CHAPTER 8

Regulatory T-Cells, FoxP3 and Atherosclerosis
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Abstract

Innate immune responses follow accumulation of modified lipids within the arterial wall thereby influencing atherosclerotic plaque progression. One of the mechanisms evolved in maintaining immunologic self-tolerance involves upregulation of regulatory T-cells, among which the CD4+CD25+ FoxP3 regulatory T-cells (Treg) are best characterized. The putative important role of Treg in the initiation of atherosclerotic lesions as well as in the progression towards unstable plaques leading to ischemic events, supported by human studies and, indirectly, by murine models. Herein, we summarize the experimental approaches taken in order to study the possible mechanisms of Treg involvement in atherosclerosis as well as the beneficial clinical potential of Treg in stabilizing atherosclerotic plaques.

Atherosclerosis, Inflammation and Autoimmunity

The immune system plays a pivotal role in the pathogenesis of atherosclerosis, the underlying cause of many cardiovascular diseases, including myocardial infarction, stroke and ischemic gangrene. Atherosclerosis involves the innate immune responses with the recruitment and activation of monocytes/macrophages that respond to the accumulation of modified lipids, mainly the oxidatively modified LDL (OxLDL) within the arterial wall. These events are possibly followed by adoptive immune responses comprising differential antigen-specific T-lymphocytes. Most of the effector T-lymphocytes in atherosclerotic lesions are CD4+ T-helper cells with the phenotype characteristic of a proinflammatory T-helper 1 (Th1) subset. Most of the T-cells bear T-cell receptors (TCR) and are often found in clusters in shoulder regions of the lesion. These cells specifically recognize antigens that are produced in relative abundance in hypercholesterolemic individuals or in plaques, including Ox-LDL and HSP 60/65 in the form of antigen-presenting cells (APC) such as macrophages or dendritic cells. The accumulation of inflammatory cells within the arterial wall leads to local production of chemokines, interleukines and proteases that enhance the influx of monocytes and lymphocytes, among which are IFN-gamma, tumor necrosis factor (TNF)-alpha and membrane CD40 ligand, thereby amplifying the immune response and promoting progression of atherosclerotic lesions.

Regulatory T-Cells, Developmental and Functional Aspects

Many mechanisms have evolved to maintain immunologic self-tolerance and to limit responses to foreign antigens. One of these mechanisms involves regulatory T-cells that actively suppress responses of effector T-cells, via homing in on peripheral tissues in order to maintain self-tolerance and to prevent autoimmunity by inhibiting pathogenic lymphocytes. Several types of regulatory

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T-cells have been identified, including IL-10-producing Type 1 regulatory T-cells (Tr1), transforming growth factor beta (TGF beta)-producing Th3 cells and the CD4+CD25+ (interleukin-2 receptor-α chain) FoxP3+ regulatory T-cells (Treg) which are best ones characterized. Tregs are natural regulatory T-cells that mature in the thymus and comprise 5% to 10% of the peripheral CD4+ T-cells. FoxP3, a forkhead family transcription factor, is a lineage-specific factor for Treg, which plays a crucial role in their suppressive function as outlined in Figure 1. Whereas initial studies characterized these cells by their co-expression of CD4 and CD25 surface markers, subsequent reports identified expression of other surface markers including CTLA-4 (Cytotoxic T-Lymphocyte Antigen 4 also known as CD152) and GITR (Glucocorticoid-Induced TNF Receptor) as well as CD103, CD62L, lymphocyte activation gene 3 protein (LAG 3), C-C chemokine receptor Type 5 (CCR5) and neurophilin, and the concomitant absence of certain markers such as CD127 (the alpha chain of the IL-7 receptor). Major progress in the understanding of the homeostasis of naturally occurring Tregs was made with the identification of FoxP3 as a requisite factor for the development of Tregs and for their suppressive functions, as will be described in detail in the section below.

Natural Treg are generated during thymic development, but are also induced in peripheral tissues during immune responses and atherosclerosis (Fig. 2). Treg express antigen receptors typical of effector T-cells and are presumably activated by peptide antigens presented by APCs. They also acquire interleukin (IL)-2 receptor for development and survival. In this context, two populations of potential Treg have been described: those that originate from a committed lineage of FoxP3-expressing cells in the thymus and those that convert from mature CD4+ cells in the periphery.

The basic characteristics of natural Treg, and adaptive Treg versus effector T-cells are summarized in Table 1. Three general models of suppression have been proposed to explain the inhibitory actions of Treg cells on activated T-cells, none of which have been completely elucidated: 1. Cell contact-dependant suppression