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REVIEW ARTICLE

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Abstract At the surface of the respiratory and digestive organs the organism first comes into contact nasally and orally with various foreign agents and substances in the air and in food. The palatine tonsils are located at the centre of this strategic region. Immunological processes, both humoral and cellular, are initiated in the different specialised compartments of the palatine tonsils, such as the crypt epithelium, lymphoid follicles and extrafollicular region. Each compartment has a typical composition of lymphocytes and dendritic cell subsets. This review summarises current data on the anatomy, histology, and pathology of the human palatine tonsils, describes their fundamental immunological functions, and provides insight into the various interactions involved in the initiation of immune responses. The palatine tonsil is the only easily accessible human lymphoid organ and is often taken as an example for lymphoid organs. Although affections of the palatine tonsils constitutes an essential part in the clinical routine, it is still controversial whether tonsillectomy is of general benefit. This is of increasing importance since it has been discovered in the last few years that the palatine tonsils are reservoir and replication sites of HIV.

Keywords Lymphocyte · Review · Tonsillectomy · Tonsillitis · Compartments

Introduction

The paired palatine tonsils are located at the transition of the mouth to the oropharynx, the common entry of both the gastrointestinal and the respiratory tract. This significant position implies a key role of the palatine tonsils as secondary lymphoid organs in initiating immune responses against various antigens that enter the body through the mouth and the nose (Brandtzaeg 1984; Bernstein et al. 1999). The palatine tonsil is a lymphoepithelial organ and belongs to the integrated mucosal immune system of the pharynx (Ogra 2000), analogous to organised lymphoid tissue in the gut (Pabst 1987; Morente et al. 1992; Cebra et al. 1998) and the lung (Sminia et al. 1989; Pabst 1992; Pabst and Tschernig 1995). Waldeyer (1884, cited by Perry and White 1998) was the first to describe a ring of lymphoid tissue in the human pharynx. Besides the nasopharyngeal tonsil (adenoids), the paired tubal tonsils and the lingual tonsil, palatine tonsils are a major component of the so-called Waldeyer's ring (Andersson et al. 1994) or Waldeyer's ring equivalent in rats (Koornstra et al. 1991). Due to easy accessibility the structure and functions of the human palatine tonsils, as a model for human lymphoid organs, have often been studied. Thus, in the past two decades our knowledge about their physiology and pathology has been greatly extended. This review summarises the basic immunological functions in a morphological context and focuses on the palatine tonsil of humans. The aspects that have to be elucidated in other species are indicated.

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Functional morphology of palatine tonsils

Macroscopic aspects

The palatine tonsils are located in the tonsillar fossa between the palatoglossal and palatopharyngeal arches (faucial arches) of the oropharynx. The muscular basis of the tonsillar fossa is dorsally the palatopharyngeal muscle, ventrally the palatoglossal muscle and the superior constrictor muscle of the pharynx, which forms its lateral wall (Richardson 1999). The blood supply of the palatine tonsil is mainly provided by the tonsillar branch either of the ascending palatine artery or of the facial artery. Other small arterial branches originate from the lingual and ascending pharyngeal arteries. The arteries enter the tonsil preferentially at the inferior pole. The lymphatic vessels lead to the submandibular lymph nodes and thereafter to

