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The role of dendritic cells in the pharynx

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Abstract The tonsils are organized as lymphoepithelial structures that play an important role in protecting both the upper respiratory and alimentary tract regions against incoming antigens. This function requires dendritic cells, professional antigen-presenting cells that act as peripheral sentinels, specializing in the uptake, processing and presentation of antigenic material. This article gives a brief review on dendritic cells with regard to their origin, life cycle and functions in the pharyngeal mucosa. The regulation of immune responses in tonsils by dendritic cells is discussed. Their importance in some disease states is also mentioned.

Keywords Antigen-presenting cells · Dendritic cells · Tonsil · Immune response

Introduction

The pharynx serves as a gate for every breath and every swallow to bring antigenic material into the organism.

Therefore, the mucous membranes have developed a protective immune system, which differs anatomically and functionally from that of the spleen and classical regional lymph nodes. The pharynx has a large amount of subepithelial lymphoid tissue encircling both its alimentary and respiratory openings, forming Waldeyer's ring, which belongs to the system of mucosa-associated lymphoid tissue (MALT). There are four large aggregations of this tissue: the nasopharyngeal tonsil, the paired tubal tonsils, the paired palatine tonsils and the lingual tonsil. The surface of the tonsil is characterized by various openings, leading into deep, narrow, blind-ended recesses called crypts, which may penetrate nearly the whole thickness of the tonsil deep into the underlying lymphoid tissue. The crypts, covered with non-uniform, reticular epithelium, substantially extend the tonsillar surface. Underlying the epithelium, numerous rounded aggregates of mainly B lymphocytes, also called follicular germinal centers, can be found, each surrounded by a crown-shaped mantle zone of dense, small lymphocytes and in-between interfollicular areas, which are predominantly populated by T lymphocytes [6]. The main functions of these structures are to sample antigens, have them surveyed locally by immune cells in order to destroy them and generate effector and memory lymphocytes, which can migrate to other mucosal sites [58]. Dendritic cells (DCs) are unique antigen-presenting cells (APCs), being able to induce primary immune responses, thus permitting the establishment of immunologic memory. A subset of these cells acts as peripheral sentinels, specializing in the uptake, processing and presentation of antigenic material. B and T lymphocytes are the mediators of immunity, but their function is under the control of DCs. Generated in the bone marrow, DCs course through the blood stream, migrate into the epithelium, respond to local cytokines, capture antigen, carry it to the secondary lymphoid organs and initiate a primary immune response in naive T lymphocytes.

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Discussion

DC lineage

DCs are derived from CD34+ bone marrow progenitors that seed peripheral tissues. Progenitor cells leave the bone marrow and reach the target tissue via the blood stream. Within these sites, they display characteristic stellate morphologic characteristics (Fig. 1). As a consequence, the DC has a high surface area, permitting intimate contact with a large number of surrounding cells. At least two distinct pathways of DC development have been identified in mice: myeloid and lymphoid. The existence of human lymphoid DCs is somewhat controversial [22]. The lymphoid and myeloid DCs differ in phenotype, localization and function [3, 52].

The development of lymphoid DCs (CD11c-) is independent on GM-CSF, relying rather on IL-3 and IL-7. They include those in the thymic medulla and many DCs in the T-cell areas of all peripheral lymphoid tissue, where they participate in T-cell activation or tolerance induction.

In the presence of growth factors such as GM-CSF and IL-4, myeloid precursor cells (CD11c+) develop the functional and phenotypic characteristics of immature DCs. The DCs found in non-lymphoid tissue can be divided into two populations: intraepithelial Langerhans' cells (LCs), which reside within the epithelium (classically of the stratified squamous type) and interstitial DCs (in the dermis and in the interstitium of parenchymatous organs). The density of skin LCs ranges from 200 to 970/mm² [11]; the density of LC in the epithelium of the oral cavity and pharynx ranges from 200 to 500/mm². The lowest LC counts are in the floor of the mouth. The clustering of LCs around the tips of subepithelial papillae is a consistent feature, especially in the buccal mucosa [5]. Once DCs have seen antigen, they exhibit a more differentiated phenotype, suggesting that these cells have responded to regulatory signals and that they have migrated via lymphatic

vessels to the lymph nodes. These cells are zone interdigitating DC (in the T-cell zone of the lymphoid tissues) and follicular DC (located in the B-cell zone of the lymphoid tissues).

In normal tonsils, both the surface and crypt epithelium have essentially equal numbers of DCs [42]. Tonsillar DCs can be subdivided into five populations based on their relative expression of HLA-DR, CD11c, CD13 and CD123 [54]. These distinct subsets of DC can play different roles in regulating immunity or tolerance, although it remains unclear whether the type of T-cell response is driven by intrinsic properties of the DC subset or by local environmental factors.

