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Dendritic Cells in Atherosclerotic Disease

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Abstract

Atherosclerosis has been considered a syndrome of dysregulated lipid storage until recent evidence has emphasized the critical contribution of the immune system. Dendritic cells (DC) are positioned at the interface of the innate and adaptive immune system. Recognition of danger signals in atheromas leads to DC activation. Activated DC regulate effector T cells which can kill plaque-resident cells and damage the plaque structure. Two types of DC have been identified in atherosclerotic lesions; classical myeloid DC (mDC) which mainly recognize bacterial signatures and plasmacytoid DC (pDC) which specialize in sensing viral fragments and have the unique potential of producing large amounts of type I interferon (IFN). In human atheromas, type I IFN upregulates expression of the cytotoxic molecule TRAIL which leads to apoptosis of plaque resident cells. This review will elucidate the role of DC in atherogenesis and particularly in plaque rupture, the underlying pathophysiologic cause of myocardial infarction.

Keywords

dendritic cells; T cells; atherosclerosis; plasmacytoid dendritic cells; apoptosis; type I interferon

Dendritic Cells in the Vessel Wall – From Healthy Arteries to Rupture-Prone Atherosclerotic Plaques

Dendritic cells (DC) are indigenous residents of healthy arteries and are typically localized in the sub-endothelial space as well as at the media-adventitia junction [1,2]. It has now been proposed that such wall-embedded DC play an important role in the surveillance of the arterial wall and in tolerization against autoantigens by silencing T-cell responses [3]. However, once activated sufficiently, vascular DC may also present autoantigens to T cells and initiate inflammatory responses directly in the arterial wall. Modification of autoantigens and molecular mimicry may lead to recognition of self-determinants in this unique tissue niche. DC are primarily activated by sensing potential dangers in an antigen-independent way via scavenger receptors recognizing typical damage-associated molecular patterns. Localization

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of DC adjacent to vasa vasorum allows them to monitor the most important access pathways to the vessel wall and screen the tissue environment for the appearance of exogenous and indigenous stressors. Millonig et al. described that already at early stages of atherosclerosis, DC appear in the subendothelial layer, particularly in areas exposed to turbulent flow conditions [4]. More than 10 years ago, Bobryshev et al. reported for the first time that DC accumulate in atherosclerotic lesions and concluded that DC may play an important role in the disease process [5]. Yilmaz et al. located DC mainly in rupture-prone areas of the atherosclerotic plaque where they exhibit a mature phenotype [6]. In accordance, we found the presence of DC to be associated with features of plaque instability [7]. Additionally, higher DC densities have been reported in carotid plaques from symptomatic patients compared with those from asymptomatic patients [8]. In addition to visualizing dendrites, typical morphologic features of DC, the presence of DC in the atherosclerotic plaque has been confirmed by using a variety of antibodies recognizing DC markers in humans and mice (CD11c, CD1a, S-100, CD83, and DC-SIGN). Recent reviews have given comprehensive insight into the diversity of immune cells in atherosclerosis [9,10]. This review aims to further elucidate the functional role of DC in atherogenesis and, in particular, in plaque destabilization ultimately leading to plaque rupture and acute coronary syndrome (ACS). DC in the vessel wall almost certainly participate in other clinical circumstances such as aortic aneurysms [11] and in-stent restenosis and balloon injury [12,13], and much can be learned from comparing their immunoregulatory functions in different settings of vascular inflammation.

