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REVIEW

Dendritic cells and their role in atherogenesis

Yuri V Bobryshev

Dendritic cells (DCs) are the most potent professional antigen-presenting cells with the unique ability of primary immune response initiation. DCs originate from bone marrow progenitors, which circulate in the peripheral blood and subsequently penetrate peripheral tissues, where they give rise to immature DCs. In peripheral tissues, DCs continuously monitor the microenvironment and, when the cells encounter 'danger' signals, DCs undergo differentiation and maturation. Maturing DCs usually migrate to lymphatic tissues, where they form contacts with T cells to initiate a primary immune response. DCs were identified in arteries in 1995 and since then, further knowledge has been gained about the peculiarities of vascular-associated DCs and their role in atherosclerosis. Immune reactions toward modified lipoproteins and other factors ignited by resident vascular DCs as well as by newly arrived DCs, which originate from blood monocytes, are believed to destabilize arterial homeostasis from very earlier stages of atherogenesis. There is a remarkable heterogeneity of DCs in atherosclerotic lesions. Some DCs mature and become capable of forming clusters with T cells directly within the arterial wall. The predictive value of the numbers of circulating DC precursors in coronary artery disease and in atherosclerosis has been assessed, and it has been shown that DCs have a role in plaque destabilization. Over recent decades, DCs have proven to be a valuable instrument in immunotherapy approaches against cancer and various autoimmune diseases, and this explains the demand that the accumulated knowledge be applied to the field of atherosclerosis immunotherapy.

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Antigen presentation is a key event in adaptive immune response.[1] Until 1973, it was believed that macrophages and B cells were the only cell types capable of presenting antigens to T cells.[1] The study by Steinman and Cohn,[2] published in 1973, showed that another type of antigen-presenting cell exists with a powerful ability to initiate adaptive immune response. The newly identified cells were designated 'dendritic cells' (DCs).[2] Since their first description, the role of DCs in immunity has been a focus of growing interest.

It is now well known that DCs are highly potent professional antigen-presenting cells responsible for capturing, processing and presenting antigen to T cells and thus, priming primary and secondary immune responses.[3–6] DCs are sensors of both the innate and the adaptive arms of the immune system.[3–10] As members of the innate immune system, DCs respond to molecules, which can be considered as 'danger' signals, by their prompt generation of protective cytokines.[3–10] As the key element of the adaptive immune system, DCs recognize and respond to dangerous molecules by eliciting the development of primary immune responses appropriate for the type of danger.[3–10] DCs have a potent antigen-presenting capacity for the stimulation of naive, memory and effector T cells.[3–10] DCs are responsible for activating not only conventional T cells but also natural killer T (NKT) cells.[7–10] DCs are also involved in the maintenance of tolerance to antigens.[3–10]

During the development of adaptive immune responses, direct contacts are formed between DCs and T cells.[3–10] In this interaction, T cells respond to peptide antigen displayed on major histocompatibility complex (MHC) class II and class I molecules present on DC surfaces.[3–10] In DC/T-cell interactions, the presence of costimulatory molecules on DCs is crucial for T-cell activation and differentiation into effector cells.[3–10] In the absence of sufficient costimulation in DC/T-cell interactions, T cells exhibit anergy or might even undergo apoptosis.[3–10] In DC/T-cell interactions, DCs secrete a spectrum of cytokines.[3–11] The secretion or lack of secretion of interleukin (IL)-12, IL-23, IL-10 and other cytokines by DCs determines their ability to polarize naive T cells into Th1, Th2, T regulatory cells (Treg) or Th17 cells.[3–11]

Faculty of Medicine, SOMS, University of New South Wales, Kensington, NSW, Australia
Correspondence: Dr YV Bobryshev, PhD, Faculty of Medicine, SOMS, University of New South Wales, High Street, Kensington, NSW 2052, Australia.
E-mail: y.bobryshev@unsw.edu.au

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The investigation of DCs in atherosclerosis represents a relatively new direction in DC research. The presence of DCs in nondiseased arteries was described for the first time in 1995,[12] and since then, knowledge has been gained that indicates the functional importance of DCs in atherogenesis. Different aspects of the participation of DCs in atherogenesis have been highlighted in a number of earlier reviews.[13–24] This review briefly summarizes the current perception of the impact of DCs in atherogenesis, with special attention to the structural complexity of the population of vascular-associated DCs.

DC FAMILY: ORIGIN AND MIGRATORY ROUTES

DC Family: Origin

According to the current paradigm, DCs originate from a common progenitor in the bone marrow.[3–6] Their development involves three stages for which the terms 'precursors,' 'immature' and 'mature' are commonly used.[3–6] Dramatic changes in the structural appearance and functional abilities of DCs during the transition through a precursor to immature then to mature stage sequence are striking and, perhaps, may be described as 'cell metamorphosis.' From a morphological point of view, the most striking feature of this 'metamorphosis' is that the structural appearance of immature DCs is more complex than that of mature DCs. DCs can be metaphorically described as wanderers which, during their life, change anatomical and tissue localizations, interacting during their migration with various other cell types. In different stages of their development and, accordingly, in different anatomical localizations, DCs fulfill different functions, which eventually allow them to reach a stage when they can activate or suppress T cells.[3–6]

In the first stage of their development, DC precursors leave the bone marrow to circulate through the bloodstream. The circulation time of DC precursors in the bloodstream varies, depending on targeted anatomical localizations. Circulating DCs are often termed 'blood DCs.'[3–6]

There are several pathways by which DC precursors can develop into immature DCs.[8–10,17,18,20–24] Different types of DCs are believed to develop through different branches of hematopoietic pathways that involve different immediate precursor cells.[2–10,25–30] Different branches of hematopoietic pathways lead to the development of DCs with different functions.[25–30] Depending on their origin and functional predisposition, there are several DC sub-populations, including myeloid DCs (mDCs) and plasmacytoid DCs (pDCs).[25–30] Accumulating evidence indicates that mDCs are required for T-cell activation, whereas 'lymphoid' DCs (pDCs) induce T-cell tolerance.[25–30] mDCs comprise subsets of 'conventional' DCs, including Langerhans cells and interstitial DCs, which express CD1c, CD11c and CD33 and secrete IL-12.[25–30] pDCs are characterized by the expression of CD123 (IL-3 receptor α-chain) and are the most potent IFN-α-producing cells in response to viral pathogens.[25–30] In contrast to mDCs, which display a 'typical' DC morphology relevant to their development stage, the appearance of pDCs is somewhat different.[31] Freshly isolated human pDCs are round-shaped cells with short processes on their surfaces.[31] At electron-microscopic examination, pDCs display the presence of eccentrically located nuclei and their cytoplasm contains a juxtanuclear Golgi apparatus and parallel arrays of cisterns of the endoplasmic reticulum.[31] The ultrastructural appearance of pDCs somehow resembles the appearance of plasma cells, which led to their definition as 'plasmacytoid' DCs.[31] However, there are obvious differences in the ultrastructural architectonics between pDCs and plasma cells.[31] Incubation of pDCs with IL-3 and the CD40 ligand induces the formation of long cell processes and eventually, pDCs acquire the morphology of interdigitating cells.[31] Apart from mDC and pDC sub-populations, blood monocytes have been shown to be able to acquire DC properties, and a sub-population of DCs that do not display stellate shape has been designated as 'pre-DCs.'[30,32,33] Increased DC numbers appear at sites of inflammation where DCs display distinct profiles of surface receptors and are functionally unique.[25–30] Inflammatory DCs have an important role in the induction of proinflammatory responses *in situ* at the sites of inflammation.[25–30] It remains unclear whether inflammatory DCs represent a separate lineage to steady-state DCs or whether they develop from steady-state blood DCs upon arrival at the inflammation site. The development of different DC sub-populations is influenced by different combinations of cytokines and growth factors.[3–10,25–30,32]

