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Dendritic Cells at the Oral Mucosal Interface

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Abstract

The mucosal lining of the respiratory and digestive systems contains the largest and most complex immune system in the body, but surprisingly little is known of the immune system that serves the oral mucosa. This review focuses on dendritic cells, particularly powerful arbiters of immunity, in response to antigens of microbial or tumor origin, but also of tolerance to self-antigens and commensal microbes. Although first discovered in 1868, the epidermal dendritic Langerhans cells remained enigmatic for over a century, until they were identified as the most peripheral outpost of the immune system. Investigators' ability to isolate, enrich, and culture dendritic cells has led to an explosion in the field. Presented herein is a review of dendritic cell history, ontogeny, function, and phenotype, and the role of different dendritic cell subsets in the oral mucosa and its diseases. Particular emphasis is placed on the mechanisms of recognition and capture of microbes by dendritic cells. Also emphasized is how dendritic cells may regulate immunity/tolerance in response to oral microbes.

Keywords

dendritic cells; oral mucosa; periodontitis; *Porphyromonas gingivalis*; cytokines; T-cells

INTRODUCTION: ORAL MUCOSA, THE MOST PROXIMAL EXTENT OF THE MUCOSAL IMMUNE SYSTEM

The enormous complexity of the immune system that lines the gastrointestinal tract is likely a reflection of the diversity of the biomass of microbes that pass through and/or colonize it (Mowat, 2003). The mucosal immune system must recognize and eliminate pathogens, while tolerating harmless commensals. This ability to discriminate friend from foe is without question the most important property of the immune system and essential for maintaining immune homeostasis. The consequence of the loss of tight regulation of immune responses is exemplified by Crohn's disease (Baumgart *et al.*, 2005) and celiac disease (James, 2005) of the small intestine. Similarly, hyperresponsiveness to antigens and allergens in the respiratory tract leads to asthma and allergic rhinitis (Upham and Stumbles, 2003). The mucosal immune response in the mouth, "gateway to the gut" (Pennisi, 2005), is the primary focus of our basic and clinical investigations. Chronic adult periodontitis, a disease of the supporting tissues of the dentition, may also result from a loss of regulation of immune responses to oral microbial flora (Jotwani *et al.*, 2001). The oral microbial flora contains > 500 taxa of oral bacteria, ~ 60% of which are cultivable (Kroes *et al.*, 1999; Paster *et al.*, 2001), and consists of both pathogenic and commensal species (reviewed in Ezzo and Cutler, 2003). We presently understand very

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little about how the oral mucosa regulates itself in the context of this bacterial burden, although one intriguing possibility is that the cellular immune response becomes tolerated at the local level by repeated exposure to bacterial endotoxin (*i.e.*, endotoxin tolerance [Muthukuru and Cutler, 2006], discussed below). Recent studies have highlighted mucosal dendritic cells as important arbiters of mucosal immune responses (Williamson *et al.*, 2002; Upham and Stumbles, 2003; Mowat, 2005). The present review will focus on oral mucosal dendritic cells in an ambitious attempt to delineate the mechanisms involved in immune responses and in tolerance at the oral mucosa. A brief historical perspective on epidermal dendritic cells (*i.e.*, Langerhans cells) will be followed by consideration of recent advances in dendritic cell identification, isolation, enrichment, ontogeny, and phenotypic/functional characterization. The human studies relating to dendritic cells in oral mucosa and its diseases will be briefly described, followed by a summary of how dendritic cells recognize and capture microbes (or are infected by them), and where they “traffic” to induce immunity or tolerance. This will be followed by a brief synopsis of regulatory dendritic cells and mucosal tolerance. We will summarize with our perception of the major gaps in understanding of the role of dendritic cells at the oral mucosal interface.

DENDRITIC CELLS: HISTORICAL PERSPECTIVE AND THE DEVELOPMENT OF DENDRITIC CELL ENRICHMENT METHODS

Paul Langerhans, while still a medical student, described a new epidermal cell in a paper entitled, “On the nerves of the human skin” (Langerhans, 1868). The cells were labeled with gold chloride and observed through a primitive light microscope (Jolles, 2002). The identity and function of these cells were enigmatic for over a century until 1973, when Inga Silberberg described Langerhans cells in contact dermatitis as “the most peripheral outpost of the immune system” (Silberberg, 1973). Langerhans cells are now known to be a subpopulation of epithelial-tissue-specific dendritic cells, recruited as chemokine receptor 6+ (CCR6+) precursors to skin and mucosa by the CC-ligand CCL20/MIP-3 α (macrophage inhibitory protein-1 α , also known as CC-chemokine ligand-20). TGF- β is also a key mediator of Langerhans cell biology and is essential for migration of Langerhans cells into skin (and for induction and maintenance of immunological tolerance) (Radeke *et al.*, 2005).

The term ‘dendritic cell’, which now refers to a family of antigen-presenting cells, including Langerhans cells, was coined in 1973 by Ralph Steinman and Zanvil Cohn, in a description of an adherent nucleated cell from the mouse spleen (Steinman and Cohn, 1973). A series of papers by the same group described the distribution, functional properties, isolation, and *in vitro* culture of mouse dendritic cells (Steinman and Cohn, 1974; Steinman *et al.*, 1974, 1975). Steinman’s group isolated dendritic cells to a high level of purity (Steinman *et al.*, 1979) and demonstrated their unique capacity to initiate T-cell immune responses (Steinman and Witmer, 1978). Dendritic cell research was still limited by the low numbers of dendritic cells, relative to other immune cells, making up only 1% of total nucleated cells in the mouse spleen (Steinman and Cohn, 1974), 0.1–1% in human blood mononuclear cells (Freudenthal and Steinman, 1990), 0.4% of human skin (Peiser *et al.*, 2003), and 0.1–2% of human gingiva (unpublished data from our laboratory).