The Circulating Pool of Dendritic Cells

In healthy individuals DC constitute about 0.3% of circulating peripheral blood mononuclear cells [14]. Circulating DC encompass immature and mature forms trafficking to different organ destinations. There are conflicting data about whether circulating DC are increased or decreased in patients with stable coronary artery disease compared to healthy controls [15, 16]. During ACS, circulating DC are markedly decreased. At the same time, DC accumulate in vulnerable atherosclerotic tissue [14]. One may speculate that circulating DC evade into inflamed tissue sites attracted by chemokines produced by the inflammatory infiltrate occupying the plaque. However, accumulation of DC into a single tissue site cannot be responsible for the major changes in the number of circulating DC reported so far. More likely, DC may also migrate into lymphoid tissues in response to systemic inflammatory activation which redirects trafficking and compartmentalization of antigen-presenting DC as well as lymphocytes. The process of redistribution of DC and their accumulation in tissue niches, such as atherosclerotic plaques, may be affected by changes in the lipid profile which are prototypic for atherosclerotic disease [17].

Recruitment of Dendritic Cells into the Atherosclerotic Lesion

Adhesion and chemotaxis are requisites for invasion of DC into the inflamed atheroma (Figure 1). Adhesion molecules such as P- and E-selectin, and VCAM-1 are responsible for tethering DC to the microvascular bed (Figure 1)[18,19]. Hypoxia, oxidized low-density lipoprotein, tumor necrosis factor-α, and inhibition of endothelial NO synthase may all augment adhesion of DC to the endothelium [20]. In addition, adhesion of DC to injured vessels may be mediated by platelets covering the lesion [21]. Conversely, statin treatment may decrease adhesion of DC [22].

Upon fixation to the vessel wall, a chemotactic stimulus is required for invasion of DC into the tissue microenvironment. CCL2 and CCL5 are potential chemotactic candidates abundantly expressed in the inflamed atheroma (Figure 1)[23,24]. These chemokines activate DC via binding to the respective G protein-coupled receptors and thereby recruit DC fixed to the vessel wall by building a gradient towards the inflamed tissue site. A recent publication of Liu et al.

has shown that fractalkine may be another important chemokine for accumulation of DC in the atherosclerotic plaque [25]. Deficiency of the fractalkine receptor CX_3CR1 resulted in decreased atherosclerosis and a decreased number of DC in atheromas. Transformed circulating monocytes are an additional source of DC. Monocytes may transform into DC under inflammatory conditions [26] with a potential role for granulocyte/macrophage colony-stimulating factor (GM-CSF) facilitating this transformation [26]. Knocking out GM-CSF resulted in a significant reduction of DC in murine atherosclerotic lesions [27]. Particularly, Ly-$6C^{low}$ monocytes may differentiate into $CD11c^{+}$ DC [28]. These cells rely on CCR5 to enter the atheroma.

Activation of Dendritic Cells

Recognition of damage-associated molecular patterns including endogenous alarm signals as well as pathogen-associated molecular patterns has checkpoint function in initiating the cascade of DC activation [29]. In turn, DC start to produce mediators of the innate immune system and express costimulatory molecules such as CD40, CD80 and CD86, which are crucial for induction of adaptive immune responses. The most thoroughly investigated receptors recognizing danger signals are Toll-like receptors (TLR, Table 1). Among them, TLR4 plays a central role in initiation and progression of atherosclerosis. This receptor has been shown to activate and mature DC in patients with ACS [30]. Markers of activation are spontaneously expressed on circulating DC from ACS patients, raising the possibility that they have been exposed to stimulatory ligands [31]. Fragments of bacteria such as lipopolysaccharides (LPS), modified autoantigens such as oxidized LDL, and heat-shock proteins are recognized by TLR4 and activate the subsequent signaling cascade [32,33]. However, a recent publication indicates that oxidized lipoproteins may also inhibit TLR4 signaling [34]. TLR2 may also play an important role in atherogenesis, possibly due to activation of DC, e.g. by Chlamydia pneumoniae [35]. Furthermore, TLR7-, TLR8-, and TLR9-recognizing motifs of nucleic acids deriving from infectious pathogens may be involved in plaque destabilization. Vessel-specific TLR expression patterns inducing distinct types of vascular inflammation may explain the selective susceptibility of different vascular beds to atherosclerosis [2,36,37]. Disturbed blood flow may determine TLR expression patterns [38]. Activation of DC may lead to loss of tolerance and may fuel a local immune response [1]. While dyslipidemia favors aggravation of local inflammation and may break tolerance against autoantigens [17], severe dyslipidemia can lead to inhibition of the production of effector cytokines via TLR [39]. High concentrations of oxidized low density lipoprotein may also cause decreased activity of DC due to increased apoptosis of DC [32]. Further, nicotine has been shown to be a strong inducer of DC [40]. However, there are contradictory data indicating immunosuppressive effects of nicotine [41]. Hypoxia and hypoxia inducible factor 1α are emerging as alternate triggers of DC activation [42]. While hypoxia specifically induces cytokine production of DC, DC maturation and the capacity to stimulate T cells are impaired during hypoxic conditions preventing self reactivity [43]. Thereby the net effect of hypoxia on the contribution of DC to atherogenesis remains to be elucidated. Also, platelets have shown to induce DC maturation thereby enhancing DC-mediated lymphocyte proliferation [21]. Finally, C-reactive protein has been implicated in activating DC, but the responsible molecular mechanisms are unknown [44]. There is some evidence that statins may prevent accumulation and function of DC [6,45,46]. Also, diltiazem has been shown to delay DC maturation in cell culture studies [47].