Cell cycle of DC

Antigen uptake

Immature DCs located in sites of antigen entry (in stratified squamous epithelium with permeation of the dendrites between keratinocytes) display a strong endocytic capacity, allowing for efficient antigen processing and major histocompatibility complex (MHC) class-II expression – considerably higher than that of other APCs (macrophages, B lymphocytes). However, they are weakly immunogenic to T cells. After perceiving the antigenic signal provided by bacterial product lipopolysaccharide (LPS), bacterial DNA, viral dsRNA or inflammatory cytokines (IL-1, TNF- α), an irreversible maturation of DC processes is initiated, which includes the loss of endocytic activity and an enhanced T-cell stimulatory capacity [52]. DCs are equipped with a number of mechanisms to perform antigen uptake [2]. Firstly, immature DCs are capable of phagocytosing particles and microbes. Secondly, they are capable of performing macropinocytosis, a process by which large pinocyte vesicles are generated, sampling extracellular fluids and solutes. Thirdly, antigen uptake is realized by receptor-mediated endocytosis, indirectly by Fc-receptors (which allow the uptake of antigen opsonized with antibody) and directly via C-lectin receptors (175 kDa macrophage mannose receptor = CD206, DEC-205 = CD205, Dectin 1, Dectin 2, DC-SIGN = CD209, BDCA-2, DCIR, DLEC, CLEC-1, asialoglycoprotein receptor) [12, 18, 28, 31, 57]. However, participation of DC lectins in the DC/T-lymphocyte interaction was defined [18]. Terminal mannose is rarely found in mammalian cell surfaces, but is a common component of the cell surface of bacteria, yeasts and parasites. Even though LCs lack classical mannose receptors, they are able to uptake mannosylated antigens. Langerin, C-type lectin involved in the formation of Birbeck granules, recently has been proved responsible for this process [56]. This is important because the efficiency of antigen presentation is 100 times higher for mannosylated antigen. Also, galectin-3, β -galactoside-binding lectin expressed differentially dependent in squamous epithelia, is present in Birbeck granules, suggesting a possible role of this lectin in the internalization of glycosylated molecules [44, 48]. The CD1a antigen, as one

Fig. 1 Langerhans' cells in human tonsillar epithelium. Arrows indicate typical dendritic extremities. CD1a antigen

Fig.2 Scheme of maturation of dendritic cells. Adapted from [2]

of the marker molecules of LC, was depicted as playing some role in the internalization and presenting of antigens of a lipidic nature [37, 47]. Once DC has captured an antigen, which also can provide a signal to mature, its skills to capture antigens rapidly decline, and DC assembles MHC class II (Fig. 2).

Antigen processing and presentation

The maturing DCs home via afferent lymphatic vessels to the paracortical T zone of the regional lymph nodes or to the interfollicular T-cell areas of tonsils, where they interact with naive T cells. Migration of DCs is enabled by freeing the contact with surrounding tissue elements (induced by LPS or TNF- α) and production of enzymes dissolving basement membrane structures (collagenases) [33]. In addition, they express costimulatory molecules, like CD 80 (B-7.1) and CD 86 (B-7.2) and accessory molecules, like intercellular adhesion molecule-1 (ICAM-1), lymphocyte function-associated antigen-3 (LFA-3) and CD70, which are required for optimal T-cell activation [12, 13]. For this antigen-specific T-cell activation, at

least two signals are required. The first signal is mediated via TCR recognition of antigen bound to MHC molecules expressed on the DC surface. The second, costimulatory molecules CD80 and CD86 on DCs interacting with CD28 receptors on T cells, contributes to an efficient T-cell response. Both of these processes lead to a rapid up-regulation of CD40 ligand (CD40L) on the T-cell surface. CD40L interacts in turn with the CD40 present on the DC, thereby strengthening the DC/T-cell contact [9]. Studies on naive T lymphocytes have shown that the quantity of CD40L expression on T cells is determined by the extent of TCR interactions, which in turn appear to be determined by antigenic affinity and DC costimulatory molecule expression [30]. Although every APC considerably expressed CD40, resting macrophages and B cells appear to have little naive T-cell-stimulating activity. On their surface, they expressed only a restricted number of costimulatory molecules, insufficient to induce satisfactory CD40L expression, which is necessary for a primary T-cell response. On the contrary, mature DCs, as mentioned previously, express many accessory molecules and therefore seem to be responsible for primary T-cell activation.

