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Review

Nanogel-based nasal vaccines for infectious and lifestyle-related diseases

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ABSTRACT

Because the mucosa is the major entry route for most pathogens, the development of mucosal vaccines is a rational approach for protecting against these undesired agents. Mucosal administration of vaccine antigen is useful for non-infectious chronic diseases as well, because of its advantages over injection routes, including comparable efficacy in the induction of systemic immune responses, less pain, and no risk of adverse events at the injection site. However, because it is difficult to effectively induce and regulate antigen-specific mucosal and systemic immune responses when antigen alone is mucosally administered, an appropriate form of mucosal delivery vehicle must be used. Antigen delivery systems involving nanogels, which act as artificial chaperones and mucosal adhesives, are a promising approach to overcoming this problem. Here, we introduce current perspectives regarding the development of nanogel-based nasal vaccines for both infectious and lifestyle-related diseases.

1. Introduction

The mucosa is an interface that separates the sterile internal environment from the non-sterile external environment of the body; in humans, the mucosa covers a surface area of more than 400 m^2. Because of its constant exposure to the external environment, where numerous commensal microorganisms and environmentally encountered antigens exist, and its large surface area, the mucosa is considered to be a major entry route for most pathogens (Kiyono et al., 2008). Therefore, developing strategies that defend against invasive pathogens at the mucosal surface is a rational approach for providing protection from infectious diseases. In general, vaccines induce more efficient mucosal immune responses (e.g., antigen-specific mucosal IgA antibody) when they are administered mucosally than when subcutaneously injected in humans (Bellanti et al., 2004). However, effective delivery of vaccine antigen via mucosal routes, including oral and nasal administration, has been difficult to achieve because the aero-digestive tract, as a boundary between the external and internal environments, is equipped with chemical and physical barrier functions as well as physiologic and immunologic functions.

Because of its prolonged therapeutic effects and low frequency of administration, vaccination has recently become an attractive concept for intervention in non-infectious chronic diseases, such as hypertension (Azegami et al., 2012; Tissot et al., 2008), obesity (Azegami et al., 2017a), and type 2 diabetes (Pang et al., 2014). Indeed, subcutaneous vaccination against angiotensin II, a key hormone in the development of hypertension, decreased the blood pressure of hypertensive men and women in a phase IIa clinical trial (Tissot et al., 2008). However, subcutaneous injection frequently caused edema and induration at the injection site (Tissot et al., 2008). Given the advantages of decreased pain and no risk of adverse events at the injection site, the concepts and technology of mucosal vaccines appear applicable to therapeutic vaccines targeting lifestyle-related diseases as well.

Nasal immunization with antigen alone often fails to induce antigen-specific mucosal and systemic immune responses sufficient for the prevention and control of infectious diseases. This failure is due to the presence of physiological defense mechanisms (e.g., mucus and ciliary movements) of the respiratory tract against inhaled materials; these mechanisms rapidly clear nasally administered antigen from the nasal cavity (Nochi et al., 2010). A nanoparticle based antigen delivery system is a promising approach for overcoming this problem and different natures of nanoparticle based nasal vaccine delivery systems have been developed and tested for the induction and regulation of antigen-specific immune responses in both mucosal and systemic

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Table 1
Challenges for the development of nanoparticle-based nasal vaccine. Several different forms of nanoparticle antigen delivery systems have been tested and shown to be effective for the induction of antigen-specific immune responses against various infectious and life-style diseases. The table provides those different nanoparticle nasal antigen delivery systems with corresponding references. Abbreviations: cholesterol-bearing pullulan (CHP), immune stimulating complex (ISCOM), poly-lactic acid (PLA), poly lactide-co-glycolic acid (PLGA), PVM/MA (polymethyl vinyl ether/maleic angydride).