Plaque Destabilizing Effector Functions of Dendritic Cells

Inclusion of DC in (bioengineered) vessels leads to infiltration of CD4 T cells [48]. DC-derived CCL19 and CCL21 have been implicated in orchestrating T-cell attraction. Further, DC also produce IL-12. This cytokine modifies the function of T cells by upregulation of the chemokine receptor CCR5, which in turn leads to accumulation of T cells into the atherosclerotic plaque

[23]. Diltiazem has been shown to inhibit IL-12 production of DC, resulting in a decreased DC-dependent T-cell activation [49]. In the atherosclerotic plaque, T cells are positioned in close vicinity to DC [50]. However, DC–T-cell interaction may also take place in adjacent lymphoid organs. DC as professional antigen-presenting cells are crucial for priming of T cells as measured by production of IFN-γ [48]. DC present processed antigens complexed with HLA molecules to ligate the T-cell receptor (TCR). Biologic consequences include clonal expansion of T cells expressing a TCR specifically recognizing the presented antigen. In support of the concept that antigen recognition occurs in the plaque microenvironment, clonally expanded T cells have been found in human plaques [51]. Costimulatory signals provided by activated DC are crucial for full-blown activation of T cells. Nicotine augments the DC-mediated capacity of T-cell activation [40]. Thus, multiple factors acting within the plaque will shape the ultimate outcome of antigen recognition and T-cell activation. Statins may suppress the ability of DC to activate T cells [45].

Activated cytotoxic CD4 T cells have the ability to destabilize the atherosclerotic plaque by killing plaque-resident cells, such as endothelial cells and vascular smooth muscle cells forming the protective inner layer (Figure 2). These cells are equipped with cytoplasmic granules containing perforin and granzyme B. Perforin forms pores that enable granzyme B to enter the target cell. Granzyme B activates caspases within the target cells thereby inducing its apoptosis. Moreover, T-cell derived cytokines such as IFN-γ induce macrophage-mediated tissue damage, e. g. by metalloproteinase-induced digestion of the extracellular matrix. In addition to regulating the effector functions of T cells, DC have also been implicated in shaping the functional activity of natural killer cells thereby further enhancing the cytotoxic potential in the atherosclerotic plaque [52]. DC may also affect activation of CD8 T cells, another important fraction of cytotoxic T cells regularly found in advanced atheromas in close vicinity to DC [11,53].