In the 1990s, methods were developed to enrich dendritic cells in large numbers. The sources for dendritic cell enrichment include mouse spleen (Crowley *et al.*, 1990), human cord blood CD34+ progenitors (Caux *et al.*, 1996, 1997), and peripheral blood precursors (Freudenthal and Steinman, 1990; Thomas *et al.*, 1993; Sallusto and Lanzavecchia, 1994). Specific cytokine cocktails—including those containing the FLT-3 ligand (a hematopoietic growth factor that induces dendritic cell expansion *in vivo*) (Marakovsky *et al.*, 1996; Pulendran *et al.*, 1997), granulocyte-monocyte colony-stimulating factor, and granulocyte colony-stimulating factor (Pulendran *et al.*, 1999; Daro *et al.*, 2000)—were shown to expand specific dendritic cell

subpopulations *in vitro*. Long-term growth-factor-dependent dendritic cell lines, referred to as D1 cells, were also developed from fetal mouse spleen and have the advantages of proliferative behavior and homogeneity (Winzler *et al.*, 1997). These technologies resulted in an explosion in the field of dendritic cell immunobiology. The powerful antigen-presenting capacity of dendritic cells has led to their use in clinical trials to overcome tumor tolerance and induce anti-tumor immunity when loaded with tumor antigens (Sheng *et al.*, 2005); however, regulatory dendritic cells are also being harnessed for their ability to down-regulate the immune response to allografts (Schlichting *et al.*, 2005) and to treat autoimmune diseases, including colitis, asthma, psoriasis, and other atopic diseases (reviewed in Akbari and Umetsu, 2005).

DENDRITIC CELL ONTOGENY: DISTINCT OR COMMON PRECURSORS?

At the heart of dendritic cell biology is whether dendritic cell subsets (Table 1) are developmentally autonomous or share a common ancestry and then differentiate in response to different environmental stimuli (Zuniga *et al.*, 2004). Early study of dendritic cell ontogeny in the rat (Klinkert, 1984; Bowers and Berkowitz, 1986), the mouse (Steinman and Cohn, 1973), and humans (Caux *et al.*, 1992) favored the presence of developmentally distinct lines of progenitor cells, myeloid and lymphoid, which can differentiate into distinct dendritic cell subsets with distinct functions (reviewed in Makala and Nagasawa, 2002). According to this specialized lineage paradigm (reviewed in Shortman and Liu, 2002), lymphoid progenitors give rise to precursors that differentiate into thymic dendritic cells (Steinman and Cohn, 1973), into interdigitating dendritic cells (*i.e.*, in T-cell-rich areas of secondary lymphoid organs) (Witmer and Steinman, 1984), and into the more recently discovered plasmacytoid dendritic cells (Grouard *et al.*, 1997). Myeloid progenitors give rise to monocyte/macrophage precursors (Romani *et al.*, 1994; Bender *et al.*, 1996), to a precursor that gives rise to Langerhans cells (Caux *et al.*, 1992), interstitial (dermal) dendritic cells (Lu *et al.*, 1995), as well as to a precursor that may yield germinal center dendritic cells (Strobl *et al.*, 1998) and peripheral blood dendritic cells (Romani *et al.*, 1994).

It is now clearer that while a degree of dendritic cell sublineage commitment does occur, the functional plasticity model is more accurate (reviewed in Shortman and Liu, 2002); that is, under specific environmental conditions, common precursors can give rise to multiple dendritic cell subtypes. For example, purified murine CD11c⁺ major histocompatibility complex class II⁺ (MHC II⁺) blood cells can differentiate into multiple dendritic cell subpopulations in the spleen, including CD8α⁺ dendritic cells, CD8α⁻ dendritic cells, and B220⁺ plasmacytoid dendritic cells, which produce interferon in response to viral infection (del Hoyo *et al.*, 2002). More recently, bone marrow plasmacytoid dendritic cells have been shown to differentiate into myeloid dendritic cells upon virus infection (Zuniga *et al.*, 2004). Interestingly, human monocyte-derived dendritic cells can transdifferentiate into functional osteoclasts in the presence of inflammatory factors monocyte/macrophage colony-stimulating factor and receptor activator of nuclear factor-κB ligand (RANK-L) (Rivollier *et al.*, 2004). This is of particular relevance to diseases involving bone, such as rheumatoid arthritis and periodontitis (Teng, 2003).

HUMAN DENDRITIC CELL SUBSETS

Dendritic cells are distinguished by phenotypic markers, anatomic location (Table 1), and distinct, though overlapping, functions. As a group, dendritic cells all lack the lineage-specific markers CD3, CD14, CD19, CD11b, CD56, and express, in common, high levels of major histocompatibility complex class II molecules; thus, the phenotypic definition of dendritic cells as lineage-HLA-DR⁺ cells has become widespread (MacDonald *et al.*, 2002). With the caveat of ontological flexibility, mentioned above, dendritic cells are currently accepted as comprising 3 distinct subpopulations, including two within the myeloid lineage (Langerhans cells and

dendritic cells) and one within the lymphoid lineage (plasmacytoid dendritic cells). At least 6 subpopulations of mouse dendritic cell have been described and are reviewed elsewhere (Ardavin, 2003). Note that follicular dendritic cells, restricted to primary B-cell follicles and distinct phenotypically and functionally from T-cell priming dendritic cells (Kosco-Vilbois, 2001), are not shown in Table 1.

Functionally, monocytic precursors of myeloid dendritic cells tend to favor a Th1-type response, and hence were called 'dendritic cell 1'. The flexibility of the Th-response induced by dendritic cells, however, is evidenced by studies *in vivo* (Pulendran *et al.*, 2001) and *in vitro* (Jotwani *et al.*, 2003), showing that myeloid dendritic cells can polarize effector responses toward Th1 or Th2, depending on the type of endotoxin or lipopolysaccharide used as a stimulant. Precursors of plasmacytoid dendritic cells tend to favor a Th2 response, and thus were called 'plasmacytoid dendritic cells-2' (Rissoan *et al.*, 1999). Plasmacytoid dendritic cells-2, activated in the presence of IL-3 and CD40 ligand, undergo maturation into dendritic cells-2, characterized by high expression levels of major histocompatibility complex products and co-stimulatory molecules, and a tendency to induce Th2 effector responses (Grouard *et al.*, 1997). In the case of myeloid dendritic cells, their ability to suppress the immune response, *i.e.*, serve as regulatory dendritic cells, is dependent largely on remaining immature (Jonuleit *et al.*, 2000). New evidence links inflammatory bowel disease (Baumgart *et al.*, 2005) with increases in circulating levels of *mature* myeloid dendritic cells, which have been proposed to break tolerance to gut commensals. In contrast to myeloid dendritic cells, plasmacytoid dendritic cells, when matured under certain conditions (*i.e.*, by CD40 ligand), can still drive T-regulatory cell differentiation (Gilliet and Liu, 2002).

