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The evolution of nasal immune systems in vertebrates

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ABSTRACT

The olfactory organs of vertebrates are not only extraordinary chemosensory organs but also a powerful defense system against infection. Nasopharynx-associated lymphoid tissue (NALT) has been traditionally considered as the first line of defense against inhaled antigens in birds and mammals. Novel work in early vertebrates such as teleost fish has expanded our view of nasal immune systems, now recognized to fight both water-borne and air-borne pathogens reaching the olfactory epithelium. Like other mucosa-associated lymphoid tissues (MALT), NALT of birds and mammals is composed of organized lymphoid tissue (O-NALT) (i.e., tonsils) as well as a diffuse network of immune cells, known as diffuse NALT (D-NALT). In teleosts, only D-NALT is present and shares most of the canonical features of other teleost MALT. This review focuses on the evolution of NALT in vertebrates with an emphasis on the most recent findings in teleosts and lungfish. Whereas teleost are currently the most ancient group where NALT has been found, lungfish appear to be the earliest group to have evolved primitive O-NALT structures.

1. Historical aspects

Tonsillectomy or the surgical removal of tonsils is a very ancient practice. Approximately 2000 years ago, Aulus Cornelius Celsus, a Roman writer and physician, described tonsil surgery by using his fingers to remove tonsils (Koempel et al., 2006; Younis and Lazar, 2002). Today, 530,000 children under the age of 15 have theirs tonsils or adenoids removed in the US every year and it is still one of the most common surgical procedures in children in this country (Cullen et al., 2009; Roland et al., 2011).

The first attempt to nasally vaccinate humans against smallpox was reported in the Golden Mirror of Medicine, Chinese medical text in 1742. Nasal vaccination was done by using powdered scabs that were blown to the nose or filling the nose with a vesicle smeared cotton (Plotkin, 2014). Thus, tonsillectomy and nasal vaccination precede our understanding of nasal immune systems.

Anatomically, the human Waldeyer's ring was first described in 1884 by von Waldeyer-Hartz as a ring of lymphoid tissue in the pharyngeal wall (Cocquyt et al., 2005; Perry and Whyte, 1998). Nasopharynx-associated lymphoid tissue (NALT) was first described as a paired of lymphoid cells accumulations in the nasal passage of rat in 1947 (Kelemen, 1947) whilst the mouse NALT was first described few decades later (Belal et al., 1977). In the subsequent years, the NALT of other mammals such as monkeys (Harkema et al., 1987; Loo and Chin, 1974) and horses (Mair et al., 1987, 1988) were described. However these studies did not include functional aspects of the nasal immune system (Kuper et al., 1992).

One of the major breakthroughs in nasal immunity field took place in the early 2000, when the first nasal vaccine for use in humans against influenza virus was licensed in the USA (FluMist) (Chen et al., 2006). To date, this vaccine remains the only nasal vaccine licensed for human use. The effectiveness and availability of this vaccine has helped the NALT community to expand basic scientific knowledge on nasal immune responses. Intranasal vaccination offers a number of advantages over other vaccination routes (Neutra and Kozlowski, 2006). Apart from the fact that is needle free and requires small amounts of antigen, intranasal delivery has been shown to stimulate not only local nasal immunity but also systemic immune responses as well as mucosal immune responses in distant mucosal sites (Fukuyama et al., 2012; Lycke, 2012; Neutra and Kozlowski, 2006; Pabst, 2015).

2. Anatomy of NALT

In endotherms, mucosa-associated lymphoid tissues (MALT) comprise a network of secondary lymphoid tissues that contain both well-organized lymphoid structures (organized MALT, O-MALT) and scattered or disseminated lymphoid cells (diffuse MALT, D-MALT) (Brandtzaeg and Pabst, 2004). Examples of O-MALT include the Peyer's patches in the gut or the tonsils in the nasopharyngeal cavity. Generally speaking we know very little about NALT (both organized and diffuse) compared to the gut-associated lym-

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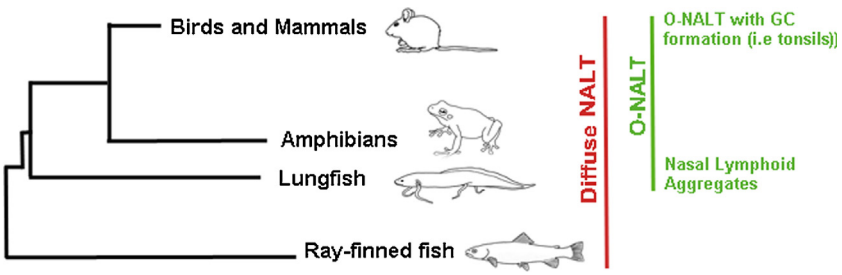

Fig. 1. Schematic diagram of the evolution of nasal immune systems in vertebrates.

phoid tissue (GALT). Furthermore, most mammalian studies focus on organized NALT (O-NALT), whereas diffuse NALT (D-NALT) has received very little attention. It is worth noting that the term "non-NALT" can also be found in the literature instead of D-NALT (Asanuma et al., 1997; Lee et al., 2015; Tamura et al., 1998). Additionally, "nasal passage (NP) leucocytes" is another term that can be found in the mammalian literature referring to D-NALT (Hiroi et al., 1998; Rodríguez-Monroy et al., 2007; Shikina et al., 2004). Despite the fact that the Society for mucosal immunology does not recommend the use of O-MALT and D-MALT (Brandtzaeg et al., 2008), numerous mammalian immunologists continue to use this terminology. Moreover, from the evolutionary immunologist point of view, O-NALT and D-NALT are useful terms considering that early vertebrates lack O-NALT (Fig. 1). In the next part of this review, we will summarize the basic anatomical aspects of NALT in different vertebrate groups.