Plasmacytoid Dendritic Cells in the Atherosclerotic Plaque

Recently, DC have been further divided into subsets, including conventional myeloid (m) and plasmacytoid (p)DC. pDC received their name because their shape resembles that of plasma cells [54], and about one third of circulating DC are classified as pDC. Various markers are used for identification of these cells. While BDCA-2 appears on immature pDC [55], CD123, the receptor for IL-3, is constitutively expressed on pDC. Typically, pDC show only low expression of CD11c while this marker is abundantly expressed by mDC. Apart from differences in morphology and expression of surface molecules, there are important functional differences between mDC and pDC (Table 2). pDC have a different TLR expression profile with abundant expression of TLR7, TLR8, and TLR9. These TLR are expressed intracellularly and recognize RNA and DNA deriving from pathogens, particularly viruses. In the atherosclerotic plaque, they may recognize viruses but also nucleotides deriving form dying cells. However, pDC may also recognize bacterial signatures [56]. It has been shown that, similar to mDC, circulating pDC are significantly reduced in patients with troponin-positive ACS [57].

pDC have the unique function of producing large amounts of type I IFN. This cytokine exerts strong antiviral effects. Furthermore, it induces marked upregulaton of the molecule TRAIL on CD4 T cells [7]. TRAIL-expressing CD4 T cells effectively kill plaque-resident cells, potentially weakening the scaffold of the lesion and rendering the plaque vulnerable (Figure 2) [58]. Moreover, type I IFN produced by pDC also sensitizes mDC by upregulating TLR4 on their surface [59]. This interaction leads to a major amplification of immune responses as mDC and pDC are concomitantly triggered with different danger signals. This may for instance happen when a viral infection activates pDC to produce type I IFN while mDC are chronically stimulated by modified lipoproteins via TLR4. In accordance, type I IFN has been found to be

associated with plaque instability in human atheromas [7]. In essence, interactions between distinct types of DC emerge as mechanisms of setting inflammatory thresholds in the atheroma, assigning a critical role to innate sensing tools in modulating the fate of the atherosclerotic lesion.

Outlook and Potential Therapeutic Immunomodulation

This review summarizes the crucial pathogenic role of DC in plaque inflammation, contributing to all stages of the atherosclerotic process. DC seem to be of particular importance in advanced vulnerable lesions. However, exploring their contribution in early stages of atherosclerosis is complicated by the extended time span through which this process proceeds. Capturing early steps in human atherosclerosis would literally require studying teenagers. DC are activated by recognition of damage-associated molecular patterns via scavenger receptors. While receptors on mDC mainly recognize bacterial signatures, pDC are specialized in recognizing viral particles. Also, modified autoantigens have the ability to stimulate DC in the atherosclerotic plaque. Activated DC participate in destabilizing the atherosclerotic plaque in two different ways. First, they are highly efficient antigen-presenting cells, determining the differentiation of T cells. A critical effector pathway exposing the plaque to risk of rupture is the activation of cytotoxic T cells. Secondly, DC induce production of proteases such as metalloproteinases which disintegrate the extracellular matrix. A close interplay among mDC, pDC, and other immune cells results in full-blown immune activation, paving the way for the detrimental rupture of the atherosclerotic plaque.

Depletion and repletion experiments in animal models of complex atherosclerotic lesions are necessary to explore which steps of the inflammatory cascade are regulated by these innate immune cells. It is important to keep in mind that DC may also be helpful in inducing tolerance against modified autoantigens in the microenvironment of the arterial wall and that this particular immune function could prove beneficial in novel therapeutic approaches to atherosclerosis. Particularly, DC may expand CD4+Foxp3+ T regulatory cells [60]. This T cell subtype is crucial for balancing immune responses and inhibits atherogenesis by secretion of transforming growth factor-beta and interleukin-10. There are ongoing efforts to develop a vaccination against autoantigens found in the atherosclerotic plaque to induce immune tolerance and avoid tissue-damaging immune responses [61]. The state of DC presenting such antigens to lymphocytes may be crucial for inducing tolerance. As the induction of immune memory may be irreversible, considerably more research on the safety of vaccination against epitopes found in atherosclerotic lesions is required. Developing experimental approaches to assign selected DC functions to certain stages of the atherosclerotic process seems particularly promising as it may be necessary to harness DC functions through diverse means. Both inhibiting unwanted immune responses and fostering protective immune responses may converge on the level of modulating DC function.