Human blood dendritic cells, while typically divided into CD11c+ myeloid dendritic cells and CD123+ plasmacytoid dendritic cells, actually consist of at least 5 non-overlapping subsets based on expression of CD123, CD1b/c, CD16, blood dendritic cells A-3, and CD34 (MacDonald *et al.*, 2002), all with distinct phenotypes and allostimulatory capacity. Notably, blood dendritic cells are distinguished from tissue dendritic cells and macrophages by a general lack of most of the C-type lectin receptors (Serrano-Gomez *et al.*, 2004). The important functions of the C-type lectin receptors in antigen-capture and their potential exploitation by invasive pathogens will be addressed in detail below.

***In situ* STUDIES OF LANGERHANS CELLS/DENDRITIC CELLS IN ORAL MUCOSA AND ITS DISEASES**

Langerhans cells are not evident in the epithelium by routine hematoxylin/eosin staining, presumably leading to their being overlooked in very early histopathological specimens from the oral cavity. However, the availability of biochemical markers such as ATPase and 5'-nucleotidase facilitated the identification of Langerhans cells in oral mucosa prior to the development of specific immunochemical markers. These early studies revealed the remarkable ability of Langerhans cells to traffic in and out of oral human mucosal grafts transplanted onto nude (immunodeficient) mice (Dabelsteen and Kirkeby, 1981). More recent human studies have identified Langerhans cells with the use of the T6 antigen, HLA-DR, in gingival organ culture (Walsh *et al.*, 1986a, 1987) and gingival and buccal mucosa (Walsh *et al.*, 1986b). The lipid antigen-presenting molecule CD1a has been increasingly used to identify Langerhans cells and immature dendritic cells in human tissues (van Loon *et al.*, 1989; Moughal *et al.*, 1992; Lundqvist and Hammarström, 1993; Sohoel *et al.*, 1995; Hussain and Lehner, 1995; Gunhan *et al.*, 1996; Winning *et al.*, 1996; Ito *et al.*, 1998; Cutler *et al.*, 1999; Myint *et al.*, 2000; Segulier *et al.*, 2000a,b; Cirrincione *et al.*, 2002; Gemmell *et al.*, 2002; Mori *et al.*, 2003). In general, the following can be surmised from studies of Langerhans cells/immature dendritic cells in human oral mucosa/gingiva:

1. The highest Langerhans cells numbers are found in non-keratinized mucosa of the soft palate, ventral tongue, lip, and vestibule, while the lowest counts are found in keratinized mucosa of the hard palate and gingiva (Daniels, 1984);
2. Langerhans cells in the gingival epithelium are very responsive to the accumulation of bacterial plaque (*i.e.*, the biofilm), migrating into the site during early gingivitis (Newcomb *et al.*, 1982; Walsh *et al.*, 1986b), and migrating out as the gingivitis becomes more chronic (*i.e.*, after 21 days) (Moughal *et al.*, 1992);
3. Oral mucosal Langerhans cells are also responsive to nickel in patients with nickel allergies (van Loon *et al.*, 1988), to oral *Candida* sp. (Daniels *et al.*, 1985; Romagnoli *et al.*, 1997), oral lichen planus (Bondad-Palmario, 1995; Walton *et al.*, 1998; Hasseus *et al.*, 2001; Villarroel *et al.*, 2002; Santoro *et al.*, 2005), lichenoid drug eruptions (McCartan and Lamey, 1997), rhomboid median glossitis (Walsh *et al.*, 1992), Verruciform xanthoma (Mostafa *et al.*, 1993), HIV infection (Sporri *et al.*, 1994), oral squamous cell carcinoma (Wang *et al.*, 2004), oral skin grafts (Katou *et al.*, 2000), and hairy leukoplakia of the tongue (Walling *et al.*, 2004);
4. Oral mucosal Langerhans cells appear properly oriented to sample the oral fluids and bacteria, with their dendrites toward the surface (Ito *et al.*, 1998);
5. Oral mucosal bacteria (*e.g.*, *Porphyromonas gingivalis* [Cutler *et al.*, 1999]) and viruses (*e.g.*, HIV [Chou *et al.*, 2000]) gain access to Langerhans cells *in situ*;
6. Langerhans cells from oral mucosa co-express activation/maturation markers (Allam *et al.*, 2003) and contribute to the mature CD83+ dendritic cell pool in the lamina propria during chronic adult periodontitis *in situ* (Jotwani and Cutler, 2003); B-cells also contribute to the CD83+ pool in the lamina propria (Mahanonda *et al.*, 2002);
7. Langerhans cells isolated *ex vivo* induce a stronger allogeneic mixed-lymphocyte reaction response than do Langerhans cells from normal skin (Table 2) (Hasseus *et al.*, 1999,2004); and
8. Langerhans cells lie close to epithelial $\gamma\delta$ T-cell receptors in health (Lundqvist and Hammarström, 1993), but in disease (chronic adult periodontitis) come close to lamina propria CD4+ T-cells (Jotwani and Cutler, 2003).