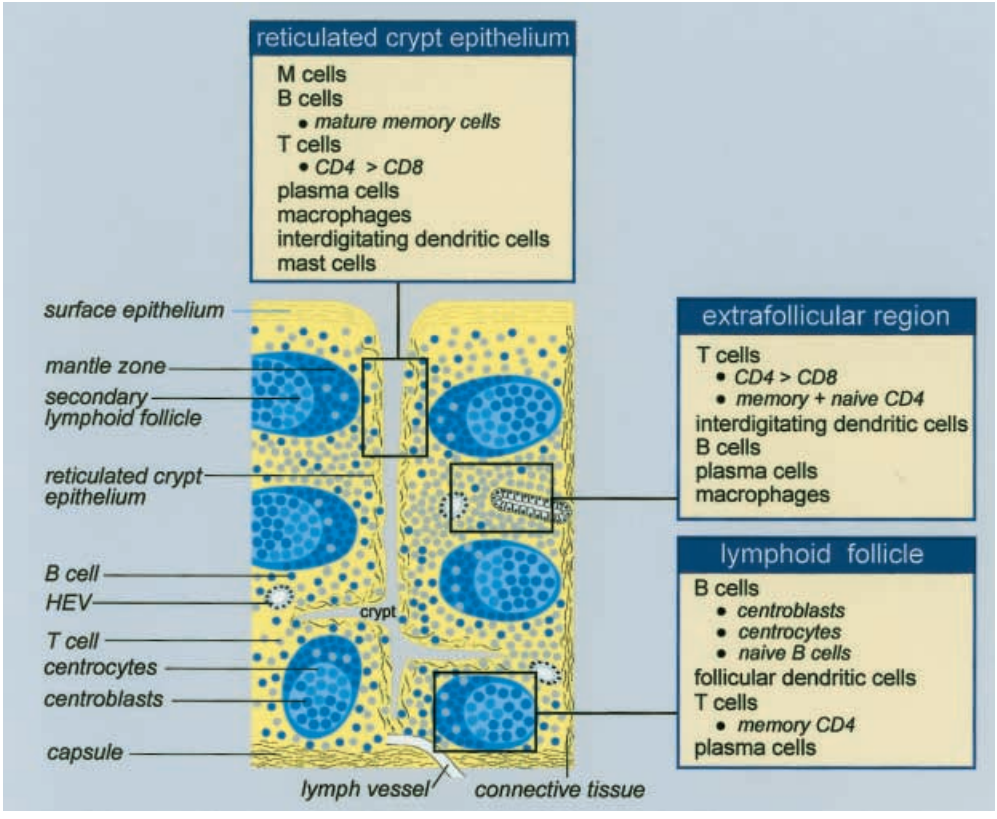

Fig. 1 Schematic diagram of the human palatine tonsil and the cell composition of different tonsillar compartments. The order of the cells in the boxes reflects their numerical proportion in the compartment (beginning with the largest cell population)

the deep cervical lymph nodes (Binns and Pabst 1988; Belz 1998). The palatine tonsils are covered by a stratified squamous non-keratinising epithelium, supported by a capsule of connective tissue, containing blood vessels, nerves and lymphatics. The size of the tonsils is most prominent during childhood and directly proportional to the bacterial load and the number of B and T cells (Siegel et al. 1982; Casselbrandt 1999). Later, age-dependent size reduction (tonsillar involution) can be observed (Jung et al. 1996).

Tonsillar crypts and epithelium

The formation of deep tubular crypts is one characteristic of the palatine tonsils of humans and pigs (Sato et al. 1990; Belz and Heath 1996). Nevertheless in some species, e.g. in dogs and rabbits, the palatine tonsils lack such crypts (Belz and Heath 1995; Gebert 1995). In humans, each palatine tonsil contains 10–30 blind-ending tubular, branched crypts, extending through the full thickness of the organ (Perry 1994) and enlarging the tonsillar surface up to 300 cm^2 (Howie 1980). Abbey and Kawabata (1988) showed that the crypts have not only branches but also anastomoses. Together with variation in number and size of the lymphoid follicles this may contribute to the diversity of configurations and size of the crypts. The content of the crypts is mainly composed of degenerated cells and cellular debris. The epithelium of the crypts is a modified form of the stratified squamous epithelium that covers the remaining oropharynx including the outer surface of the tonsil (Perry 1994). The degree of reticulation (e.g. the number of intraepithelial lymphocytes) of the epithelium varies enormously (Reibel and Sorensen 1991). Characteristic of the reticulated crypt epithelium is the coexistence of epithelial and non-epithelial cells and, in places, the predominance of the latter as well as disruptions of the basement membrane (Fig. 1). The reticulated crypt epithelium, also called lymphoepithelium (Perry and Whyte 1998), plays a key role in the initiation of immune responses in the palatine tonsils (Karchev and Kabakchiev 1982; Belz and Heath 1995). In the crypts, luminal antigens are taken up by specialised cells of the reticulated squamous epithelium which resemble the intestinal membranous (M) cells characteristic of the domes of Peyer's patches (Gebert 1995; Gebert et al. 1996). M cells endocytose antigens at their apical membrane, transport these in vesicles to their basolateral membrane and exocytose them to intra- and subepithelial spaces where they come into contact with lymphoid cells (Gebert 1995, 1996, 1997a, 1997b). The tonsillar M cells comprise a few percent of all epithelial cells of the crypts and typically possess microvilli on their apical surface in humans (Howie 1980) and rabbits (Gebert 1995, 1996). The transport function of M cells not only provides a continuous "sampling" of antigens, but also serves as a gateway for mucosal infections or immunisations (Karchev and Kabakchiev 1984; Neutra et al. 1996; Gebert 1997b). M cells are of critical clinical relevance because various pathogens use M cells as an