The population of DCs in the body is highly heterogeneous.[2–10] Although many attempts to classify DC sub-populations have been made in the past few years, the complete model has not yet been established. DCs can be classified according to their anatomical location, morphological appearance, antigen expression, presumed origin, the T-cell response they initiate and their physiological/pathophysiological state ('steady-state DCs', 'inflammatory DCs').[3,25–28] In the steady state, the properties of DCs markedly vary according to the anatomical location. Steady-state DCs can be further divided into migratory or lymphoid tissue resident cells. Migratory DCs sample antigen in peripheral tissues before migrating through the lymph to lymphoid organs, whereas lymphoid tissue resident DCs are believed to arrive from the blood as precursors and develop *in situ* into DCs capable of activating T cells.[25–28] Lymph nodes thus contain a mixture of both of these DC types.[29]

Immature DCs: Morphology

As soon as DC precursors reach and penetrate peripheral tissues, most of them take up residence at sites of potential entry of 'dangerous factors.'[3–6,34] Different monocyte populations can give a rise to DCs in tissues as well.[32,33] DC precursors' penetration of peripheral tissues marks the second stage of their development, termed 'immature DCs.' In this stage, DCs can be identified in essentially all tissues, even though in any location, they represent only a minor cell type,

Table 1 Distribution and histological nomenclature of dendritic cells (DCs) in normal tissues

Cell type	Location	Major functional role	Distinctive structural feature(s)
Blood dendritic cells	Peripheral blood	Migratory form of DCs	Nil
Langerhans cells	Epidermis of the skin; stratified squamous epithelium of the esophagus	Antigen uptake/processing	Lag+ Birbeck granules and atypical granules
Interstitial dendritic cells		Antigen uptake/processing	Moderately developed tubulovesicular system
Vascular dendritic cells	Intima and adventitia, arteries	Antigen uptake/processing	Moderately developed tubulovesicular system and Lag+ Birbeck granules
Interdigitating dendritic cells	Lymph node paracortex/splenic periarteriolar lymphatic sheath	Antigen presentation	Well-developed tubulovesicular system
Follicular dendritic cells	Germinal centers	Regulation of B-cell memory	Well-developed tubulovesicular system

usually constituting <0.5–1% of the total cell population. In addition to the penetration of circulatory DCs into peripheral tissues, many 'individual tissues' may generate their 'own' DCs locally from reservoirs of immediate DC precursors, rather than depending on the continuous flux of DCs from the bone marrow.[26]

Immature DCs are predominantly concentrated along epithelial and body cavity surfaces, and are most frequently present in the skin as well as in the respiratory and digestive systems[3–6] (Table 1). In these locations, DCs continuously monitor the microenvironment by sampling and examining the extracellular content for the identification of dangerous signals.[3–6,34] From a morphological point of view, immature DCs are highly differentiated cells. In different locations, immature DCs display different structural features. The surface of immature DCs is characterized by the presence of long, thin cell processes, described as dendrites, as well as short veils.[3–6] Some immature DCs contain unique cytoplasmic structures. Langerhans cells, described in 1868 as stellate cells in the epidermis of the skin, represent the most intensely studied example of the immature stage of migratory type DCs.[3,35–41] Langerhans cells contain unique organelles, termed 'Birbeck granules,' which have the shape of a tennis racket or are rod-shaped structures with a central lamina consisting of bands of high electron density, regularly or intermittently interrupted by bands of low electron density.[3,35–41] Birbeck granules contain specific molecules, termed 'Lag-antigen' and 'langerin' (CD207).[3,38,40–42] Other distinctive cytoplasmic structures of Langerhans cells include atypical dense granules and a tubulovesicular system, which represents modified and hypertrophied conglomerates of the smooth endoplasmic reticulum and complex Golgi.[3,36,39] Atypical dense granules resemble lysosomes but the presence of an electron-transparent oriole between the limiting external membrane and the electron-dense core allows distinguishing of these two organelles.[3,39] Atypical granules can transform into Birbeck granules.[3,39] Birbeck granules, atypical granules and the tubulovesicular system have been found to be involved in the recognition and processing of antigen-related information collected from the surrounding extracellular space.[3,40–42] The presence of Langerhans cells is not limited to the epidermis of the skin, and Langerhans-like cells can be identified in the gastrointestinal system, particularly in the esophagus.[3] Other subtypes of immature DCs, distributed throughout peripheral tissues, are characterized by the presence of a tubulovesicular system and atypical granules, the structural transformations of which do not usually lead to the formation of Birbeck granules. Immature DCs in the lung are often termed 'lung DCs,' immature DCs in the liver are 'liver DCs,' in the heart they are 'heart DCs' and so on.[3] Immature DCs, which lack Birbeck granules and are located in interstitial spaces in the majority of organs, are conventionally termed 'interstitial DCs.'[3]

Antigen Uptake by Immature DCs

In peripheral tissues, immature DCs continuously monitor the microenvironment and efficiently evaluate the antigenic samples collected from the extracellular space by phagocytosis, by high-volume fluid-phase macropinocytosis, by receptor-mediated endocytosis, or by direct contact with necrotic, apoptotic or virally infected cells, and by other mechanisms.[3–7,34,43–46] Internalized antigens are degraded into short peptides that are loaded onto nascent class I and class II MHC molecules for subsequent display on the cell surface. As DCs in their immature stage are not yet able to stimulate T cells, they are often termed 'processing' DCs.[3,43–46] Processing DCs can also be described as 'activated DCs.'[3] *In vivo*, processing DCs usually exit the nonlymphoid tissues to migrate through the afferent lymph into the lymphoid regional lymph nodes.[3–6,36]

Migration of Processing DCs in the Lymphoid Organs

As soon as activated DCs enter the lymph, they undergo marked structural alterations, including a dramatic shrinkage of the tubulovesicular system and the disappearance of atypical and Birbeck granules; the cellular surface also

changes with long dendrites being replaced by flapper-like cytoplasmic veils that are continuously extended and retracted.[3,36] DCs in the afferent lymph are termed 'veiled cells.'[2–6,36] Structurally, veiled DCs appear as low-differentiated cells but they can be distinguished from lymphocytes by their more complex cell surface.[3,36] It seems that, at present, it is impossible to establish from which peripheral tissue such veiled cells have arrived.

Structural and Functional Alterations of Veiled DCs in the Lymphoid Organs

Veiled DCs, having entered the lymph organs from the afferent lymph, progress to the last stage of their development, which provides the organism with mature DCs.[3–6,36] In the lymphoid organs, veiled DCs transform into the so-called 'interdigitating cells' (or 'interdigitating DCs').[3,36] This transformation is accompanied by changes in the cell surface. Veils become replaced by long cellular processes (dendrites), and the tubulovesicular system undergoes remarkable hypertrophy.[3,36] Accumulating evidence suggests that in interdigitating cells, the tubulovesicular system is involved in antigen processing and antigen presentation.[3] By their appearance, interdigitating cells resemble interstitial DCs, but the tubulovesicular system in interdigitating cells is much more developed than in interstitial DCs.[3] In the lymphoid organs, DCs complete their maturation process which involves the downregulation of endocytotic activity and the upregulation of adhesion molecules (CD11a, CD50, CD54 and CD58), costimulatory molecules (CD40, CD80/B7.1, CD86/B7.2) and antigen-presenting molecules, including the class I and class II of MHC proteins.[2–10] The expression of the CD83 molecule, a member of the immunoglobulin superfamily, marks the complete maturation of DCs.[3,7–10,47,48] Coexpression of adhesion, costimulatory and antigen-presenting molecules enables DCs to form contacts with, and to eventually activate, T cells.[2–10] Despite the observation that the activation of T cells occurs predominantly in the lymphoid tissues, it is well appreciated that in at least some pathological conditions, the maturation of DCs can occur in the peripheral nonlymphoid tissues where DCs become capable of clustering with lymphocytes.[2–10]

DCs AND ATHEROSCLEROSIS

Structural Features and Heterogeneity of DCs in Human Atherosclerotic Arteries

Small numbers of DCs locate in the subendothelial layer of the intima of apparently normal, nondiseased human arteries.[12,49–53] Since the first description of DCs in the arteries,[12] knowledge has been gained that indicates the structural complexity of the population of vascular-associated DCs. Resident vascular-associated DCs have been designated 'vascular DCs' (VDCs).[12] VDCs, recently described within the tertiary lymphoid structures in the aortic adventitia of the atherosclerotic vessels, might represent a unique sub-population of DCs.[54]