Lymphocyte activation

In addition to cell surface changes, concurrent changes in cytokine production by DCs also occur after maturation (IL-12, IL-8, TNF- α , MIP-1 α = macrophage inflammatory protein) [12]. The CD11c⁺ DC1 subset produces IL-12, which promotes the development of T-helper-1 phenotype (Th1), which is important in the generation of cytotoxic CD8⁺ T cells [25]. It is essential for immunity to intracellular parasites. The CD11c⁻ DC2 subset fails to produce IL-12 and thus induces T cells to produce predominantly Th2 cytokines [32]. Th2 response is important in the generation of immunity to extracellular infection and in allergic responses. The type of response, i.e. Th1 or Th2, is probably influenced by the type of tissue from which the DCs migrate and the type and dose of antigens encountered [7]. IL-10, a cytokine that decreases inflammatory responses (IgE, IL-5, GM-CSF production), induces development of the DC3 subset with impaired immunostimulatory capacity resulting in inappropriate T-cell stimulation leading to anergy [14].

Dendritic cells also interact directly with B cells [15]. The DCs stimulate the differentiation of naive B cells into IgM-producing plasma cells, an effect mediated by IL-12. In response to IL-10 and prostaglandin E₂, DCs have also been observed to promote immunoglobulin class switching towards IgA [17].

DCs can regulate effectors of innate immunity via both direct DC/NK cell interaction and indirect cytokine-mediated interaction through the release of IFN- α , thereby leading to enhanced antitumor and antiviral activity of NK cells [2].

Finally, once antigen presentation has been achieved, DCs undergo apoptosis through Fas/FasL killing in secondary lymphoid tissues (Fig.3) [59]. This provides an

Fig.3 Dendritic cell life cycle in the tonsil. Progenitor CD34+ DCs leave the bone marrow and reach tonsillar epithelium as immature DCs. Circulating precursor DCs can directly encounter antigens that induce cytokine production, which can activate macrophages and natural killers (innate immunity). After antigen uptake, immature DCs migrate to the interfollicular area of tonsils and start the maturation process (expression of MHC II, costimulatory molecules, presentation of antigen). Mature DC can directly interact with antigen-specific naive B cells that migrate into the follicular germinal center and differentiate in memory cells or antibody secreting plasmatic cells. B cells become activated also after contact with T cells and DCs. T cells, activated by interaction with mature DC, migrate towards the injured tissue. Helper T-cell-derived cytokines activate macrophages and natural killer cells. Cytotoxic T cells attack and kill an infected target. After interaction with lymphocytes, DC undergo apoptosis

explanation for why DCs have never been observed in the efferent lymphatics.

DCs and disease

Infectious disease

DCs are generally the first immunological cells to encounter foreign organisms. A challenge of the airway mucosal surface with bacteria-derived stimuli leads to rapid recruitment of large numbers of DC precursors in the epithelium, a maximum is reached within 1 h after exposure. These cells rapidly mature and migrate to regional lymph nodes over the ensuing 48 h; a similar finding has also been reported in relation to the gastrointestinal tract [35, 36].

In normal tonsils both the surface and crypt epithelium have essentially equal numbers of DCs. This microanatomical distribution of DCs is significantly altered in infected tonsils. Fewer numbers of DCs are found in the surface epithelium and greater numbers in the crypts and extrafollicular areas. An increased total bacterial concentration is

correlated with increased numbers of DCs in the surface epithelium. One can speculate that chronic hyperplastic tonsillitis contributes to the hosting of mucosal immunological responses, while non-hyperplastic chronic tonsillitis, which is devoid of abundant lymphoid tissue and exhibits fewer DCs, is immunologically incompetent [8, 42, 43].

Mature DCs are not considerably present in the human tracheobronchial mucosa in the 1st year of life, but their occurrence seems to be triggered by infectious stimuli [55].

DCs are implicated in the life cycle of pathogens. A number of viruses (HIV, cytomegalovirus, measles virus, coronavirus, influenza virus, herpes virus and respiratory syncytial virus) use molecules expressed by DCs as receptors. DCs provide a means for viruses to access other cells and to impair DC function, thus escaping immune surveillance.

HIV

The DC system is also involved during HIV infection, because dendritic cells normally express CD4, a receptor for HIV. The virus can be transported and can replicate in immature DCs, whereas the mature DC efficiently transmits infection to surrounding CD4+ T cells. HIV induces syncytia by the fusion of an infected DC with T cells. These syncytia have been found at the surface of MALT, such as tonsils [19]. HIV disease leads to a reduction in the number of DCs in the periphery and decreases their capacity to stimulate T-cell effector function. The decline in stimulatory capacity is probably the result of the loss of immunologically important molecules of DCs in HIV infection. Rather than battling with the infection, DCs assist in its spread by transmitting HIV to T cells and disseminating the disease away from mucosal sites [26, 45].