More recently, dermal and plasmacytoid dendritic cells have been identified in oral mucosa with the use of subset-specific antibodies. In general:

1. Lysosome-bearing (Cutler and Jotwani, 2004) dermal dendritic cells increasingly infiltrate the lamina propria of oral mucosa/gingiva during oral bacterial infections, such as chronic adult periodontitis (Jotwani *et al.*, 2004), and decrease after treatment of chronic adult periodontitis (Dereka *et al.*, 2004);
2. Dermal dendritic cells also infiltrate the lamina propria increasingly in oral lichen planus (Regezi *et al.*, 1994; Santoro *et al.*, 2005), recurrent aphthous ulcers (Natah *et al.*, 1997), and oral fibrovascular lesions (Regezi *et al.*, 1992); and
3. Dermal dendritic cells contribute to the CD83+ mature dendritic cell pool in the lamina propria of chronic adult periodontitis (Jotwani *et al.*, 2001; Jotwani and Cutler, 2003); moreover, these mature CD83+ dendritic cells form immune conjugates with CD4+ T-cells in the oral lymphoid foci (Fig) (Jotwani and Cutler, 2003). The least is known about plasmacytoid dendritic cells in oral mucosa, though recent studies have indicated that plasmacytoid dendritic cells infiltrate the epithelium and lamina propria of oral lichen planus (Santoro *et al.*, 2005) and express Toll-like receptors for viral antigens (Liu, 2005).

***In vitro* STUDIES OF DENDRITIC CELLS AND ORAL BACTERIA**

In vitro studies of dendritic cells with oral mucosal microbes are sparse. Dendritic cells from the mouse (Pulendran *et al.*, 2001) and humans (Jotwani *et al.*, 2001, 2003; Aroonrerk *et al.*, 2003; Cohen *et al.*, 2004; Jotwani and Cutler, 2004; Kanaya *et al.*, 2004) have been used to begin to look at how dendritic cells interact with oral microbes and agonists implicated in chronic adult periodontitis. Analysis of our data (Jotwani and Cutler, 2004) shows that entry of the oral pathogen *P. gingivalis* into monocyte-derived dendritic cell *in vitro*, leading to suboptimal maturation of monocyte-derived dendritic cells, requires that *P. gingivalis* expresses the major fimbriae (FimA), a bacterial adhesin required for virulence and induction of periodontitis by this species (Evans *et al.*, 1992). *P. gingivalis* also expresses a unique immunosuppressive lipopolysaccharide (Pulendran *et al.*, 2001; Jotwani *et al.*, 2003; Cohen *et al.*, 2004) and proteolytic enzymes, the gingipains (Potempa *et al.*, 2003). Efforts from our group have shown that the lipopolysaccharide of *P. gingivalis*, relative to that of *E. coli*, stimulates dendritic cells to secrete IL-10, but not IL-12, *in vitro* (Jotwani *et al.*, 2003) and *in vivo* (Pulendran *et al.*, 2001). Combined with weak dendritic cell maturation by *P. gingivalis* lipopolysaccharide, this leads to the induction of a Th2-effector response. The unique activity of *P. gingivalis* lipopolysaccharide has been attributed, in part, to its selective activation of the PI3K-Akt pathway *via* Toll-like receptor 2 (Martin *et al.*, 2003). *P. gingivalis* lipopolysaccharide has also been shown to inhibit p38 phosphorylation and MAP kinase activation (in endothelial cells) by other lipopolysaccharide moieties (reviewed in Bainbridge and Darveau, 2001), and to stimulate expression of the toleragenic markers ILT-3 and B7-H1 by dendritic cells (Cohen *et al.*, 2004). Probiotic bacteria (*e.g.*, Lactobacilli), beneficial in the treatment of ulcerative colitis, induce a dendritic cell phenotypic change similar to that of *P. gingivalis* lipopolysaccharide (Hart *et al.*, 2004). Based on blocking antibody studies and the use of stably transfected dendritic-cell-specific ICAM-3-grabbing non-integrin-positive cell lines, our new unpublished data (not shown), gathered from the use of whole live bacteria, suggest that *P. gingivalis* may target C-type lectin receptors (*e.g.*, dendritic-cell-specific ICAM-3-grabbing non-integrins) on dendritic cells for entry, and, possibly, for blunting of dendritic cell maturation, although the contributions of its fimbriae and its lipopolysaccharide in this regard have not yet been unraveled. The lipopolysaccharides of *H. pylori* NCTC 11637 and of certain strains of *K. pneumonia* contain Le^X and mannose, respectively, that preferentially bind to dendritic-cell-specific ICAM-3-grabbing non-integrins, instead of Toll-like receptors, thus blunting dendritic cell activation/maturation (Appelmek *et al.*, 2003). Interestingly, mannose is a major component sugar of *P. gingivalis* lipopolysaccharide (Koga *et al.*, 1985), constituting 9–12% of sugars (Bramanti *et al.*, 1989). Fucose, a sugar with particularly high affinity for dendritic-cell-specific ICAM-3-grabbing non-integrins (Appelmek *et al.*, 2003), has been specifically shown to block the binding of *P. gingivalis* fimbriae (*i.e.*, to human lactoferrin) (Sojar *et al.*, 1998). Bacterial species that target C-type lectin receptors (discussed in detail below) are unique in their ability to survive in the host and induce chronic life-long infection.

The potential role of dendritic cells in aggressive periodontitis (formerly localized juvenile periodontitis) has also been analyzed *in vitro* (Barbour *et al.*, 2002; Al-Darmaki *et al.*, 2003, 2004; Kikuchi *et al.*, 2004). *Actinobacillus actinomycetemcomitans*, an etiological agent in localized aggressive periodontitis (a more acute form of periodontitis), appears to activate/mature dendritic cells and induce a Th1-response (Kikuchi *et al.*, 2004). *In vitro* modeling has led to the hypothesis of a novel mechanism for how dendritic cells may promote elevated IgG2 responses observed in patients with localized aggressive periodontitis: Platelet-activating factor, which was accumulated more efficiently by dendritic cells than macrophages (Al-Darmaki *et al.*, 2003), promotes Th1-responses, required for optimal IgG2 production (Al-Darmaki *et al.*, 2004).