Notwithstanding the wide structural heterogeneity of cells in the DC family, they, including DCs, present in the arterial wall, exhibit distinct ultrastructural features, including a unique tubulovesicular system, which allows them to be unambiguously identified.[3,12,36,39] The tubulovesicular system represents highly modified and hypertrophied conglomerates of complex Golgi and smooth endoplasmic reticulum.[55]

In the normal intima, structurally low-differentiated VDCs are predominantly present in close proximity to the endothelium (Figure 1a–c), whereas VDCs with a moderately developed tubulovesicular system are localized throughout the thickness of the tunica intima, mostly being concentrated in the subendothelial space (Figure 2a and b). By means of their long cellular processes, VDCs form multiple contacts between each other and with other cell types (Figures 3a–c and 4a–e). In some processes, cisterns of the tubulovesicular system can be highly hypertrophied (Figure 3a–c), which could indicate that these DCs are activated.[12,50]

Ultrastructural investigations of the normal arterial intima and early atherosclerotic lesions have shown that, although the transitional stages between VDCs displaying different structural appearances can be found, the heterogeneous VDC

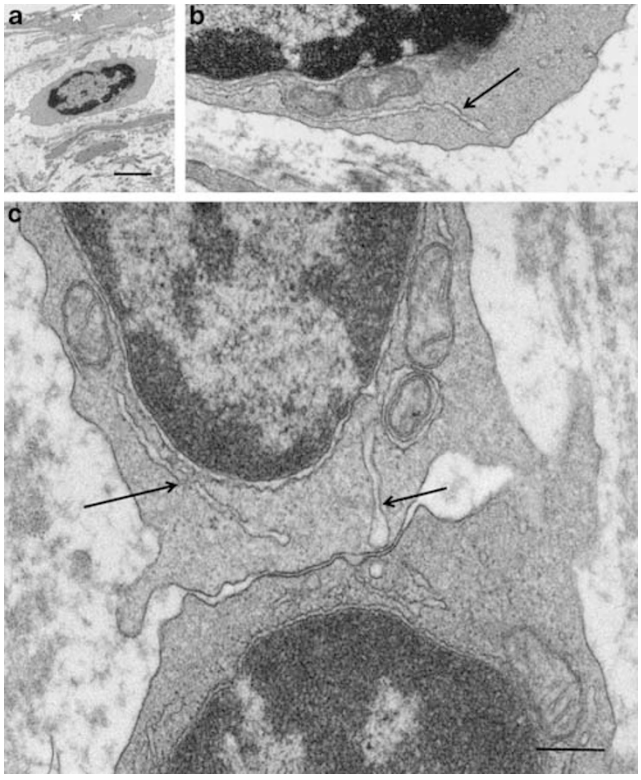

Figure 1 Low-differentiated cells showing signs of their differentiation into dendritic cells (DCs) in the subendothelial layer of the arterial intima (**a–c**). Panel b is a detail of panel a. In panel a, the star marks the endothelium. In panels b and c, cisterns of the developing tubulovesicular system are marked by arrows. Human aorta. Electron microscopy (EM). Bars = 3 μm (**a**), 1 μm (**c**).

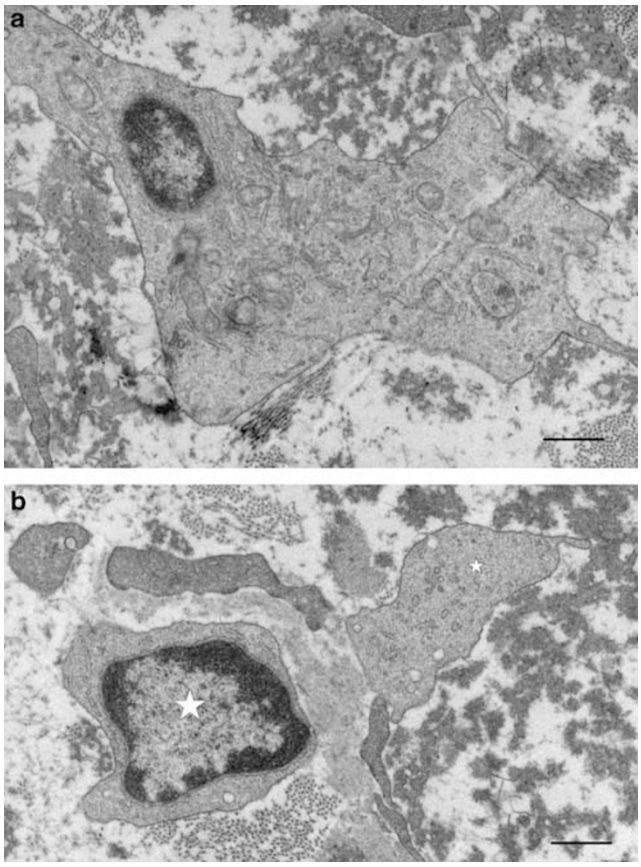

Figure 2 Typical appearance of DCs in the arterial intima (**a**, **b**). The tubulovesicular system is moderately developed, whereas the cytoplasm lacks lysosomes. (**b**) The continuity between the cell body (marked by the large star) and DC processes is not usually obvious in ultra-thin sections. The small star marks a DC process. Human aorta. EM. Bars = 2 μm (**a**, **b**).

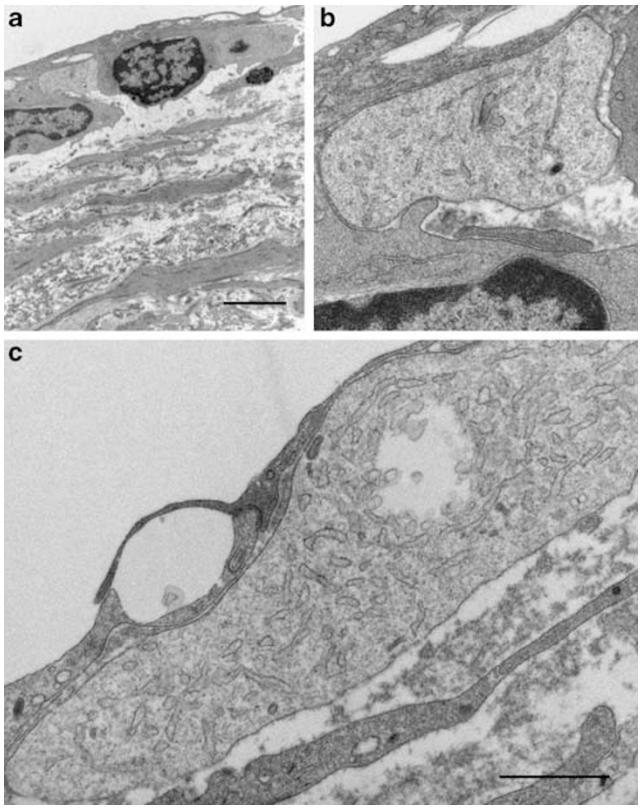

Figure 3 DC processes, containing hypertropically developed cisterns of the tubulovesicular system, are in direct contact with the luminal endothelium (**a**–**c**). In panel a, a DC process located within a cell cluster formed by lymphocytes. Panel b shows a detail of figure (**a**). Human aorta. EM. Bars = 5 μm (**a**), 1 μm (**c**).

population nevertheless falls into two main structural types: type I and type II VDCs (Figure 5a).[56] The cytoplasm of type I VDCs is enriched with well-developed cisterns of the tubulovesicular system, but these cells lack lysosomes or other kinds of electron-dense granules (Figure 2a and b). It might seem unusual that a cell could not have lysosomes, but it has been shown that DCs are capable of degrading antigens without the participation of lysosomes.[44,45] DCs can bypass the antigen-internalization stage by the processing of antigens extracellularly and by loading antigenic peptides onto empty, surface class II MHC molecules.[44,45] Perhaps, type I VDCs use this property. In contrast to type I VDCs, the cytoplasm of type II VDCs is characterized by the presence of a prominent number of atypical dense granules (Figure 5b and c),[56] which have been shown to represent precursors of Birbeck granules in Langerhans cells in the epidermis of the skin.[3,37] However, in Birbeck granules in Langerhans cells, the central lamina is intermittent, whereas in Birbeck granule-like structures in type II VDCs, the central lamina is continuous (Figure 6a–c), which might indicate that type II VDCs represent a unique cell type within the DC family.[57] Another difference between Langerhans cells and type II VDCs can be revealed by immunohistochemistry using anti-Lag-antigen and anti-langerin antibodies: it has been shown that type II VDCs are immunopositive for Lag-antigen,[57] but no langerin immunopositivity can be detected in the arterial wall.[58] Both Lag-antigen and langerin are known to be present in Birbeck granules in Langerhans cells in the skin.[3,37,39–42] Perhaps, the absence of the intermittence in the central lamina of Birbeck granule-like structures is associated with the lack of langerin in Birbeck granule-like structures in type II VDCs.

