covered by a pseudostratified columnar epithelium (Cagici et al., 2005; Jafek et al., 2002). Notably, tight junction molecules (e.g. occludin, JAM-A, ZO-1, ZO-2, claudin) are expressed in the human upper airway and nasal epithelial cells (Ogasawara et al., 2011). These structures make the human nasal epithelium poorly permeable, while anatomical and histological differences, associated to variations in the immunological systems observed between rodents and humans (Mestas and Hughes, 2004), might explain