RECEPTORS ON DENDRITIC CELL/LANGERHANS CELLS FOR RECOGNITION OF MICROBES, ACTIVATION OF MATURATION

To provide immediate protection against invading pathogens, dendritic cells and other antigen-presenting cells must quickly respond to bacterial structures (*e.g.*, lipopolysaccharide, peptidoglycan), called pathogen-associated molecular patterns (reviewed in Geijtenbeek *et al.*, 2004; Netea *et al.*, 2004). This is accomplished through a major class of signaling receptors called Toll-like receptors (Underhill and Ozinsky, 2002; Kopp and Medzhitov, 2003). The specificity of Toll-like receptor recognition for several important pathogen-associated molecular patterns has been identified, including: recognition of peptidoglycan, bacterial lipoproteins, and zymosan by Toll-like receptor 2; double-stranded RNA by Toll-like receptor 3; most lipopolysaccharide and heat-shock proteins by Toll-like receptor 4; flagellin by Toll-like receptor 5; and CpG (DNA strands of cytosine, purine, and guanine) motifs of bacterial DNA by Toll-like receptor 9 (Akira and Hemmi, 2003). Many studies have reported additional microbial ligands for Toll-like receptors, as summarized in other reviews (Akira and Hemmi, 2003; Takeda *et al.*, 2003). In addition, an increasing number of reports suggest that endogenous ligands—such as heat-shock proteins, fibronectin, and hyaluronic acid oligosaccharides—are also recognized by Toll-like receptors and may be involved in autoimmune processes (Beg, 2002).

There is a marked difference in the patterns of Toll-like receptors on myeloid and plasmacytoid dendritic cells that mediates distinctive responsiveness to viral and bacterial structures. Classic myeloid CD11c⁺ dendritic cells are highly responsive to bacterial structures, for which they express Toll-like receptors 1, 2, 4, 5, and 6, but they also respond to double-stranded RNA viruses, poly-I:C (Toll-like receptor 3), and single-stranded RNA viruses (Toll-like receptors 7, 8) (Jarrossay *et al.*, 2001; Kadowaki *et al.*, 2001). In contrast, CD123⁺ plasmacytoid dendritic cells do not express Toll-like receptors 2 and 4 and are thus relatively unresponsive to bacterial structures, but do express Toll-like receptors 7 and 9 and so respond strongly to single-stranded RNA viruses and herpes viruses, respectively. Plasmacytoid dendritic cells respond to viruses by secreting massive amounts of type 1 interferons (α , β) (Ito *et al.*, 2005), which are potent antiviral immunoregulators. It is important to emphasize that some Toll-like receptors, *e.g.*, Toll-like receptors 9 (Datta *et al.*, 2003) and 7 (Beignon *et al.*, 2005), function inside the dendritic cell. Thus, the ability of dendritic cells to internalize certain foreign antigens is an important step in the activation of innate and adaptive immune responses.

Immature dendritic cells are particularly well-equipped to capture antigens through phagocytosis, pinocytosis, and endocytosis *via* different groups of receptor families, such as: (i) Fc receptors for antigen-antibody complexes; (ii) scavenger receptors for bacteria, effete components, such as modified host molecules (*e.g.*, low-density lipoproteins), and apoptotic cells (reviewed in Peiser *et al.*, 2002); and (iii) C-type lectin receptors for glycoproteins.

C-TYPE LECTIN RECEPTORS CAPTURE MICROBES, CROSS-TALK WITH TOLL-LIKE RECEPTORS, AND ARE TARGETED BY PATHOGENS

Depending on their tissue localization and differentiation state, dendritic cells, Langerhans cells, and certain tissue macrophages are specialized to capture specific micro-organisms by the expression of distinct sets of C-type lectin receptors (reviewed in van Kooyk and Geijtenbeek, 2003; van Kooyk *et al.*, 2004). Studies from our laboratory have shown increased expression of C-type lectin receptors in human gingiva, including Langerin (CD207), mannose receptors (CD206), and dendritic-cell-specific ICAM-3-grabbing non-integrins (CD209), with Langerin decreasing in the gingival epithelium in chronic adult periodontitis, while mannose receptors and dendritic-cell-specific ICAM-3-grabbing non-integrins increase in the lamina

propria in chronic adult periodontitis (Jotwani and Cutler, 2003; Jotwani *et al.*, 2004). The C-type lectin receptors consist of types I and II transmembrane receptors, which serve a function very different from that of the Toll-like receptors. C-type lectin receptors function primarily to interact with conserved carbohydrates shared by a large group of micro-organisms, and internalize these pathogens for processing and antigen-presentation. Accordingly, C-type lectin receptors contain carbohydrate recognition domains for binding to sugars (*e.g.*, mannose, fucose, galactose, and β -glucans) and glycosylated proteins. Moreover, while Toll-like receptors rapidly transmit information about the pathogen (*i.e.*, pathogen-associated molecular patterns) through Toll-Interleukin 1 receptor activation domains, culminating in nuclear import of NF- κ B and transcription of co-stimulatory molecules and pro-inflammatory cytokines (*e.g.*, IL-1 β , IL-12, IFN- γ) (Janeway and Medzhitov, 2002; Underhill and Ozinsky, 2002; van Kooyk *et al.*, 2004), C-type lectin receptors appear to lack these activation domains, and thus do not generally lead to dendritic cell maturation and cytokine secretion (van Kooyk and Geijtenbeek, 2003; van Kooyk *et al.*, 2004). The C-type lectin receptor Dectin-1 (Brown *et al.*, 2003; Gantner *et al.*, 2003), however, appears to cooperate with Toll-like receptor 2 in responding to its natural ligand β -glucan (*i.e.*, yeast). Mannose receptor (CD206) functions in an antagonistic fashion to the Toll-like receptor, responding to mannosylated lipoarabinomannans (Nigou *et al.*, 2001) by activating an anti-inflammatory immunosuppressive program (Chieppa *et al.*, 2003) and may induce T-regulatory cells (van Kooyk *et al.*, 2004). These antagonistic activities may be mediated by immunoreceptor tyrosine-based activation motifs or immunoreceptor tyrosine-based inhibitory motifs, respectively (Figdor *et al.*, 2002). Thus, although Toll-like receptors and C-type lectin receptors recognize different determinants and have distinct functions, there may be cross-talk between the two; moreover, the balance of Toll-like receptor/C-type lectin receptor triggering (Fig.) may influence the outcome of the immune response (van Kooyk *et al.*, 2004). The physiological function of C-type lectin receptors may be to recognize glycosylated self-antigens for the induction of immune tolerance (Geijtenbeek *et al.*, 2004).