Although there are several other markers available for the identification of DCs in human arteries, such as S100, CD1a, CD1d, fascin, DC-LAMP and DC-SIGN,[12,49–52,59–67] it is not yet known what portions of the total DC population in the arterial wall can be detected by these markers. It seems that S100 (S100A1 and S100B) is currently the most reliable marker for the visualization of at least the major portion of DC population in the human arterial intima (Figure 7a–c). Although S100 is not exclusively specific to DCs and it is expressed by neuronal cells, S100 specifically identifies DCs

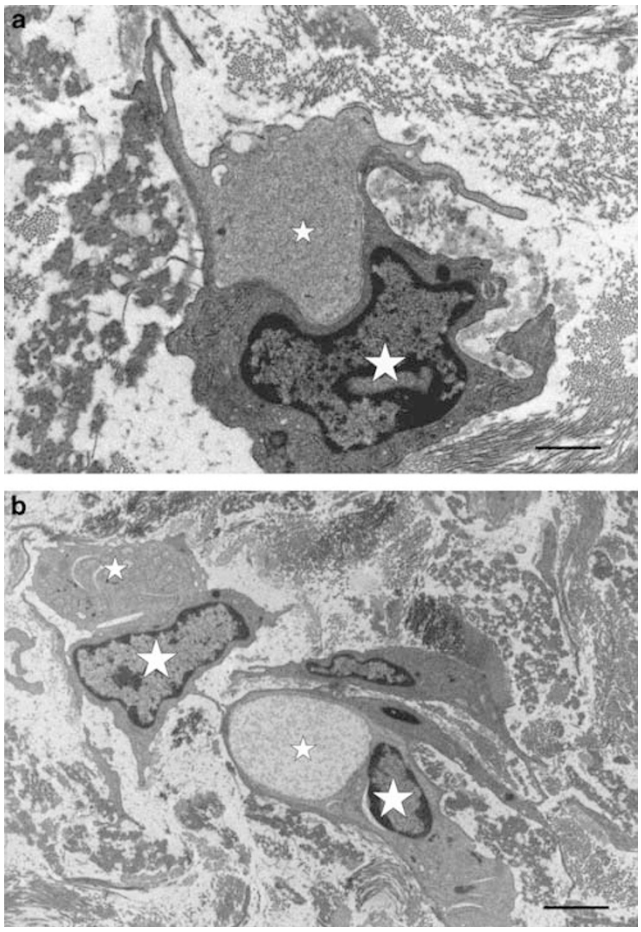

Figure 4 Complex associations between intimal cells (large stars) formed by DC processes (small stars) in early atherosclerotic lesions (**a**, **b**). Human aorta. EM. Bars = 1 μm (**a**, **b**).

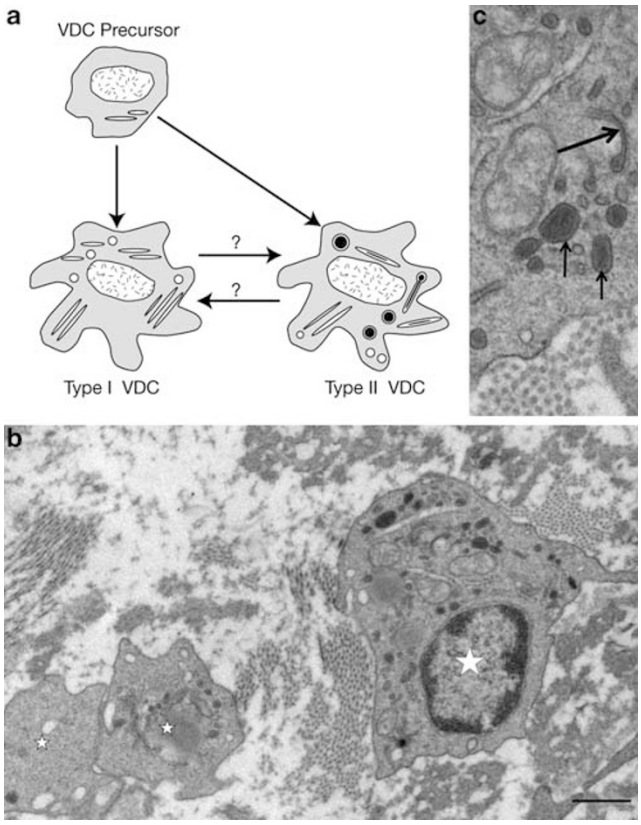

Figure 5 Phenotypic heterogeneity of DCs in the arterial intima (**a**–**c**). (**a**) Schema illustrating the structural features and possible relationship between the two phenotypes of vascular DCs (type I and type II VDCs). (**b**, **c**) DC, the cytoplasm of which contains atypical granules and Birbeck granule-like structures (type II VDCs). Panel c is a detail of panel b. In panel b, the large star marks DC body, whereas DC processes are marked by small stars. In panel c, a Birbeck granule-like structure is shown by the large arrow, whereas small arrows show atypical dense granules. (**b**, **c**) Human aorta. EM. Bar = 5 μm (**b**).

in the arterial intima because the latter and two-thirds of the internal part of the tunica media are not innervated.[49] Fascin (55-kDa actin bundling protein p55) is also a suitable marker for identification of DCs.[64,67] In contrast to the consistent expression of CD1a by Langerhans cells in the skin,[3] CD1a is expressed only by a relatively small portion of the DC population in the arterial wall and the intensity of CD1a expression is markedly lower than that in the skin. Nevertheless, the presence of CD1a+ cells and networks formed by CD1a+ DCs has been well demonstrated in a number of studies.[51,52,60,61,63,68,69] Similarly, as it occurs with CD1a expression, only a small portion of DCs in the arterial wall express CD1b and CD1d.[69,70] Molecules of the CD1 family are known to represent a large cluster of nonpolymorphic, MHC class-I-like molecules that bind distinct lipid-based antigens, which become recognizable by T cells.[71,72] The most studied group of T cells that interact with lipid antigens is NKT cells, which characteristically express a semi-invariant T-cell receptor for CD1d recognition.[72] Thus, CD1d can be used for the evaluation of the number of DCs, which has a potential to recognize lipid-based antigens in different types of atherosclerotic lesions.[70,73,74] CD11c, an integrin expressed preferentially by murine DCs,[75–77] can be used for the identification of DCs in human arteries as well.