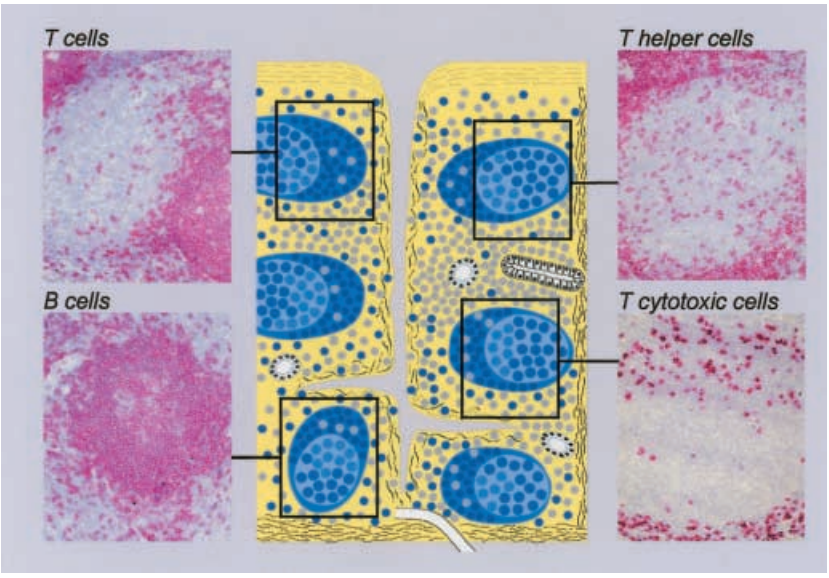

Fig. 2 Photomicrographs of the human palatine tonsil demonstrating the typical distribution of T cells (CD3+; *red*), B cells (CD20+; *red*), T helper cells (CD4+; *red*) and T cytotoxic cells (CD8+; *red*). Note that CD4 and CD8 are not only expressed on T helper and T cytotoxic cells, respectively, but also on some non-lymphoid cells. Alkaline phosphatase anti-alkaline phosphatase (APAAP) technique. ×100

entry site to invade the host (for review see Gebert et al. 1996; Neutra et al. 1996; Gebert 1997b).

T cells and immunoglobulin-expressing B cells can be found in all regions of the epithelium with no distinct pattern of distribution. Patchily distributed macrophages and dendritic cells also contribute to the non-epithelial cell population; plasma cells are predominantly located around intraepithelial capillaries (Bernstein et al. 1999). The multitude of immunocompetent cells within the crypt epithelium obviously form a separate lymphoid micro-compartment in the palatine tonsil.