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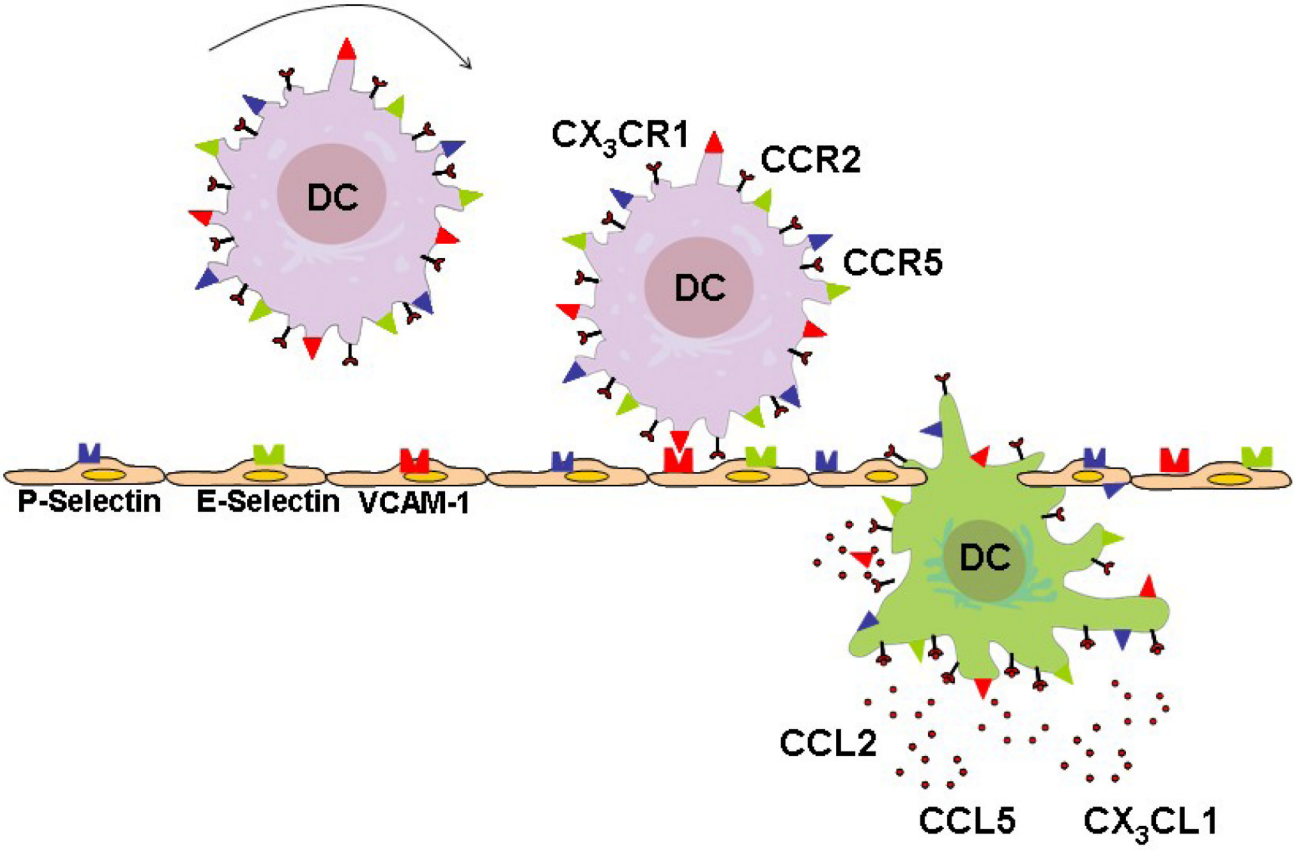

