Editorial

Potential role of dendritic cells in atherogenesis

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Dendritic cells (DCs), originally described by Steinmann and Cohn in 1973, play a crucial role in initiation of an immune response: they are the key antigen presenting cells (APCs) [1]. They originate from hematopoietic stem cells in bone marrow, migrate as immature precursors within the monocyte cell population in the blood stream, and emigrate into different tissues. Within these tissues, DCs differentiate (Fig. 1) and become active in taking up (pinocytosis; phagocytosis) and processing antigens bound to molecules of the major histocompatibility complex (MHC-I or MHC-II). In response to antigen-processing DCs mature, migrate to the T-cell areas of secondary lymphoid organs and activate naïve T and B-lymphocytes. DCs with antigen-peptides bound to MHC-I molecules stimulate and activate cytotoxic T-lymphocytes [2]. Re-expression of antigens to MHC-II molecules results in stimulation of T helper cells with profound immune regulatory effects.

1. Dendritic cells and atherogenesis

The main theories of atherogenesis are the ‘response to injury’ [3], the ‘response to altered lipoprotein’ [4] and during the last years the ‘immunological’ hypotheses [5]. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY)-study, published previously, documents by using immunhistochemical methods, that inflammatory activity represents the first step towards atherosclerosis development in young adults. An accumulation of activated T-lymphocytes, dendritic cells, macrophages and aberrant MHC class II expression on cells can be noticed in the intima predisposed to the development of atherosclerotic lesions later in life particularly if classical risk factors are present [6]. Also in animal models of experimental atherogenesis dendritic cells are found clustered around arterial branch-points where they localise with T-lymphocytes and macrophages. Furthermore, the presence of dendritic cells in normal arterial intima suggests T-cell sensitisation [7,8]. And finally, analogous to the mucosa-associated lymphoid tissue (MALT), Wick et al. established the description vascular-associated lymphoid tissue (VALT) for accumulations of mononuclear cells in the arterial intima which provides a local defense mechanism.

The following candidate-antigens that may lead to cellular immune reactions in atherogenesis are discussed: (a) modified lipoproteins (e.g. oxidized-LDL); (b) denatured macromolecules from plaque-material; (c) neoantigens: heat shock proteins (HSPs) or endothelial surface antigens; (d) antigens of infectious organisms such as herpes virus, cytomegalovirus or Chlamydia pneumoniae.

Modified lipoproteins (e.g. ox-LDL) are one of the endogenous activators of immune response. In vitro studies show that elevated levels of ox-LDL would favor a rapid generation of mature dendritic cells from monocytes [10]. Autoantibodies to ox-LDL are considered to have a protective role in atherogenesis. In an experimental model with ox-LDL immunized animals induction of atherosclerosis was not possible [11]. Furthermore it could be demonstrated that activated dendritic cells that overexpress heat shock proteins (HSP60/65) might be responsible for T-cell activation within the arterial wall [9]. In early intimal lesions HSP70 is overexpressed exclusively by DCs [12].

In the present issue of Cardiovascular Research Alderman and coworkers [13] demonstrate that ox-LDL induces a balanced immunogenic cascade. They show that DCs are activated and mature, under the influence of mildly oxidized LDL, and with continuous stimulation T-cell activation and proliferation occurs, representing a chronic inflammatory response. Surprisingly, in the presence of more highly oxidised LDL finally apoptosis of DCs is observed. Thus, highly-oxidized LDL would serve to limit T-cell activation due to DC elimination by apoptosis.

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Fig. 1. Antigen presentation by dendritic cells and lymphocyte responses. Antigens: modified low density lipoproteins, e.g. oxidised LDL (ox-LDL); neoantigens, e.g. heat-shock-protein (HSP), bacteria, virus. Pinocytosis and phagocytosis by dendritic cells. Antigen presentation: Antigen-major histocompatibility-complex (MHC)-II. Interaction with T-cell-receptor (TCR). T-lymphocyte-stimulation: T-helper-cells (Th1; Th2); cytotoxic T-cells, B-lymphocyte-stimulation. Interferon-γ (IFN-γ). Interleucin (IL).

2. Perspectives

The immunological hypothesis for the development of atherosclerosis postulates an immune/autoimmune reaction against candidate-antigens as a main initiating factor. This first inflammatory step of atherogenesis has been shown to be reversible, but continuous presence of classical risk factors for atherosclerosis will lead to irreversible severe lesions. Therefore, it is necessary to treat the vascular-associated lymphoid tissue (VALT) in the early step of atherogenesis. Due to their special immunostimulating properties DCs appear to be predestined for the induction of an immunomodulation. Similar to first experiences in the fields of immunotherapy of malignancies and autoimmune diseases, a genetic modification of autologous dendritic cells may induce an efficient cytotoxic or protective immune response. In the field of cell therapy in vitro treatment of DCs with candidate-antigen (i.e. ox-LDL, HSP) or alternatively genetic modification of these cells could provide new strategies in therapy of atherogenesis.

References