Lymphoid follicles

Primary lymphoid follicles are present in human tonsils from the 16th gestational week on, and germinal centres are formed shortly after birth (Brandtzaeg 1996). Lymphoid follicles in the palatine tonsils are round or elliptical, can be seen just beneath the epithelium and are sites of intense B cell maturation and differentiation as well as T cell activation (Fig. 2). Secondary lymphoid follicles containing germinal centres are composed of a dark zone, with large numbers of proliferating B blasts also known as centroblasts, a (basal and apical) light zone, predominantly containing centrocytes, and a mantle zone with naive B cells (Banchereau et al. 1994; Brachtel et al. 1996; Fig. 1). Using monoclonal antibodies, five distinct mature B cell subsets (from Bm1 = naive B cell to Bm5 = memory B cell) have been identified in the human tonsil (Liu et al. 1994a,b; Pascual et al. 1994). In the interaction between T and B cells in the germinal centre a distinct memory T cell subset, the follicular B helper T cells (T_{FH}) play an important regulatory role (Schaerli et al. 2000). In addition to B and T lymphocytes, the tonsillar lymphoid follicles contain a network of follicular dendritic cells (FDC) and a special subset of germinal centre dendritic cells that activate germinal centre T cells (Liu and Arpin 1997). FDC are able to retain high amounts of immune complexes on their plasma membranes for long periods (Cormann et al. 1986; Noble et al. 1996; Dieu et al. 1998) and thereby act as antigen-presenting cells that offer an appropriate environment for the proliferation and differentiation of germinal centre B cells (Heinen et al. 1988; Brandtzaeg 1996). Furthermore, FDC play a role in the modulation of the susceptibility to apoptosis of B cells within lymphoid follicles (Tsunoda et al. 2000). Ultrastructurally, seven distinct FDC populations were recognised in the lymphoid follicles (Rademakers 1992), but it is still unclear whether they are associated with functional differences. Analogous to the B cell distribution, FDC precursor cells are predominantly localised in the dark zone, whereas highly differentiated FDC subtypes are present in the light zone.

Extrafollicular region

The extrafollicular region contains T cells (primarily with the helper phenotype, $CD4^+$; Fig. 2), interdigitating dendritic cells (IDC), macrophages and specialised venules, the so called high-endothelial venules (HEV; Fig. 1). The HEV are necessary for the entry of T cells and B cells from the blood into the tonsils (see below). In the extrafollicular area, a specific mixture of cytokine producing cells (e.g. IL-1α and TNF-α from macrophages as well as IDC, IL-2, IL-4 and IFN-γ from T cells) and antibody production is found (Hoefakker et al. 1993).

Immunology of palatine tonsils

The localisation of the palatine tonsils is favourable for the exposure to foreign material and pathogens and their transport to lymphoid cells. The greatest immunological

activity of the tonsils is found at the age of 3 to 10 years (Richardson 1999). Up to the age of 60 Ig-positive B cells substantially decline in all compartments of the palatine tonsil, whereas the overall change in T cells is limited (Shido et al. 1984; Yamanaka et al. 1992; Kuki et al. 1996; Bergler et al. 1999). Moreover, numbers of FDC and IDC are largely reduced in the age-dependent tonsillar involution (Brandtzaeg et al. 1978).

First step in the immune response

When antigens enter the oropharyngeal cavity the reticulated crypt epithelium is the first tonsillar compartment that is challenged immunologically (Karchev 1988; Brandtzaeg and Halstensen 1992; Yamanaka et al. 1996). The membranous (M) cells not only transport the antigens across the epithelial barrier, but also form a specific intraepithelial micro-compartment that brings together high concentrations of foreign antigens, lymphocytes, and antigen-presenting cells such as macrophages and dendritic cells (Brandtzaeg et al. 1999). However, the interactions of the M cells and the different cells of the immune system in this micro-compartment during the initiation of a cellular or humoral immune response are still poorly understood (Brandtzaeg et al. 1999).

The lymphoid cells found in the spaces of the reticulated crypt epithelium of the human palatine tonsil are mainly composed of B lymphocytes and T helper cells (CD4+). The immune response additionally requires the help of different cytokines. Cytokines are peptides involved in the regulation of immune processes and are predominantly produced at sites of local antigen stimulation (Andersson et al. 1994; Harabuchi et al. 1996) by intraepithelial lymphocytes, other lymphoid cells and non-lymphoid cells. Intraepithelial T cells can produce a great variety of cytokines [e.g. IL-2, IL-4, IL-6, TNF-α, TNF-β (now called: LT-α), INF-γ, TGF-β]. Nevertheless, a few cytokines (e.g. IL-8, IL-1α) can only be found in the crypt epithelium and not in extrafollicular regions (Andersson et al. 1994).