In addition to the usefulness of Lag-antigen for the identification of DC subtypes,[57] the heterogeneity of DCs in the arterial intima can be shown by the application of BDCA-1 (CD303) and BDCA-2 (CD1c) antibodies, which identify myeloid and plasmacytoid types of DCs, respectively (Figure 8a and b). Immature and mature DCs can be distinguished by the use of anti-CD83, specifically expressed by mature DCs.[47,48] In atherosclerotic lesions, CD83+ DCs often form clusters with T cells (Figure 8c and d), which is in agreement with a speculation that direct activation of DCs might occur directly within the arterial wall.[60] CD83+ DCs in atherosclerotic lesions express costimulatory molecules CD80 and CD86.[61,62] The presence of mature DCs expressing CD83, CD80 and CD86 in atherosclerotic plaques has been shown not only by immunohistochemistry but also by quantitative PCR analysis.[62]

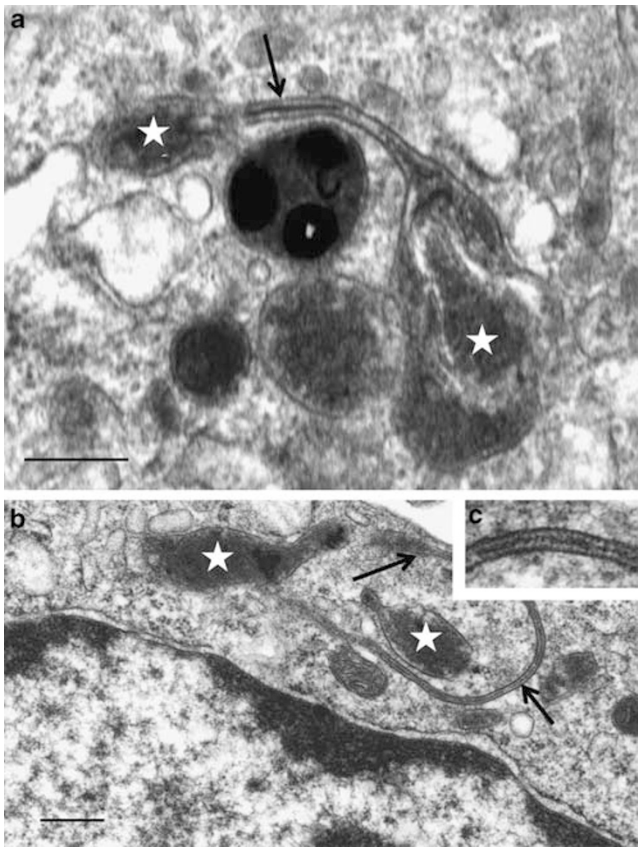

Figure 6 Transformation of atypical granules (stars) into Birbeck granule-like structures (arrows) in DCs in the arterial intima (**a**–**c**). Panel c is a detail of panel b. Human aorta. EM. Bars = 0.1 μm (**a**), 0.2 μm (**b**).

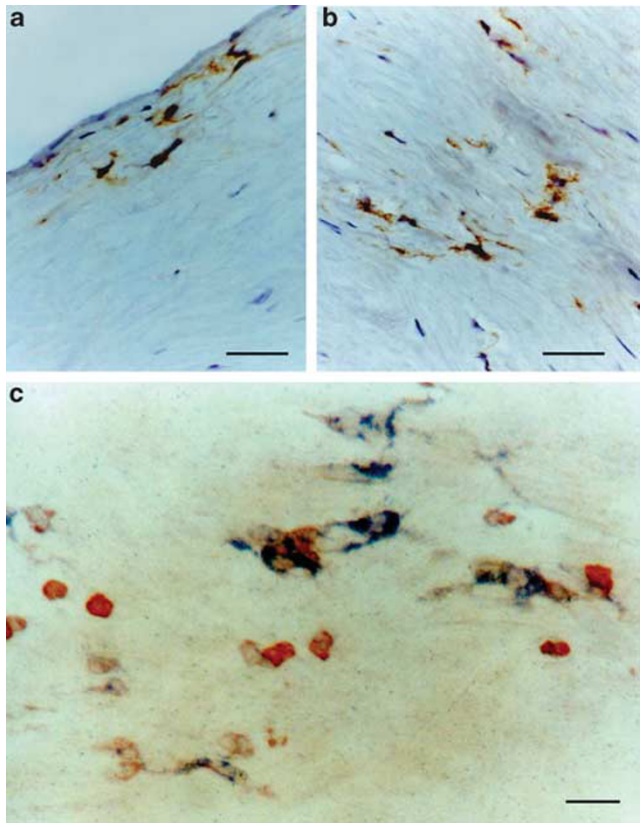

Figure 7 DCs in athero-predisposed areas of the human aorta (**a**–**c**). In panels a and b, DCs were visualized using anti-S100 (Dako) in tissue specimens without signs of atherosclerosis. ABC immunoperoxidase reaction; counterstaining with Mayer's hematoxylin. (**c**) Double immunostaining showing direct contacts between DCs (blue) and T cells (red) revealed in an *en face*-stained intimal sheet ('Hauthcen' specimen). S100 antigen was visualized with Fast Blue substrate, whereas visualization of CD3 antigen was produced with 3-amino, 9-ethylcarbazole (AEC) substrate. Bars = 25 μm (**a**–**c**).

The population of DCs seems to become increasingly heterogeneous during the development of atherosclerotic lesions.[60] In addition to intimal resident VDCs, blood monocytes migrate into the intima through the luminal endothelial cell monolayer and, depending on the micro-environmental conditions such as the content and composition of cytokines,[78] may differentiate either into macrophages or into DCs.[78,79] In some circumstances, even macrophages could become capable of dedifferentiation and acquisition of the DC phenotype.[80,81]

Mapping of DCs in advanced atherosclerotic plaques shows that DCs are distributed highly irregularly throughout plaques.[60] DCs are most frequently present in areas of neovascularization in the shoulders of plaques.[60] Interestingly, not all foci of plaque neovascularization are associated with the presence of prominent numbers of lymphocytes, but all areas of neovascularization consistently contain DCs.[60] One cannot exclude the fact that advanced atherosclerotic plaques receive new portions of DCs and DC precursors, invading plaques together with microvessels of neovascularization, which originate from adventitial *vasa vasorum*. This possibility is supported by observations of DCs in the adventitia of the normal arteries where DCs are predominantly located in close proximity to the capillaries of *vasa vasorum* on the media–adventitia junction.[80,81] Ingrowths of *vasa vasorum* together with the lymphatics to advanced atherosclerotic plaques might facilitate the exchange of DC precursors and maturing DCs between the 'arterial tissue' and lymph.[60] A scheme in Figure 9a depicts DC distribution in an atherosclerotic plaque and indicates their possible migratory routs. Neovascularization areas without prominent numbers of lymphocytes (NA) (Figure 9a and b; Table 2) might represent 'recent' ingrowths of adventitial *vasa vasorum* capillaries into the atherosclerotic intima. In neovascularization areas containing large numbers of lymphocytes (NA-II), frequent contacts between DCs and lymphocytes are common (Figure 9a and c).

Significance of DCs in the Maintenance and Breakdown of the Arterial Homeostasis: Theoretical Speculations and Experimental Insights

In 1997, Wick *et al*[82] postulated that VDCs have an important role in the maintenance of arterial homeostasis.