Type of nanoparticle	Target disease/pathogen	Animal model	Efficacy	Ref.
CHP	Hypertension (angiotensin II type 1 receptor)	rat	Attenuation of the devlopment of hypertension	Azegami et al. (2017a)
CHP.	Obesity (ghrelin)	mouse	Attenuation of weight gain	Azegami et al. (2017b)
CHP	*Streptococcus pneumomiae*	mouse, macaque	Protection agansint lethal challenge with *S.pneumoniae*	Kong et al. (2013); Fukuyama et al. (2015)
CHP	Influenza virus	mouse	Protection agansint lethal challenge with influenza virus	Nagatomo et al., (2015)
CHP	*Clostridium botulinum*	mouse	Protection agansint lethal challenge with *botulinum* toxin	Nochi et al. (2010)
chitosan	*Escherichia coli* O157:H7	mouse	Attenuation of bacterial shedding after oral administration of *E. coli* O157:H7	Doavi et al. (2016)
chitosan	Hepatiti B virus	mouse	Induction of antigen-specific systemic and mucosal antibody responses	Pawar and Jaganathan (2016); Tafaghodi et al. (2012)
chitosan	Influenza virus	mouse	Induction of antigen-specific systemic and mucosal protective antibodies	Liu et al. (2015)
chitosan	Influenza virus	rabbit	Induction of antigen-specific systemic and mucosal antibody responses	Dehghan et al. (2014)
chitosan	Asthma (*Dermatophagoides farinae*)	mouse	Attenuation of airway inflammation after challenge with *D.farinae*	Liu et al. (2009)
chitosan/PLGA	Foot-and-mouth disease virus	cattle	Partial prevention and attenuation of foot-and-mouse disease	Pan et al. (2014)
chitosan/pullulan	Diphtheria toxoid	mouse	Induction of antigen-specific systemic immune responses	Cevher et al. (2015)
glycol-chitosan/PLGA	Hepatiti B virus	mouse	Induction of antigen-specific systemic and mucosal immune responses	Pawar et al. (2013)
ISCOM	Influenza virus	mouse, sheep	Induction of antigen-specific systemic and mucosal antibody responses	Coulter et al. (2003)
lipopeptide	Group A *Streptococcus*	mouse	Induction of antigen-specific systemic antibody responses	Zaman et al. (2014)
lipopeptide/liposome	Group A *Streptococcus*	mouse	Induction of antigen-specific systemic and mucosal antibody responses	Ghaffar et al. (2016)
lipopeptide/PLGA	Group A *Streptococcus*	mouse	Induction of antigen-specific systemic and mucosal antibody responses	Marasini et al. (2016)
liposome	Influenza virus	mouse	Protection agansint lethal challenge with influenza virus	Tai et al. (2011)
liposome	Influenza virus	mouse	Reduction in virus replication in lung	Ninomiya et al. (2002)
maltodextrin	*Toxoplasma gondii*	mouse	Protection against lethal challenge with *T.gondii*	Dimier-Poisson et al. (2015)
maltodextrin	Hepatiti B virus	mouse	Induction of antigen-specific systemic and mucosal immune responses	Debin et al. (2002)
PLA	*Yersinia pestis*	mouse	Protection against lethal challenge with *Y.pestis*	Eyles et al. (1998)
PLGA	Bovine parainfluenza 3 virus	calf	Induction of antigen-specific nasal IgA antibody	Mansoor et al. (2015)
PLGA	Bovine respiratory syncytial virus	calf	Induction of mucosal IgA antibody and reduction in occurrence of respiratory diseases	Kavanagh et al. (2013)
poly-ε-caprolacone/chtiosan	Hepatiti B virus	mouse	Induction of antigen-specific systemic and mucosal antibody responses	Jesus et al. (2016)
poly-ε-caprolacone/chtiosan	Influenza virus	mouse	Induction of antigen-specific systemic and mucosal immune responses	Gupta et al. (2011)
polystyrene	*Streptococcus aureus*	mouse	Attenuation of proliferation of *S.aureus* after infection	Misstear et al. (2014)
PVM/MA	*Shigella flexneri*	mouse	Protection against lethal challenge with *S.flexneri*	Camacho et al. (2011); Camacho et al. (2013)