Figure 1. Recruitment of Dendritic Cells into the Atherosclerotic Plaque

DC are tethered to activated endothelium covering atherosclerotic plaques with the help of adhesion molecules including P-Selectin, E-Selectin, and VCAM-1. Production of chemokines in the atherosclerotic lesion determines which cells enter the lesion. The chemokines CCL2, CCL5, and CX_3CL1 are abundantly expressed in the lesion and build a gradient towards the lesion in the vessel wall. DC express the corresponding receptors CX_3CR1, CCR2, and CCR5 and follow the gradient towards the atheroma. Transmigration through the endothelium is associated with phenotypic changes of DC.

DC = dendritic cells

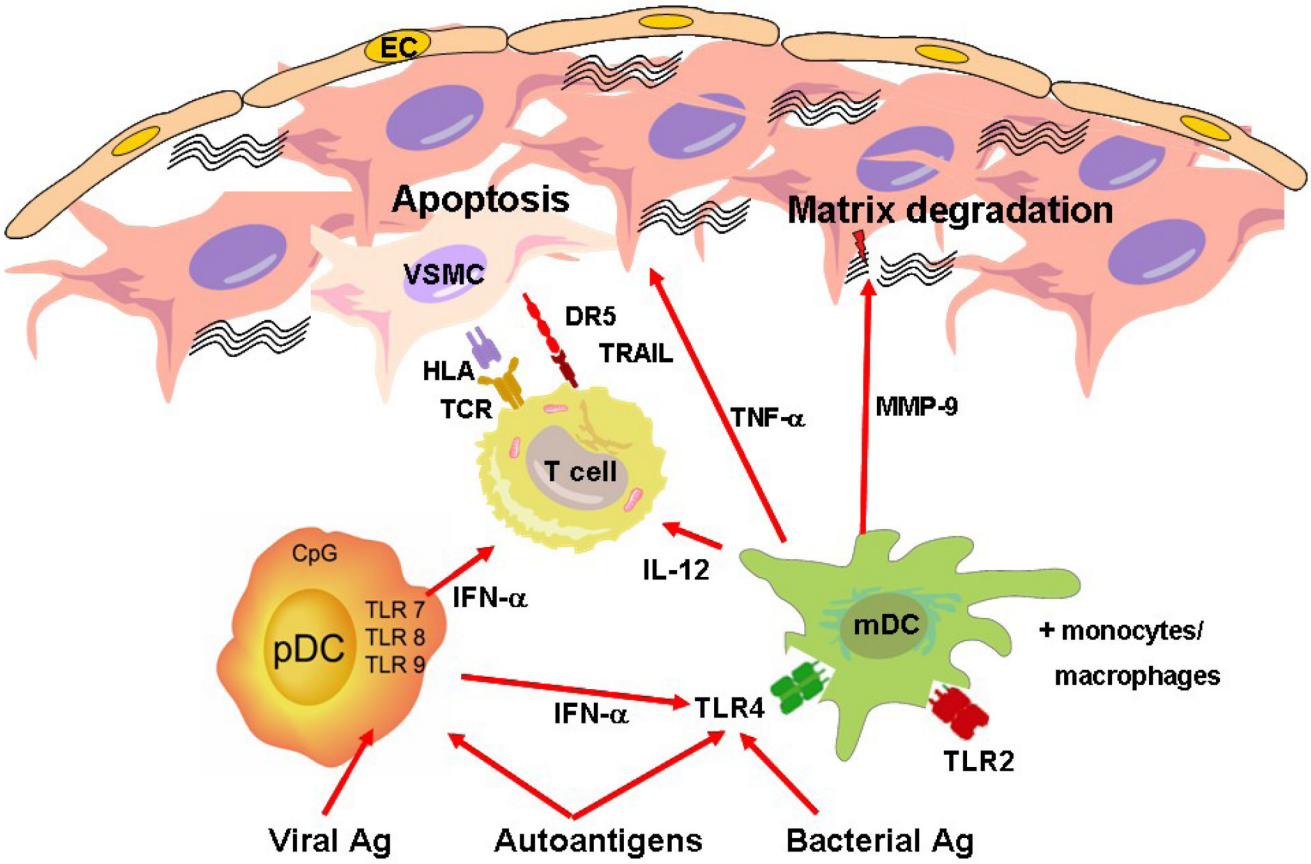

Figure 2. The Role of Dendritic Cells in the Atherosclerotic Plaque

mDC are activated by exogenous and endogenous danger signals binding to TLR2 and TLR4. Activated mDC produce effector molecules such as metalloproteinases degrading the extracellular matrix. Further, they trigger the recruitment of cytotoxic T cells via production of IL-12. pDC are mainly activated by viral antigens binding to intracellular receptors such as TLR9. Activated pDC produce vast amounts of IFN-α. This cytokine enhances the sensitivity of other antigen-presenting cells by upregulation of TLR4. Furthermore, it upregulates the expression of the proapoptotic molecule TRAIL on T cells thereby multiplying their cytotoxic potential. These TRAIL-expressing T cells have the ability to kill plaque-resident cells such as activated VSMC and EC expressing the death receptor DR5.

VSMC = vascular smooth muscle cells, EC = endothelial cells, mDC = myeloid dendritic cells, pDC = plasmacytoid dendritic cells, MMP = metalloproteinase, DR5 = death receptor 5, TNF-α = tumor necrosis factor-alpha