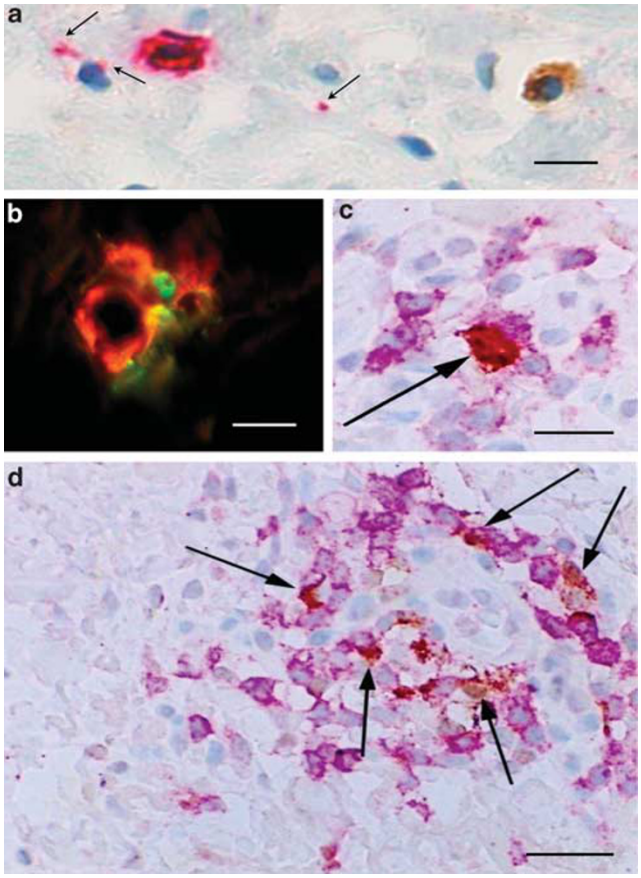

Figure 8 Different types of DCs and DC maturation in atherosclerotic lesions (**a**–**d**). (**a**) Double immunostaining showing the presence of both myeloid (rose) and plasmacytoid (brown) types of DCs in the arterial intima. Arrows show cross-sections of DC processes. BDCA-1 and BDCA-2 (Santa Cruz Biotechnology) were used for the identification of mDCs and pDCs. Panel b shows close apposition of pDCs (BDCA-2 +) (green) to endothelial cells (von Willebrand factor +) (red) in an area of neovascularization in an advanced atherosclerotic plaque, revealed by immune fluorescent technique using a combination of RPE- or FITC-labeled secondary antibodies. (**c**, **d**) Clustering of mature DCs (brown) (arrows) with T lymphocytes (rose). Double immunostaining: DCs were identified with anti-CD83 (PharMingen), whereas T cells were identified with anti-CD3 (Dako); combination of ABC immunoperoxidase reaction (brown reaction product) and Fast Red substrate kit (rose reaction product); counterstaining with Mayer's hematoxylin. Human aorta specimens. Bars = 25 μm (**a**), 75 μm (**b**), 40 μm (**c**, **d**).

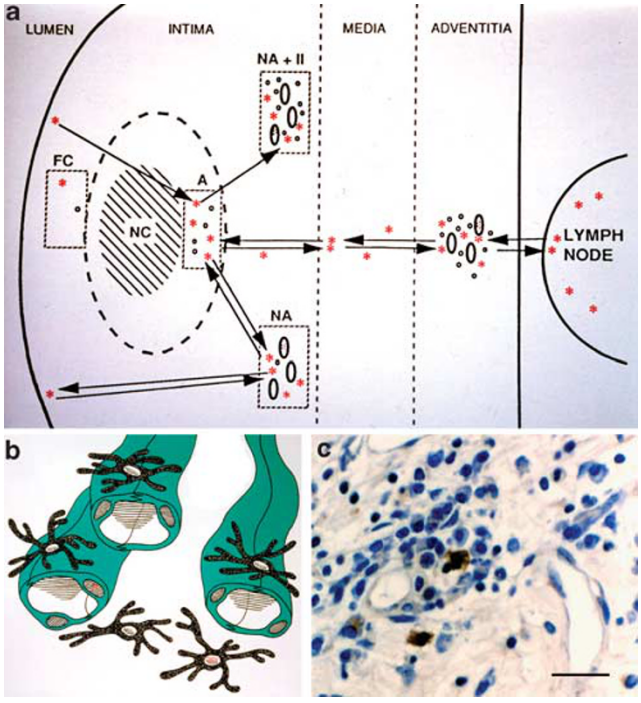

Figure 9 Distribution of DCs in atherosclerotic plaque (**a**–**c**). (**a**) Scheme of DC distribution in an atherosclerotic plaque and their possible migration (explanation in text). Red asterisks (*) indicate DCs; small black circles (o) indicate T cells; ellipse indicates capillary from the neovascularization plexus in the plaque and capillary of *vasa vasorum* in the adventitia. FC—fibrous cap; NA + II—neovascularization area associated with prominent inflammatory infiltrates; NA—neovascularization area not associated with signs of inflammation; A—an area without neovascularization surrounding the necrotic core; NC—the necrotic core. Arrows indicate the possible DC migration routes. (**b**) Scheme illustrating association of DCs (black) with capillaries in areas of plaque neovascularization. (**c**) DCs in an area of neovascularization enriched by immune-inflammatory cells (NA + II). DCs were visualized using anti-fascin (Dako). ABC immunoperoxidase reaction; Counterstaining with Mayer's hematoxylin. Bar = 40 μm.

Wick *et al* and colleagues have developed a concept of vascular-associated lymphoid tissue (VALT), which is analogous to the mucosa-associated lymphoid tissue of the respiratory and gastrointestinal tracts.[58,82] VALT consists of a small number of VDCs, T cells and resident macrophages distributed throughout the subendothelial layer of the arterial intima along the luminal endothelial monolayer.[51,52,58,82] VDCs represent the key element, integrating other cell types within VALT into focal cellular networks and screen 'vascular tissue' for potentially harmful antigens.[58,82] The existence of such cellular networks has been demonstrated by ultrastructural and immunohistochemical examinations of

Table 2 Frequency of immune-inflammatory cells in different areas of complicated atherosclerotic plaque (cells per vision field, 10 × 40 magnification; see Figure 9a)

Cell type	Area subdivision			
	FC	NA+II	NA	A
DCs	+	++/+++	++/+++	±
T-cells	+	+++	+	±
Macrophages	+	+	+	++/+++

FC, fibrous cap; NA+II, neovascularization areas associated with massive inflammatory infiltrates; NA, neovascularization areas not associated with signs of inflammation; A, areas surrounding the necrotic core.

Semi-quantitative graduating scale (− to +++) for estimating cell numbers:

For dendritic cells (DCs): − indicates that no cells were detected; + indicates 1–2 cells; ++ indicates 2–5 cells; +++ indicates >5 cells.

For T cells and macrophages: − means cell number <2% of the total cell population; + <20%; ++ ~50%; +++ >50%.

human large arteries, including the aorta, carotid and coronary arteries.[12,58,60,82] In the arterial wall, VDCs may have a role in not only the surveillance but also in the tolerization against autoantigens by silencing T-cell responses, just as this occurs in other anatomical locations.[83,84]

Assessment of the numbers of VDCs in the intima of atherosclerosis-prone and atherosclerosis-resistant areas of the nondiseased human aorta has found that, in atherosclerosis-prone areas, there were more VDCs than in atherosclerosis-resistant areas.[12] In atherosclerosis-prone areas, VDCs were found to form cell clusters.[85] The increased numbers of VDCs have also been identified in the intima of the carotid arteries of children, 8 weeks to 10 years of age, at sites subjected to major hemodynamic stress and predisposed to the development of atherosclerosis.[68] The accumulation of clustering DCs in other pathological conditions has been reported to be an earlier indicator of the development of autoimmune disease.[3]

According to the autoimmune hypothesis of atherosclerosis proposed by Wick *et al*,[58,82] VALT activation by autoantigens is responsible for the initiation of immune responses in the arterial wall, which eventually lead to atherosclerotic alteration. Modification of various molecules and lipoproteins, as well as molecular mimicry may lead to the recognition of self-determinants by VDCs. The observations of VDCs, accumulating and clustering in atherosclerosis-prone areas of arteries,[12,85] are supportive of the concept that immune mechanisms are involved in the formation of atherosclerotic lesions from the very early stages of the disease.[13,16,58,82]

The identification of DCs in the arteries of animal models[86–88] has facilitated the investigation of the impact of DCs in atherosclerosis. Necropsy observations and theoretical speculations[12,49,50,58,82] have received support from experimental animal studies, which focused on the elucidation of the functional significance of DCs in atherogenesis.[75,76,89–93] Ludewig *et al*[94] were the first to report a link between immune-mediated arterial inflammation and cholesterol-induced atherosclerosis in a transgenic mouse model, mediated by DCs. Angeli *et al*[95] demonstrated that dyslipidemia associated with atherosclerotic disease systemically alters the DC function. Despite that oxidized low-density lipoproteins (oxLDLs) could be potentially dangerous for the survival of DCs, a study by Packard *et al*[96] showed that DCs can maintain antigen-processing and antigen-presenting capabilities, which allow them to efficiently prime T cells under hypercholesterolemic conditions associated with atherosclerosis. An experimental study by Liu *et al*[97] demonstrated that DC accumulation in arterial lesions is associated with plaque growth and inflammation. Further understanding of the impact of DCs in atherosclerosis has been achieved in a recent study by Gautier *et al.*[77] Gautier *et al*[77] have created a mouse model in which the lifespan and immunogenicity of DCs were enhanced by specific overexpression of the antiapoptotic gene hBcl-2 under the control of the CD11c promoter. In either LDL receptor-deficient or apolipoprotein E-deficient backgrounds, DC-hBcl2 mice exhibited an expanded DC population associated with enhanced T-cell activation, a Th1 and Th17 cytokine expression profile, as well as elevated production of Th1-driven IgG2c autoantibodies directed against oxidation-specific epitopes.[77] However, this proatherogenic signature was not associated with the acceleration of atherosclerotic plaque progression because expansion of the DC population was unexpectedly associated with an atheroprotective decrease in plasma cholesterol levels.[77] Conversely, a depletion of DCs in hyperlipidemic CD11c-diphtheria toxin receptor/apolipoprotein E-deficient transgenic mice resulted in enhanced cholesterolemia, thereby arguing for a close relationship between the DC population and plasma cholesterol levels.[77] These experiments have convincingly demonstrated that DCs are central to the atherosclerotic process because they are directly implicated in both cholesterol homeostasis and immune response.[77]