It is becoming evident that some pathogens subvert the immune response by specifically targeting C-type lectin receptors, particularly dendritic-cell-specific ICAM-3-grabbing non-integrins and mannose receptors. This benefits the pathogen by down-regulating intracellular signaling in dendritic cells, inhibiting maturation and cytokine secretion, activities that are necessary for effective adaptive immunity. Such pathogens include HIV-1, *Mycobacteria tuberculosis*, *Helicobacter pylori*, *Klebsiella pneumonia*, *Candida albicans*, and *Schistosoma mansoni* (reviewed in van Kooyk and Geijtenbeek, 2003). The central feature of pathogens that interact with dendritic-cell-specific ICAM-3-grabbing non-integrins is that they cause chronic infections that last a lifetime, and they manipulate Th1/Th2 balance, to persist at the disease site (van Kooyk and Geijtenbeek, 2003). Notably, high expression of dendritic-cell-specific ICAM-3-grabbing non-integrins, as we have observed in chronic adult periodontitis (Jotwani and Cutler, 2003; Jotwani *et al.*, 2004), is dependent on Th2-type cytokines, linking high expression of dendritic-cell-specific ICAM-3-grabbing non-integrins by dendritic cells to Th2 polarization (Relloso *et al.*, 2002), as induced by *P. gingivalis* lipopolysaccharides (Pulendran *et al.*, 2001; Jotwani *et al.*, 2003).

IMMUNE INDUCTIVE AND EFFECTOR SITES: GUT-ASSOCIATED LYMPHOID TISSUE AND ORAL LYMPHOID FOCI

After capturing foreign antigens, dendritic cells migrate to immune inductive sites and initiate the adaptive immune response, but can also re-stimulate a local response in peripheral tissues, *i.e.*, effector sites. In the case of the oral mucosa, very little is known about these inductive and effector sites. Much better-characterized is the gut-associated lymphoid tissue, in which inductive sites include Peyer's patches and mesenteric lymph nodes (reviewed in Mowat, 2003). The predominant gut-associated lymphoid tissue effector site is the villus lamina

propria, covered by a single layer of epithelium containing intra-epithelial lymphocytes, lamina propria lymphocytes, and dendritic cells (Spahn *et al.*, 2001). Orally administered antigens in the gut lumen pass through M-cells (epithelial cells specialized for sampling viruses and bacteria) and are taken up and processed by Peyer's patches' dendritic cells (Liu and MacPherson, 1995), or are directly sampled by dendritic cells in the villus lamina propria (Rescigno *et al.*, 2001; Niess *et al.*, 2005).

The prototypical oral inductive sites, contained within Waldeyer's ring, consist of oropharyngeal tissues and nasopharyngeal lymphoid tissue (Wu *et al.*, 1997). The latter include palatine tonsils, nasopharyngeal tonsils (adenoids), and lingual tonsils (Fujimura *et al.*, 2004). In humans, the M-cells of nasopharyngeal lymphoid tissue are ultrastructurally and functionally similar to those in Peyer's patches and colonic lymphoid follicles (Fujimura, 2000). Nasal administration of antigens (Fujimura *et al.*, 2004) is being explored to stimulate mucosal immune responses. Oral mucosa also appears capable of inducing tolerance to mucosally delivered antigens. Contact hypersensitivity responses to nickel in humans are blunted by previous oral contact with nickel-containing dental braces (Van Hoogstraten *et al.*, 1991). Moreover, in mouse and guinea pig models, oral mucosal application of antigens leads to specific and strong induction of tolerance upon systemic sensitization (Van Hoogstraten *et al.*, 1992, 1993). Sublingual immunotherapy (*i.e.*, under the tongue) was the preferred site of administration of allergen extracts in several controlled clinical trials aimed to suppress responses in atopic dermatitis, asthma, and eczema (Pajno *et al.*, 2003). Not clear in these studies is the actual mechanism of induction of oral mucosal tolerance, or, for that matter, the cells responsible for the induction of tolerance responses (Van Wilsem *et al.*, 1994).

The lymph nodes that drain mucosa are also worth repeating in this context, since they appear to play a critical role in the induction of immunity and tolerance. Mesenteric lymph nodes are essential for tolerance to orally administered antigens, while Peyer's patches can be removed surgically (Enders *et al.*, 1986) or knocked-out genetically (Spahn *et al.*, 2002) without abrogating immunity or tolerance (reviewed in Mowat *et al.*, 2004). Murine studies suggest that buccal mucosa dendritic cells capture antigen and migrate to cervico-mandibular lymph nodes, where antigen is presented (Eriksson *et al.*, 1996). However, the identity of the dendritic cell subsets that participate in oral mucosa immune responses or migrate in the steady-state to cervico-mandibular lymph nodes is not clear.

Analysis of our published data suggests that oral lymphoid foci in interdental papilla may represent effector sites for local immune responses (Fig.). This is based on double-immunofluorescence analysis showing the organizational structure of lymphoid and myeloid elements, with lamina propria dendritic cells engaged with large numbers of CD4+ T-cells, which include CD45RA+ and CD45RO+ subsets (Jotwani *et al.*, 2001, 2003). Oral lymphoid foci are evocative of the gut-associated lymphoid tissue villus lamina propria, with the major difference being the thickness of the oral mucosal epithelium, and keratinization of the gingiva (although the pocket epithelium is not keratinized). CD1a+ Langerhans cells infiltrate the oral/gingival epithelium, while large numbers of dendritic-cell-specific ICAM-3-grabbing non-integrin-positive dermal dendritic cells infiltrate the gingival lamina propria, particularly in chronic periodontitis. Both Langerhans cells and dermal dendritic cells appear to contribute to the pool of maturing CD83+ dendritic cells in the lamina propria (Jotwani and Cutler, 2003). Perhaps the closest equivalent to oral lymphoid foci are isolated lymphoid follicles, identified in the murine small intestine (Hamada *et al.*, 2002). However, the presence of germinal centers, seen in lymphoid follicles or inductive sites (Newberry and Lorenz, 2005), has not yet been identified in oral lymphoid foci.

