Commentary
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Facets of Dendritic Cell Function: Who would Think about Cardiovascular Diseases?

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Commentary

Dendritic cells (DCs) hold a central role in immunological processes which are mounted to improve survival after infection and injury [1]. DC function included immune reactions that can be assigned to one of the three categories: (i) antigen capture, processing and presentation to lymphocytes in lymphoid organs, (ii) mediating innate and adaptive responses that are potent and qualitatively matched to disease causing agents, (iii) development of DC subsets with different properties regarding antigen presentation, maturation and location [2]. In summary, the function of DCs comprises antigen recognition as well as the regulation and control of immune responses. Over the last years it became evident that DCs act as key players in a large number of diseases such as infectious diseases, cancer, autoimmunity and allergy. Moreover, DCs play a crucial role in disease development and progression of cardiovascular diseases (CVDs), which represents the most frequent causes of death worldwide, with an estimated 17.3 million deaths per year [3].

Circulating *vs.* Tissue-residing Dendritic Cells

Circulating peripheral blood DCs make up between 0.01% and 0.1% of the circulating white blood cells and contain at least two DC subsets. These include the myeloid DCs (mDCs) which express HLA-DR, CD11c and CD33, and the plasmacytoid DCs (pDCs) of the lymphoid lineage which express CD123 instead of CD11c or CD33. Both subsets are able to induce lymphocyte activation, but only the myeloid subset can process soluble antigens [4]. Further characterization of circulating DCs identified the blood dendritic cell antigens (BDCAs) which allow a continuing subset classification of pDCs into the BDCA2+ and BDCA4+ as well as of mDCs into the BDCA1+ and BDCA3+ subset. Tissue-residing DCs can be found in the skin, lung, liver, heart, kidney, spleen, intestinal tract and in the lymph nodes [5]. A large number of subsets have been characterized for the different organs, while each subset holds a specialized function, e.g. the epidermal Langerhans' cells or the Kupffer cells in the liver. In pathological processes, DCs can be found in the inflamed or injured tissue where they exert their biological function. Often this biological function has not been investigated in detail, because biopsy material is difficult to access. Circulating and tissue-resident DC homeostasis are closely connected to each other because circulating DCs can be recruited and replace the tissue-resident DCs. For example, animal studies showed that cardiac DCs were replaced within 2-4 weeks after irradiation [5]. This knowledge about the mutual interaction between blood and tissue DCs is slightly taking its place in research studies. The majority of research work focus either on circulating DCs or tissue-resident DCs.

DCs Involved in CVDs

CVDs are accompanied by or cause immunological reactions and therefore, involve DCs in the pathogenesis of the disease. For example, atherosclerotic changes in blood vessels are accompanied by an infiltration of T cells, monocytes and DCs which invade the vascular wall to the places of atherosclerotic lesions where they produce proinflammatory cytokines [6]. The proinflammatory environment leads to plaque destabilization and a further recruitment of immune cells such as T cells, mDCs and pDCs to the plaque region [7]. Different DC subsets have been identified in atherosclerotic plaques (Table 1), but further functional characterization of these subsets are still lacking.

DC subset	Phenotype	Reference
Interdigitating and vascular DCs	Fascin+	[22-24]
Vascular DCs	S100+	[22,24,25]
Immature DCs	CD209+	[24]
Interdigitating mature DCs	DC-LAMP+	[22]
Mature DCs	CD83+	[22,24,25]
pDCs	CD123+	[25-27]
pDCs	BDCA2+	[23,25]
pDCs	BDCA4+	[24]
mDCs	CD11c+	[26,27]
mDCs	BDCA1+	[23,25]
DCs	Langerin+	[25]

Table 1: Reported DC subsets in human atherosclerotic plaques.

The interplay of circulating and tissue-resident DCs has been investigated in patients suffering from coronary artery disease (CAD). Yilmaz et al. showed that a reduction of circulating DCs correlated with an increase of DCs in the atherosclerotic vascular wall which led to the conclusion that DCs and their subsets mDCs and pDCs are independent predictors of CAD [8]. In earlier studies stenotic vein coronary bypass grafts showed increased levels of tissue DCs which were positive for S100, CD1a and CD40 [9,10]. Infiltration of DCs was also reported for necrotic and active inflammatory lesions in myocarditis [11]. It is assumed that the cardiac DCs which showed the typical DC morphology with large cellular processes exert the destructive effect on myocytes. The effects of cardiac DCs were also