Approximately 50–90% of the intraepithelial lymphocytes are B cells (A. Gebert, unpublished data; Perry and White 1998). The majority of B cells in the crypt epithelium are mature memory B cells (Fig. 1) with a high antigen-presenting potential (Banchereau et al. 1994; Liu et al. 1995), permitting an early contact between antigen-presenting B cells and T cells, and leading to a rapid secondary antibody response. Various Ig isotypes are produced in the palatine tonsils. Approximately 82% of the immunocytes in the germinal center produce IgD, 55% IgM, 36% IgG and 29% IgA (Korsud and Brandtzaeg 1980). The IgA is a substantial component of the tonsillar humoral immune system. The production of the J-chain by Ig-producing cells is crucial for the epithelial transport of Ig polymers by the transmembrane secretory component (SC), also called polymeric immunoglobulin receptor. The distribution of J-chain positive immunocytes of various Ig classes is dependent on the localisation of the cells (e.g. 29% of the germinal centre IgA immunocytes and 51% of the IgA immunocytes in the extrafollicular region; for review see Bernstein et al. 1999). Despite the numerous IgA producing cells, no SC is expressed in the epithelium of palatine tonsils (Brandtzaeg 1987). However, immunoglobulins are passively transferred into the crypt.

Second step in the immune response

After passing the crypt epithelium inhaled or ingested antigens reach the extrafollicular region or the lymphoid follicles. In the extrafollicular region, IDC and macrophages process the antigens and present them to $CD4^+$ T lymphocytes (Brandtzaeg and Halstensen 1992). T_{FH} cells then stimulate follicular B lymphocytes so that these proliferate and, while migrating from the dark zone of the lymphoid follicle to the light zone, develop into antibody-expressing B memory cells and antibody-producing plasma cells (Quiding et al. 1995; Brandtzaeg 1996). The presence of antigen enables B cells to survive this migration while in the absence of stimulation they undergo apoptosis (Tabe et al. 1996; Tsunoda et al. 2000). Tonsillar plasma cells can produce all five Ig classes (IgG [~65%], IgA [~20%], IgM, IgD, IgE) helping to combat and prevent infection (Brandtzaeg 1996). Furthermore, the antigen contact of memory B cells in the lymphoid follicles is an essential part of the generation of a secondary immune response (Quiding et al. 1995). Although the number of T cells in the lymphoid follicles is limited (Fig. 2), these few cells have a strong influence on the fate of B cells: T cells are capable of expressing several cytokines (e.g. IL-4) that inhibit the apoptosis of B cells (Clark and Ledbetter 1994; Schriever et al. 1997).

Lymphocyte migration

Lymphocyte traffic is essential because only few immunocompetent cells specific for an individual antigen are available in a non-affected tonsil (Pabst et al. 1998). To study physiological lymphocyte migratory routes in human palatine tonsils is almost impossible, because specimens collected after tonsillectomy are mostly inflamed, hypertrophied or otherwise affected and therefore do not usually represent a “normal” human tonsil. Thus, additional data from animal studies are needed for a better understanding of lymphocyte trafficking in these organs. Extravasation of lymphocytes from the blood to the palatine tonsils and back is essential for the immunological competence of these organs (Westermann and Pabst 1990; Koornstra et al. 1992; Baekkevold et al. 1999). It has recently been reported that the chemokine ELC (Epstein-Barr virus-induced molecule 1 ligand chemokine or CCL19) is transcytosed to the luminal surfaces of HEV and participates in the extravasation of T cells (Baekkevold et al. 2001). Experiments in pigs and rats showed that lymphocytes migrate continuously