Recent experiments using DCs for vaccination in mouse models of atherosclerosis confirmed that DCs are functionally significant in atherogenesis.[98–100] Vaccination using mature DCs pulsed with oxLDL-induced oxLDL-specific T cells with a lowered Th1 response, increased the levels of oxLDL-specific antibodies and reduced lesion size.[98] Hjerpe *et al*[99] have reported that DCs pulsed with malondialdehyde modified LDL aggravate atherosclerosis in ApoE (−/−) mice.

Tissue Microenvironment in Atherosclerosis and DC Function

The number of DCs increases in the early development of atherosclerotic lesions.[49] This might occur as a result of either the induction of intensified differentiation of silent VDC precursors that preexist in the subendothelial layer, possibly from embryonic stages, or alternatively, as a result of the migration of monocytes and other DC precursors into the intima from the bloodstream.[60,78,79] In the second scenario, the interaction of DC precursors with the luminal endothelium is of special importance.[101]

Chemotactic stimuli and the involvement of adhesion molecules are necessary for the invasion of DCs into the intima.[101] Chemokines, such as CCL2, CCL5 and fractalkine, and adhesion molecules such as P-selectin, E-selectin and vascular cell adhesion molecule-1 (VCAM-1) are implemental in the accumulation of DCs in the arterial intima.[17,20,21,24,101] CX3CR1 deficiency has been shown to impair DC accumulation in the arterial wall in a mouse model.[97] Under *in vitro* conditions, DC adhesion and migration through the endothelium are modulated by changes in endothelial function.[101,102] DC adhesion and transmigration are markedly increased after exposing endothelial cells to hypoxia and TNF-α, known as stimuli that accelerate atherogenesis.[101,102] The inhibition of endothelial NO synthase increased DC binding and transmigration, whereas the augmentation of endothelial NO synthase activity has been

found to prevent DC adhesion.[101] Increased adhesion of DCs to endothelial cells *in vitro* is promoted by oxLDL.[101]

In the arterial intima, immature DCs can be activated by various stimuli.[101–106] Cellular components, released from dying cells, collectively called damage-associated molecular patterns and pathogen-associated molecular patterns that originate from microbes and viruses can induce the activation and maturation of DCs.[7–9] Ultrastructural analysis of the nondiseased intima of athero-prone areas of the aorta has shown that in this location, there is a casual presence of dying cells and cells exhibiting signs of destruction.[12] Cellular debris is a typical feature of intimal thickenings.[107]

Atherosclerotic plaques contain a large number of necrotic cells.[108,109] Viruses and microbes can be identified in some atherosclerotic lesions,[110,111] with components of Chlamydia pneumoniae being detectable in the cytoplasm of DCs.[112] DCs receive signals through various pattern-recognition receptors, including Toll-like receptors (TLRs), cell-surface C-type lectin receptors and intracytoplasmic NOD-like receptors.[7–9] DCs sense the lipid environment by nuclear hormone receptors, such as peroxisome proliferator-activated receptors (PPARs), liver X receptors (LXRs) and others.[113,114] The most investigated receptors for recognizing signals are TLRs.[15,115,116] TLR4 which has a central role in the initiation and progression of atherosclerosis is expressed by DCs in the arterial wall.[117,118] Modified autoantigens, such as oxLDL, heat-shock proteins (HSPs) and fragments of bacteria, such as lipopolysaccharides, are recognized by TLR4, followed by the activation of the subsequent signaling cascade.[15,117–123] TLR2 may contribute to atherogenesis, possibly activating DCs due to the presence of Chlamydia pneumoniae in atherosclerotic lesions.[122] TLR7, TLR8 and TLR9, which recognize motifs of nucleic acids deriving from infectious pathogens and from dying cells, may also be involved in DC activation.[115,116,121] It has been suggested that vessel-specific TLR expression patterns can induce distinct types of vascular inflammation as result of selective susceptibility of different regions of the vascular tree to atherosclerosis.[121]

Antigens, such as oxLDL and HSPs, bind to TLRs and to scavenger receptors.[13,15,115,123,124] The formation of oxLDL and otherwise modified LDL and their accumulation in the arterial intima are key events in atherosclerosis.[108] From the very early stages of atherosclerotic alteration, the arterial intima represents a vicinity of increased coaccumulation of oxLDL and DCs.[13,83] DC function has been shown to be affected by oxLDL and otherwise modified LDL.[124–126] Nickel *et al*[124] have reported that DCs are capable of the uptake of LDL *in vitro* and that the pronounced oxLDL uptake capacity is associated with the expression of LOX1, CD36 and CD205 molecules on the DC surface.[124] Similarly, this occurs with macrophages wherein LOX-1, CD36 and CD205 act as scavenger receptors for DCs.[124] However, in contrast to macrophages, the vast majority of DCs in atherosclerotic lesions do not transform into foam cells.[127] The understanding of DC protective mechanisms against excessive lipid accumulation may be instrumental in the development of approaches for the suppression of foam cell formation in atherosclerosis.

Oxidized LDLs promote mature DC transition from monocytes and induce prominent DC clustering.[125,126] The interaction of DCs with oxLDL leads to DC maturation, triggered, at least in part, by activation of the NFκB-pathway.[124] This interaction also induces a proinflammatory cytokine profile in DCs. The production of pro-atherogenic cytokines IL-6 and IL-13 occurs, whereas the release of anti-atherogenic IL-10 is reduced.[124] DC-derived IL-13 appears to be one of the critical factors for DCs to acquire the capability to induce Th2 cytokine production.[124] Mature oxLDL-presenting DCs are essential for priming naive T cells that induce the formation of subsets of oxLDL-specific T cells.[124] The ability of oxLDL to induce CD83 upregulation *in vitro*[124] may explain that up to 70% of DCs in some foci of atherosclerotic plaques are mature and capable of clustering with T cells.[61]

During the last few years, the mechanisms and factors affecting the differentiation and maturation of DCs have been intensely studied in both *in vitro* and *in vivo* experimental settings, relevant to atherosclerosis.[128–138] It has been shown that Apolipoprotein A-I, the major protein component of serum high-density lipoproteins, inhibits DC differentiation and maturation.[132] PPAR-α agonists ciglitazone and fenofibrate also inhibit oxLDL-induced maturation and immune functions of DCs *in vitro*.[133,134] Advanced glycosylation end products can promote atherosclerosis by inducing maturation of DCs.[135] In advanced atherosclerotic plaques, especially in areas around the lipid cores which lack neovascularization, DC function can be affected by hypoxia.[136–138]

In atherosclerotic lesions, activated DCs display an abundance of HSP-70, indicating that the activation of DCs might be linked to cell stress.[139] Upon activation, DCs produce mediators of the innate immune system and undergo a maturation process which involves the expression of costimulatory molecules such as CD80 and CD86, which are crucial for the induction of adaptive immune responses.[3–10] Mapping of the distribution of DCs in atherosclerotic lesions has shown that DCs are most frequently present in areas enriched with T cells[60] and, particularly so, within inflammatory infiltrates where DCs are found to cluster with T cells (Figures 7c and 8c, d). CD83 + DCs in plaques produce the T cell-attracting chemokines CCL19 and CCL21.[140] DCs clustering with T cells display the intercellular cell adhesion molecule-1 and VCAM-1,[60] interactions of which with leukocyte function-associated antigen-1 and very late activation antigen-4, respectively, are essential for T-cell activation.[141] In DC/T-cell interactions, DCs display CD40[60,142] and express high levels of HLA-DR[60] and CD1 molecules.[60,73,74]