2.1. Rodents and humans

The anatomy and structure of O-NALT have been widely studied in rodents (Mestecky et al., 2005). Murine NALT is composed of a pair of organized mucosal organs located on the roof of the soft palate at the entrance to the nasopharyngeal duct (Liang et al., 2001). NALT in mouse is considered by some to be analogous to the Waldeyer's ring in human which consists of the adenoids and tonsils (Kuper et al., 1992). Thus, in both mice and humans, O-NALT is strategically placed in the upper airways to combat air-borne antigens. Perhaps, this anatomical observation historically hindered the investigation of NALT in non-terrestrial vertebrates.

It is important to highlight that O-NALT of rodents and humans appears to be significantly different anatomically speaking. In rodents, NALT is located in a single localization bilateral at the entrance of the nasopharyngeal duct whereas in human studies conducted in children, O-NALT was mostly found in the middle concha and it consisted of disseminated lymphoid, subepithelial follicles (Debertin et al., 2003). The results from this study indicated that children have O-NALT structures in addition to a Waldeyer's ring (Debertin et al., 2003). Additionally, these differences underscore the fact that mice may not be the best models for human nasal immunity studies.

Similar to the Peyer's patches in the gut, O-NALT structures are located underlying specialized portions of the epithelium known as follicle-associated epithelium (FAE). Additionally, high endothelial venules (HEVs) control lymphocyte trafficking into O-NALT (Kiyono and Fukuyama, 2004). O-NALT structures also have distinct B-lymphocyte and T-cell zones (Bailey et al., 2005; Brandtzaeg and Pabst, 2004). Germinal center formation occurs in O-NALT in response to infection or antigenic stimulation (Zuercher et al., 2002).

As mentioned earlier, both mice and humans also possess diffuse lymphoid cells situated on the mucosa of the nasal passages called (D-NALT) (Liang et al., 2001). D-NALT includes myeloid cells and lymphoid cells (both B and T cells). The similarities and differences between mammalian O-NALT and D-NALT are summarized in Table 1.

2.2. Other mammals

In this section, we are going to focus on reports pertaining four groups of mammals: cattle, sheep, canines and rabbits. The studies in these species have been motivated by the importance of nasal vaccination in veterinary medicine.

In cattle, the tonsil (O-NALT) was first described in 1992 (Schuh and Oliphant, 1992). Cattle tonsils are located at the entry of the pharynx and are equivalent to the Waldeyer's ring in humans (Rebelatto et al., 2000). During development, adenoid can be detected at 95 days of gestation. Moreover, ciliated, microvillus cells and a loose accumulation of mononuclear cells in lamina propia is visible at 120–150 days of gestation. Small lymphoid follicles form at 4–5 months of gestation following by the appearance of goblet cells after 5 months of gestation (Schuh and Oliphant, 1992). Tonsils are well developed at birth in cattle. However, germinal center formation and increase in MHC class II expression only occur in the late natal and early post-natal period (Schuh and Oliphant, 1992). Moreover, cattle infected with foot-and-mouth disease virus (FMDV) showed increased expression of TLR-4 in NALT, indicating the importance of type I IFN responses in NALT against FMDV (Zhang et al., 2006).

Sheep O-NALT structures, similar to horse O-NALT, are clustered posterior to the opening of the Eustachian tube (Mair et al., 1988; Stanley et al., 2001). Thus, ovine NALT is highly organized and consists of discrete B and T cells areas similar to those found of humans and rodents. Furthermore, it has been shown that sheep NALT is covered by ciliated and non-ciliated cells which play an important role in antigen uptaking and processing (Stanley et al., 2001).

Peeters et al. reported the absence of typical O-NALT structures in the nasal mucosa of dogs without respiratory disease (Peeters et al., 2005). Waldeyer's ring in the dog consists of the lingual tonsil, the palatine tonsils, the soft palate tonsil and the pharyngeal tonsil or adenoid (Billen et al., 2006). The nasopharyngeal mucosa in dogs appears uniform and the nasopharyngeal tonsil is not obvious (Billen et al., 2006). The latter might be due to the fact that dogs breathe through both the nose and the mouth; therefore, exposure of the canine nasal and nasopharyngeal mucosa to inhaled antigens is decreased. This may explain why the pharyngeal tonsil is less developed in dogs than horses, cattle, sheep and pigs (Billen et al., 2006).

Casteleyn et al. (2010) histologically examined the presence of NALT in rabbits by sectioning the nasal cavity. Rabbits appear to have well organized NALT in their nasal cavities including clustered I and II lymphoid follicles separated by interfollicular regions as well as isolated lymphoid follicles. Interestingly, in the middle third of rabbit nasal cavity, NALT occupied the largest space. The rabbit and human nasal cavities occupy a similar volume considering their respective body masses. However, in comparison with rodents, O-NALT in the rabbit is more abundant. Therefore the sim-