Table 1

Immune Triggers Activating DC in Atherosclerotic Disease

Receptor	Ligand	Source
TLR2	Lipoproteins, Peptidoglycans, Lipoteichoic acid	Gram-positive bacteria, Mycoplasma, and other pathogens
	entry-mediating envelope gp, gp B (gB) and gp H (gH)[62]	CMV
	?	HSV
	Heat shock protein 60	Human and chlamydial
	Lipopolysaccharides	Porphyromonas gingivalis
TLR3	Double-stranded RNA	Viruses
	?	CMV
TLR4	Lipopolysaccharides	Outer membrane of gram-negative bacteria
	Lipoteichoic acids	Gram-positive bacteria
	Protein F	Respiratory syncytial virus
	Heat shock protein 60	Human and chlamydial
	Outer membrane protein?	Chlamydia
	Oxidized LDL (inhibitory role?), minimally modified LDL	Human
	Fibronectin Extra Domain A	Human
TLR5	Flagellin	Bacteria with flagella, e.g. Salmonella
TLR7	single stranded RNAs	Virus
TLR9	Unmethylated CpG motifs	Bacterial DNA
	DNA from CMV, HSV, Hepatitis B Virus	Virus
	Human DNA?	Dying cells?

modified from de Kleijn et al. [63]

Table 2

Comparison of Myeloid and Plasmacytoid Dendritic Cells

Dendritic Cell Subtype	Myeloid	Plasmacytoid
Circulating numbers*	0.2%	0.1%
Preferentially-expressed Toll-receptor profile	TLR2, TLR4, (TLR5)	TLR7-TLR9
Site of TLR expression	Cell surface	Cytoplasm
Recognition of		
Pathogens	Bacterial fragments, e.g. LPS	Viral fragments, e.g. RNA
Autoantigens	Oxidized LDL, HSP60	DNA from dying cells?
Typical effector cytokines	IL-12, TNF-α, IL-6	Type I interferon
Effector function	Activation of T cells via HLA-antigen complexes and costimulatory molecules	Regulation of cellular functions via type I interferon, e.g. induction of TRAIL on T cells
Crosstalk	Sensitized to TLR4 ligands by pDC-derived type I interferon	Upregulation of TLR4 expression on mDC

* % of peripheral blood mononuclear cells