Histiocytosis X

This disease is characterized by a pathological accumulation of a particular type of histiocyte showing features of LCs. The lesional cells contain Birbeck granules, as well as expressing phenotypes found on normal LCs such as CD1a, HLA-DR, HLA-DQ and S-100 [16]. The term histiocytosis X is used to denote three related diseases. Letterer-Siwe disease, which affects children below the age of 4, is the most severe and rapidly progressive; it is usually fatal in the disseminated form. Hand-Schüller-Christian disease is the intermediate chronic, disseminated form seen in juveniles. Eosinophilic granuloma is a relatively benign unifocal disease of all ages that most often involves bone. Intraosseous defects are the predominant feature of two-thirds of these cases, of which 75% affect the skull base or mandible, usually posteriorly. Soft tissue involvement is also not rare [34]. It remains unclear whether histiocytosis X is a neoplastic process or only a reactive hyperplasia. Soft tissue lesions arise from peripheral LC located in the epithelium, but it can only be speculated as to whether intraosseous lesions arise from sites of residual bone marrow containing LC precursors.

Neoplasia

DCs play an important role in several steps of anti-tumor immunity, including: (1) recognition of tumor molecules by DC precursors, (2) direct and IFN- γ -mediated killing of transformed cells by NK-cells activated by DC, (3) capture and presentation of tumor-associated antigens (TAA) by immature DCs, (4) selection and activation of TAA-specific T cells and (5) homing of TAA-specific T cells to the tumor site [2]. However, DCs isolated from cancer patients show an impaired ability to present antigen as a product of decreased expression of costimulatory molecules CD80 and CD86 [10]. Tumors can prevent DC differentiation and maturation by the release of IL-6, IL-10, VEGF or can skew the T-cell response towards type 2 [1]. Increased expression of FasL on tumor cells may induce apoptosis of DCs [53]. Recent data have shown that the infiltration of DCs into primary tumor lesions is associated with significantly prolonged patient survival and reduced incidence of recurrent or metastatic disease in patients with different human cancers, including head and neck squamous cell carcinoma (HNSCC) [20, 21, 23, 24, 46]. Fewer DCs were observed in metastatic lesions than in primary tumors [38]. They are located between the tumor cells and in the stroma of head and neck cancers, especially in the areas of inflammatory cell infiltration. The presence of DCs in tumors indicates that the organism has activated the immune surveillance system and is trying to present tumor antigens [60]. Few DCs were found in the early stage of precancerous lesions of the larynx; as the degree of dysplasia rises, more DCs infiltrate the lesion [50]. It is interesting that tobacco and alcohol consumption, factors known to predispose to the development of head and neck squamous cancer, is also associated with increased epithelial DC counts [5].

The unique ability of DCs to induce and encourage primary immune responses makes them optimal candidates for vaccination protocols in cancer (see the recent reviews [4, 40, 51]). The current knowledge of DC biology is being used in clinical trials of cancer therapy, including malignant melanoma, non-Hodgkin's lymphoma and prostate cancer [29, 39, 41]. DCs are generated *in vitro* from peripheral blood monocytes or CD34+ precursors obtained from bone marrow. Afterwards, they are exposed to tumor antigens in different forms: viral vectors, naked and plasmid DNA, RNA, liposomes with nucleic acid or protein, apoptotic tumor cells and tumor lysates. Activated DC or DC-activated T lymphocytes are then intravenously administered to the patients or injected directly into the tumor. The clinical results are quite satisfactory, showing partial or complete tumor regression. Little has been investigated about the efficacy of DC immunotherapy for the treatment of HNSCC because squamous cell carcinoma-specific antigens remain unknown. However, DCs pulsed with apoptotic squamous cell carcinoma cells can induce an antitumor effect both *in vivo* and in animal models [27, 49]. It is a promising strategy for the treatment of a poorly immunogenic tumor, especially when tumor-specific antigens are unknown.

Conclusion

The tonsils are organized as lymphoepithelial structures that play an important role in protecting both the upper respiratory and alimentary tract regions against incoming antigens. This function requires dendritic cells, professional antigen-presenting cells that act as peripheral sentinels, specializing in the uptake, processing and presentation of antigenic material combined with an ability to detect a wide variety of antigenic signals. These signals induce profound changes in the physiology of dendritic cells, facilitating the efficient stimulation, encouragement and regulation of both innate and adaptive immunity.

In the present review, the importance of DCs in some disease states is also being revealed. The most promising clinical use of DCs appears to be cancer immunotherapy. Even in its earliest phases, DC vaccination has demonstrated antitumor activity in patients with advanced cancer.

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