An experimental *in vivo* study has shown that trafficking of monocyte-derived DCs from atherosclerotic plaques occurs during lesion regression, but little DC emigration has been detected from progressive plaques, suggesting that the progression of atherosclerotic plaques may result not only from

the robust monocyte recruitment into arterial walls but also from the reduced emigration of DCs from lesions.[143] This finding is in agreement with studies of human arterial tissue, which have indicated that only some DCs may migrate to the lymph nodes, whereas other DCs may activate T cells directly within the intima.[60] The fact that successful antigen presentation might occur directly within the arterial wall is supported by the identification of clonally expanded T cells in atherosclerotic plaques.[144] Isolated VDCs have been reported to be capable of presenting antigen to transgenic T cells as effectively as bone marrow-derived mDCs.[20] It is believed that the migratory routes of other activated DCs, which avoid contacts with T cells within plague, might be similar to the migratory routes known for Langerhans cells of the skin.[60] After engulfing antigen in the arterial wall, DCs might migrate as veiled cells through the afferent lymph into regional lymph nodes where they fulfill their antigen-presenting function. Supporting this possibility are immunohistochemical observations which have shown that the number of interdigitating cells in para-aortic and jugulodigastric lymph nodes attached to atherosclerotic arterial wall segments exceed those in the lymph nodes attached to non-atherosclerotic arterial segments.[60] DCs might migrate from the intima to the adventitia and thence to lymph nodes, but it cannot be excluded that can also be an exchange of DCs back and forth between the arterial wall and lymph nodes (Figure 9a). It has also been suggested that some DCs could emigrate to the blood stream.[16,143]

Apart from the formation of direct contacts with T cells (Figures 7c and 8c, d), DCs in atherosclerotic lesions have been found to have direct contacts with B cells (CD20+), and this immunohistochemical finding has been confirmed by electron-microscopic observations.[145] Follicular DCs (FDCs) are known as cells that facilitate antigen recognition by B cells in follicles in lymphoid organs.[3] This kind of DC is not bone marrow derived and is purely a resident of the follicles of secondary lymphoid organs.[3] In atherosclerotic lesions, no expression of markers specific to FDCs has been detected which allows speculation that atherosclerotic lesions contain an unusual subset of DCs capable of forming contacts with B cells and plasma cells.[145]

The significance of this DC subset in the eliciting of antibody production requires investigation. Interestingly, complement component C1q, which is expressed by interdigitating cells and FDCs in the spleen, and which is believed to be involved in capturing immune complexes,[146,147] is also expressed by some DCs in atherosclerotic lesions.[148]

Impact of DCs on Plaque Destabilization

In atherosclerotic plaques, the number of DCs increases with most DCs accumulating in plaque shoulders, which represent plaque rupture-prone regions.[60,61] Yilmaz *et al*[61] have found that up to 70% of DCs in the shoulders of vulnerable carotid plaques express markers of DC activation, such as CD83 and DC-LAMP. In plaque rupture-prone regions, activated DCs were found to form direct contacts with T cells.[60,61] Apart from conventional T cells, NKT cells have been found to form T-cell/DC contacts.[73] Cell clusters, consisting of activated DCs and T cells, are associated with plaque destabilization.[60,61,140] Enhanced recruitment of immune cells through neovessels into plaque shoulders has been linked to the high expression of chemokines/chemokine receptors.[140]

It has been reported that DC numbers in plaques are markedly elevated in patients with acute ischemic symptoms.[61] In statin-treated patients, atherosclerotic plaques contain significantly lower numbers of DCs than plaques in patients without statin treatment.[61] The beneficial effects of statins in atherosclerosis might be explained by the inhibition of the maturation process and antigen-presenting function of DCs, as shown in *in vitro* experiments.[149–151] The numbers of circulating DC precursors in coronary artery disease (CAD) and in patients with cerebrovascular disease (CVD) are of increasing interest.[152–154] The numbers of mDCs and pDCs have been assessed in a number of studies, and the results are indicative of the clinical importance of evaluating the predictive values of the number of different DC types in CAD and CVD.[152,154] It has been shown that patients with stable CAD have lower levels of circulating DC precursors than do healthy individuals.[152,154] This decrease seems to be an independent predictor of the presence of, and subsequent therapeutic procedure in, stable CAD.[152,154] In patients with CAD and patients with unstable angina pectoris, DC function is altered.[152–157]

DCs as a Possible Instrument in Atherosclerosis Immunotherapy

It may be quite some time before vaccination trials for atherosclerosis can begin.[158,159] Perhaps, DCs might be used for vaccination in atherosclerosis.[160] As DCs not only activate T cells but also tolerize T cells to antigens that are innate to the body (self-antigens),[3–10] it may be possible to engage DCs in the disarming of damaging immune responses in atherosclerosis.[160] This might be achieved by either using different types of 'natural' DCs or by producing *in vitro* 'synthetic' DCs with desirable properties.[160] In atherosclerosis immunotherapy, DCs could be used for the regulation of Th1/Th2 balance or Th17 response. DCs might be exploited to expand CD4+Foxp3+ Treg cells. Therapeutic intervention in atherosclerosis might also involve the direct targeting of DCs *in vivo* and may include manipulating the functions of myeloid and lymphoid subsets of DCs.[160] Approaches using DCs in atherosclerosis immunotherapy might be similar to or different from those already used for cancer immunotherapy.[3,161–166]

It has been reported that immunization with oxLDL or with specific epitopes of the apolipoprotein B-100 component of LDL represents a promising therapeutic approach against atherosclerosis.[167–169] Perhaps, oxLDL-pulsed DCs or DCs pulsed with components of LDL could be used for vaccination as well, using approaches developed for cancer

immunotherapy. One of the approaches currently used in cancer immunotherapy is based on a technique, in which DCs are isolated from the peripheral blood and pulsed *ex vivo* with the appropriate antigen before being used for vaccination.[3,161,162] Perhaps, vaccination with oxLDL-pulsed DCs in such a manner might avoid the side effects of direct vaccination with oxLDL. For purposes of the vaccination, DCs can be pulsed not only with oxLDL. DCs obtained from the peripheral blood can be pulsed *ex vivo* by cultivating them with a total extract or suspension of atherosclerotic plaque tissue, obtained, for example, from patients undergoing carotid endarterectomy.[160] Vaccination of a person with their 'own' DCs, pulsed by their 'own' antigens, might tend to be more suitable and efficient due to the existence of individual peculiarities in the development of atherosclerosis.[160] The incubation of 'own' DCs with 'own' danger factors *ex vivo* would imitate events as they occur in plaques *in situ* in a patient. As the presentation of antigen complexes to T cells in the absence of costimulatory signals could lead to the anergy and apoptosis of T cells, the expression of costimulatory molecules on pulsed DCs can be adjusted, as desired, *ex vivo* before vaccination. Remarkable achievements in the development of techniques for the ligation of costimulatory molecules have made it possible to generate DCs with desirable properties.[3,161–166] Recent experimental studies, using DCs for vaccination in mouse models of atherosclerosis, support a possibility that DCs might represent a valuable instrument in atherosclerosis immunotherapy.[98–100]

CONCLUDING REMARKS

Atherosclerosis is a chronic immune-inflammatory disease. Atherosclerotic plaques contain inflammatory infiltrates consisting of activated T cells. Antigen-specific T-cell activation depends on the interactions of T-cell receptors with antigens presented by MHC and CD1 molecules by DCs. DCs have critical antigen-presenting and antigen-priming roles in the initiation of atherosclerosis. Various signals that promote the activation of DCs drive the maturation of DCs to prime self-specific responses and drive the perpetuation of vascular inflammation. These signals include, in particular, oxLDL and infection. Some DCs undergo maturation and cluster with T cells and B cells directly within atherosclerotic lesions, whereas others migrate to lymphoid organs. There now exists a rising demand to exploit the properties of DCs in addressing the need for atherosclerosis immunotherapy.

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DISCLOSURE/CONFLICT OF INTEREST

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