REGULATORY DENDRITIC CELLS, MUCOSAL TOLERANCE, AND *P. gingivalis*

Regulatory or toleragenic dendritic cells can induce immune tolerance at Peyer's patches, mesenteric lymph nodes, and the lung, through their ability to stimulate functional CD25⁺ and CD25⁺ mucosal T-regulatory cells (Stumbles *et al.*, 1998; Alpan *et al.*, 2001; Hauet-Broere *et al.*, 2003; Akbari and Umetsu, 2005). Myeloid dendritic cells are toleragenic in the peripheral tissues and lymph nodes when they present self-antigen in the steady state, *i.e.*, in the immature state, in the absence of acute infection and inflammation. In the presence of bacterial infection or injury, however, myeloid dendritic cells migrate and mature, expressing co-stimulatory molecules necessary for immune activation (Steinman and Nussenzweig, 2002). Interestingly, plasmacytoid dendritic cells can drive T-regulatory cell differentiation even when matured by CD40 ligand (Gilliet and Liu, 2002). In addition, mucosa of the intestine and lung have a specialized conditioning effect on dendritic cells, polarizing their maturation toward a regulatory or toleragenic phenotype against non-self-antigens, such as commensal bacteria (Mowat *et al.*, 2004). The immunomodulators IL-10, TGF- β , and PGE₂ are particularly important in this regard. Our lab is particularly interested in the immunoregulatory role of IL-10, based on several lines of evidence: (i) IL-10 can induce differentiation of both human and mouse CD4⁺ T-cells into T-regulatory 1 (Tr1) cells (Groux *et al.*, 1997); (ii) CD25⁺ T-regulatory cells have recently been observed to increase in the oral mucosa in chronic adult periodontitis (Nakajima *et al.*, 2005); (iii) certain bacterial pathogens-such as the upper respiratory tract pathogen *Bordetella pertussis* (McGuirk *et al.*, 2002) and lipopolysaccharide of *P. gingivalis* (Pulendran *et al.*, 2001; Jotwani *et al.*, 2003)-evade T-helper responses by stimulating IL-10; (iv) IL-10-producing T-cells infiltrate gingival mucosa in chronic periodontitis (Gemmell and Seymour, 1998); (v) high levels of IL-10 are present in mucosal transudates (*i.e.*, crevicular fluid) of experimental gingival inflammation (Cutler *et al.*, 2000); and (vi) IL-10 is relatively resistant to reduction by repeated stimulation with lipopolysaccharide, *i.e.*, endotoxin tolerance, but not so the pro-inflammatory cytokines (Muthukuru *et al.*, 2005). *In vitro*, monocytes/macrophages tolerated by *P. gingivalis* or *E. coli* lipopolysaccharide down-regulate NF- κ B-mediated pro-inflammatory cytokines/co-stimulatory molecules and stimulate a very weak allogeneic mixed-lymphocyte reaction response (Muthukuru and Cutler, 2006). Interestingly, Toll-like receptor mRNA is down-regulated in chronic adult periodontitis tissues (Muthukuru *et al.*, 2005), and the immunoregulatory molecule SH2-containing inositol phosphatase, an inhibitor of NF- κ B signaling (Kalesnikoff *et al.*, 2002; Sly *et al.*, 2004), is up-regulated (Muthukuru and Cutler, 2006), suggesting that local induction of endotoxin tolerance is one mechanism for re-establishing oral mucosal immune homeostasis.

SUMMARY

Overall, there has been very little concerted effort to establish the role of the oral mucosa, regardless of nasal lymphoid tissue, as an immunologic organ, particularly whether there exist germinal centers or follicles in oral lymphoid foci, its equivalent in the oral mucosa. Moreover, the role of oral mucosal dendritic cell subpopulations in mediating immunity and tolerance at the local level is presently unclear. Addressing these questions will require highly purified dendritic cell and T-cell populations, as well as the use of animal models and organotypic cell culture models of oral mucosa, to determine: (i) how oral tolerance to commensals/self-antigen or immunity against pathogens is mediated, in the context of the oral mucosal milieu; (ii) how different dendritic cell subsets are able to recognize and respond to bacterial and viral antigens that colonize or infect the oral mucosa; (iii) how micro-environmental factors (*e.g.*, cytokines, growth factors) regulate antigen-presenting cells and T-cell responses; and (iv) the role of locally activated dendritic cells in alveolar bone destruction (*i.e.*, in chronic adult periodontitis),

either by formation of conjugates with RANK-L-expressing CD4⁺ T-cells (Teng *et al.*, 2000; Teng, 2003) or by direct transdifferentiation of dendritic cells into osteoclasts. Addressing these questions is essential to efforts to develop molecular targets for immunotherapy of host diseases that afflict the oral cavity and other sites in the body.

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Figure.