investigated after myocardial infarction (MI). One pathological process following MI is the uptake and presentation of myocardial peptides by DCs and the subsequently T cell activation [7]. There is a temporary loss of circulating DCs due to their migration into the myocardium early after MI for seven days when numbers of circulating DCs return to baseline levels without changing in the following months [12]. During the post-MI healing process, DCs act as immunoprotective regulators by controlling the monocyte/macrophage homeostasis via the activation of regulatory T cells (Tregs), CD4+ and CD8+ T cells [7]. Changes of cardiac DCs were also found in dilated cardiomyopathy (DCM), where a reduction of DC subsets (mDCs, pDCs, mature DCs and immature DCs) and of maturation markers (fascin, CD11c, CD209, CD83 and BDCA-4) was reported [13]. Furthermore, circulating DCs in patients with heart failure (HF) have been analyzed, but no clear consensus about their role in this disease has been found in clinical studies so far. The behavior of DCs may depend on the fact if HF is acute or chronic as well as of the clinical presentation (New York Heart Association, NYHA class) of HF. Distinct types of end-stage HF such as DCM and ischemic cardiomyopathy (ICM) resulted in heart transplantation (HTx). In the field of transplantation immunological processes play a central role in therapy and clinical decisions. Clinical studies that monitored DCs after HTx focused on the identification of valuable markers of immune function status after transplantation [14]. Interestingly, all studies following HTx detected the two main DC subsets mDCs and pDCs via the expression of the surface markers in the lineage cocktail 1 (CD3, CD14, CD16, CD19, CD20, CD56), HLA-DR, CD11c and CD123 [14-19]. These studies demonstrated that DC incidence and subset distribution differed substantially between recipients before and after HTx as well as in healthy subjects, and may have the potential to monitor the individual immune status [7]. These data suggest that DC homeostasis is altered after transplantation, whereby surgery, stress and the immunosuppressive regimen seem to have a major impact.

DC Facets and the Problem of Translating DC Biology

The patient's immune response consists of a multiplicity of cellular events which are regulated and controlled by DCs that orchestrate antigen presentation and clonal selection, summarized as the immune recognition repertoire, as well as lymphocyte growth, differentiation and memory, summarized as the immune response repertoire [2]. In CVDs, both types of DC function play a role in disease development and progression. This central role predestines DCs as targets or tools for biomarker studies and therapies. However, many aspects of DC function are unclear and have to be investigated in preclinical studies. This project requires suitable and valid animal models for both: CVDs and the immune system. The ideal animal model of CVD will mimic the human subject metabolically and pathophysiologically, will be large enough to permit physiological and metabolic studies, and will develop end-stage disease comparable to those in human [20]. Currently, a large number of animal models for CVDs exist which have been developed to address cardiovascular complications including atherotrombotic and cardiac diseases [21]. Mouse and rat are characteristically resistant to CVDs, but genetic modification of several target genes led to stable CVD animal models and is easy to achieve in rodents. However, CVDs have a complex multifactorial nature and genetic as well as environmental factors play a significant role in cardiovascular pathophysiology [21]. Therefore, it is difficult to match a particular CVD with a single experimental model [21]. Furthermore, studying the immune system and their effects in distinct organs is still a challenge in animal models. For example, the immune systems of mice and men differ in considerable aspects [5]. Although there are humanized mouse strains that carry parts of the human immune systems, studies with these mice in the field of CVDs are not known. Potential larger animal models such as pig and sheep are problematic due to cost, ethical considerations or poor pathophysiological comparability to humans [20]. Despite the necessity for intensive basic science in the field of DCs, the call for more patient-based research is getting stronger [2]. Human studies are limited to observational studies that describe the occurrence, development and distribution of DCs in the blood or the peripheral tissue. In the case of CVDs, the most studies investigated circulating DCs, but these studies fail to provide information about the processes that are initiated after DC activation or tissue-specific DCs [7]. An intensified clinical research should include studies measuring simultaneously both circulating as well as tissue-resident DCs. Observations of these studies would promote the understanding of the DC network and their interactions in the human body. One limitation of this concept is the availability of biopsy material which is necessary to investigate tissue-resident DCs. Regarding CVDs, biopsy withdrawal is connected to additional risks for patients and, in many cases, not includable in the clinical routine. This might be the reason why only a few human studies with low patient numbers compared DCs in the tissue with peripheral blood DCs (e.g. studies in the field of HTx and atherosclerosis), whereas the role of DCs in hypertension and in HF is still widely unexplored [7]. Furthermore, study results are often not comparable (e.g. in case of atherosclerosis) because different markers were used for DC classification. Consequently, a clear consensus is required for the functional and phenotypical characterization of DCs for the sake of comparability of study results [7]. Basic research with patients differs substantially from current outcome studies as well as drug licensing studies, which are designed to test whether existing practices and concepts are clinically effective [2]. In conclusion, there are still too many gaps in the knowledge of DC function, distribution and maturation that impede the implementation of experimental and therapeutic approaches in the clinic. However, according to the current results of DC function in CVDs it seems to be promising to further develop standardized assays to explore the role of circulating and tissue-resident DCs which might be open the door for novel preventive and therapeutic options in CVDs.

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