from the blood into the tonsils via HEV and return into the circulation via the lymph (Nowara and Pabst 1986; Girard and Springer 1995; Westermann et al. 1996). In an immunohistochemical study Zidan et al. (2000) demonstrated that, in human palatine tonsils, neither the entry nor the exit is restricted to a specific lymphocyte subset (e.g. CD4+ or CD8+) or site. Several adhesion molecules (e.g. L-selectin and ICAM-1) and also cytokines and chemokines (Schaerli et al. 2000) are necessary for the entry of lymphocytes into the tonsils. As discussed recently by Casamayor-Palleja et al. (2001), chemokines produced in the tonsillar crypts (e.g. SDF-1, BCA-1 and MIP-3alpha) attract memory B cells and play a role in retaining them in the crypt.

Nevertheless, little is known about other factors that regulate the transit of lymphocytes within the different compartments of lymphoid organs and their exit into lymphatics that drain into regional lymph nodes.

Immunopathological aspects of palatine tonsils

Tonsillitis and tonsillectomy

The healthy palatine tonsils are sites of continuous stimulation of lymphoid cells and this has been interpreted as a permanent activation (so-called "physiological inflammation" of tonsils) (Surjàn 1987). Up to now only few systematic studies exist, comparing recurrent or chronically inflamed tonsils with "normal" ones (Korsud and Brandtzaeg 1981). Tonsillitis occurs if the activity and proliferation of pathogens in the tonsillar lymphoid tissue exceed the protective potency of activated lymphoid and immunoglobulin-producing cells (Scadding 1990). In this situation, especially in chronic or recurrent cases, surgical tonsillectomy is a common therapeutic approach (Ying 1988), but is still controversial (Witt 1989; Bock et al. 1994). It remains unclear whether its benefit exceeds its harm, i.e. the elimination of enormous numbers of immunocompetent cells occasionally resulting in a decreased level of serum IgA (Harper et al. 1995; Hotta et al. 1996; Brandtzaeg 1999). Furthermore, it has to be taken into consideration that large palatine tonsils alone are not necessarily an indication for tonsillectomy, because tonsils are normally much larger in children than in adults and physiologically involute during adolescence (Mattila and Tarkkanen 1998; Bergler et al. 1999).

HIV-1 reservoir and replication site

In the last few years increasing interest has been focussed on the possible role of tonsils as reservoir and replication site of the HIV-1 (Pantaleo et al. 1991; Frankel et al. 1997; Perry and Whyte 1998). Frankel et al. (1996) and Wenig et al. (1996) examined human tonsillar material from HIV-1 infected patients. They found a distinct cell population with marker for HIV-1 RNA as well as the dendritic cell marker S-100 but no other leukocyte markers. In all cases these cells were exclusively located in the crypt epithelium, whereas Heath et al. (1995) found highly infectious FDC in lymphoid follicles of palatine tonsils in HIV-1 infected patients. The tonsils therefore appear to play an important role in HIV-1 storage and replication from the beginning of disease and even in asymptomatic individuals.

Conclusions

In this article we have focused on the morphological and immunological aspects of the human palatine tonsils. With regard to the exposed position of these lymphoepithelial organs at the gateway to the oropharynx, the palatine tonsils are probably of crucial importance in the defence against foreign pathogens. Since the palatine tonsils can easily be reached by routine surgical intervention in humans and in some animal models, they are ideal for investigations on lymphocyte migration and maturation, and for studies on age-dependent changes in lymphoid organs. In the last two decades, the work of numerous researchers has enabled more detailed insight into the complex immunological interactions and processes of palatine tonsils and their impact on distant sites in the human body. However, several questions concerning their immunopathology and pathomorphology still remain unanswered and should be investigated in further studies.

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Note added in proof In a recent publication (Summers et al. 2001) five different subsets of dendritic cells have been characterised in detail in human tonsils.

Summers KL, Hock BD, McKenzie JL, Hart DN (2001) Phenotypic characterization of five dendritic cell subsets in human tonsils. Am J Pathol 159:285–295