Oral lymphoid foci (OLF): local site for induction of immunity vs. tolerance? Analysis of inter-papillary tissue in chronic adult periodontitis (CAP) reveals an organizational structure that we have termed OLF. OLF consist of: (i) Langerhans cells (LC) and $\gamma\delta$ T-cells in the epithelium, with double-positive maturing CD1a+CD83+ LC just under the basement lamina; (ii) dermal dendritic cells (DDC) and macrophages infiltrate the lamina propria, with double-positive dendritic-cell-specific ICAM-3-grabbing non-integrins (DC-SIGN + CD83 + dermal dendritic cells (DDC) deeper within the lamina propria; (iii) immune conjugates are formed in the lamina propria, consisting of CD83+DC and B-cells and naïve and memory CD4+ T-cells; (iv) plasma cells infiltrate the lamina propria, while polymorphonuclear leukocytes (PMN) migrate through and out of the gingival crevice. Shown is the ability of *P. gingivalis* and its pathogen-associated molecular patterns (PAMPs) (e.g., lipopolysaccharide [LPS], fimbriae [fim]) to invade the gingival/pocket epithelium and gain access to LC. Toll-like receptors (TLRs) and C-type lectin receptors (CTLRs) expressed by DDCs play counter-regulatory roles in responses to bacteria, their PAMPs. TLRs stimulate DC activation, leading to expression of co-stimulatory molecules (CD40, CD80, CD86), maturation (CD83), and secretion of IL-12, TNF α , all of which favor a Th1 effector response. CTLRs function specifically to take up bacteria and self-antigen (Ag), but lack Toll-Interleukin-1R (TIR) activation domains for DC maturation and cytokine secretion, thus favoring a Th2 or regulatory (Treg) response. The cross-talk between TLR and CTLRs is a 'toggle switch' between immunity and tolerance.

Table 1**Human Dendritic Cells in Different Tissues**

Dendritic Cell	Surface Marker Expression
Blood	
Myeloid dendritic cell (DC1)	CD11b, CD11c, CD1a, CD1b, CD1c/BDCA-1, BDCA-3
Plasmacytoid/lymphoid DCs (DC2)	CD123, BDCA-2, BDCA-4, CD45RA
Peripheral tissues	
Langerhans cells (LCs) (in epidermis)	CD1a, HLA-DR, Langerin/Lag, CCR6, E-cadherin, CD62L, DEC-205, Intra MHCII, CLA
Dermal (interstitial) dendritic cells (in lamina propria)	DC-SIGN, factor XIII, MMR, CD11b
Lymphatics	
Veiled cells (in afferent lymph)	CD80, CD83, CD86, CCR7, CD11a, CLA, surface MHCII
Secondary lymphoid organs	
Interdigitating dendritic cells (in dome and inter-follicular region of Peyer's patches)	Dc-LAMP, DEC-205, CD80, CD83, CD86, CCR7, surface MHCII
Germinal center DCs	CD2, CD4, CD11c, CD35, CD45RO, CD64

Shown are the predominant dendritic cells in the tissues/fluids indicated. Compiled from: Banchereau and Steinman (1998), Banchereau *et al.* (2000), Makala and Nagasawa (2002), and Shortman and Liu (2002).

Abbreviations: BDCA, blood dendritic cell antigen; DC-SIGN, dendritic-cell-specific ICAM-3-grabbing non-integrin; CCR7, C-chemokine receptor; CLA, cutaneous lymphocyte antigen; DC-LAMP, dendritic cell-lysosomal-associated membrane protein; intra-MHCII, intracellular type II major histocompatibility complex; MMR, macrophage mannose receptor.

Alternative names for cell markers: CD11a, LFA- α subunit; CD11b, complement receptor (CR) 3; CD11c, complement receptor (CR) 4; CD62L, L-selectin; CD64, Fc- γ receptor I; CD80, B7-1; CD86, B7-2; CD123, IL-3 receptor α ; CD205, DEC-205; Langerin, CD207; MMR, CD206; DC-SIGN, CD209.

Table 2**Further Explanations of Expressions Used in the Text**

Allo-MLR: allogeneic mixed-lymphocyte reaction, involving <i>in vitro</i> culture of antigen-presenting cells with non-major histocompatibility complex-matched lymphocytes to determine proliferation of lymphocytes
Effector sites: anatomic sites, <i>e.g.</i> , peripheral tissues, where antigen-presenting cells induce further stimulation and differentiation of T-, B-cells
Endotoxin tolerance: unresponsiveness of innate immune cells to endotoxin or to TNF- α and IL-1 β induced by repeated exposure to endotoxin (lipopolysaccharide)
Flt-3l (FLT-3 ligand): hematopoietic growth factor that induces dendritic cell expansion <i>in vivo</i>
Inductive sites: anatomic sites, <i>e.g.</i> , secondary lymphoid tissues, where the adaptive immune response is initiated, <i>i.e.</i> , antigen-presenting cells present processed antigen, in the context of major histocompatibility complex, to naïve T-cells for the first time.
Pattern recognition receptors: germ-line encoded receptors (<i>e.g.</i> , Toll-like receptors or TLRs) on immune cells that enable them to recognize highly conserved molecular structures specific to the microbes (<i>i.e.</i> , pathogen-associated molecular patterns, PAMPs)
Regulatory dendritic cell: a sub-population of dendritic cells that migrate to the regional lymph node in the immature steady state and induce tolerance induction (<i>e.g.</i> , T-regulatory cells)
TcR $\gamma\delta$ T-cells: innate-like T-cells that populate, especially, intestinal epithelium, recognize different ligands than short peptides seen by alpha/beta T-cells in the context of major histocompatibility complex class I or class II
TIR activation domains: conserved cytosolic proteins shared by Toll-like receptors and IL-1 receptors that activate signal transduction, leading to nuclear import of NF κ B.
Tolerance: Antigen-specific unresponsiveness of the adaptive immune system, achieved in the bone marrow and thymus (central tolerance) or in the peripheral tissues/lymph nodes (peripheral tolerance). Tolerance is achieved by the deletion of (<i>e.g.</i> , self-antigen) reactive B- or T-cells (central), or by controlled expression of co-stimulatory molecules on dendritic cells and/or induction of T-regulatory cells to control auto-reactive T-cells that escape central tolerance (peripheral)
Toleragenic: capable of inducing tolerance
T-regulatory cells (Treg): T-cell subsets generally characterized by the expression of specific markers (<i>e.g.</i> , CD123, CD25, FoxP3) and by their ability to actively suppress T-cell-mediated immune responses through direct contact and/or by secretion of regulatory cytokines IL-10, TGF- β