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REVIEW TOPIC OF THE WEEK

Adaptive Immunity Dysregulation in Acute Coronary Syndromes

From Cellular and Molecular Basis to Clinical Implications

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ABSTRACT

Although the early outcome of acute coronary syndrome (ACS) has considerably improved in the last decade, cardiovascular diseases still represent the main cause of morbidity and mortality worldwide. This is mainly because recurrence of ACS eventually leads to the pandemics of heart failure and sudden cardiac death, thus calling for a reappraisal of the mechanisms responsible for coronary instability. This review discusses recent advances in our understanding of how adaptive immunity contributes to the pathogenesis of ACS and the clinical implications that arise from these new pathogenic concepts. (J Am Coll Cardiol 2016;68:2107–17) © 2016 by the American College of Cardiology Foundation.

In patients with acute coronary syndrome (ACS) and systemic evidence of inflammation, the higher frequency of activated T cells compared with stable angina (SA) (1–4) suggests that the sudden changes leading to coronary instability might be related to mechanisms involving T-cell immunity. In this review, we discuss recent advances in our understanding of how adaptive immunity contributes to the pathogenesis of ACS.

HELPER T-CELL DYSREGULATION IN ACS

Helper T cells ($CD4^+$ lymphocytes) are the key regulators of adaptive immunity. After T-cell receptor (TCR) activation by antigen-presenting cells (APCs), T cells differentiate into functionally polarized helper T cells, classified according to cytokine production, surface markers, and the expression of lineage-specifying transcription factors. The cytokine environment controls the induction of different T-cell subsets by the amount of antigen and by TCR-mediated signal strength (5,6). The principal helper T-cell subsets are the Th1, Th2, Th17, and follicular helper (Tfh) $CD4^+$ T cells. Moreover, a subpopulation of Th1 cells, characterized by defective cell surface expression of the costimulatory molecule CD28, is expanded in different chronic inflammatory conditions (7). Emerging subsets of helper T cells are Th22 (characterized by interleukin [IL]-22 production) and Th9 (producing IL-9) cells (6), but their role in ACS is still uncertain.

Patients with ACS have skewed T-cell differentiation, oriented toward aggressive effector phenotypes and defective regulatory T cells (Tregs), the lymphocyte compartment able to suppress the excessive immune response (**Table 1**). Overall, such T-cell abnormalities characterize about one-half of patients with ACS (8). In this subset of patients with ACS, helper T-cell dysregulation might affect the biological outcome of the immune response and contribute to plaque destabilization through multiple damaging pathways (**Figure 1**).

Th1 CELLS. Th1 cells are characterized by the production of interferon-gamma (IFN-γ) and by the expression of the transcription factor T-bet. They contribute to tissue destruction and participate in the pathophysiology of autoimmune diseases, such as

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

APC = antigen-presenting cell

CREB = cyclic adenosine monophosphate response element-binding protein

IFN = interferon

Ig = immunoglobulin

IL = interleukin

ITIM = immunoreceptor tyrosine-based inhibition motif

LDL = low-density lipoprotein

PTPN22 = protein tyrosine phosphatase nonreceptor type 22

RA = rheumatoid arthritis

SA = stable angina

SLE = systemic lupus erythematosus

TCR = T-cell receptor

TNF = tumor necrosis factor

Treg = regulatory T-cell

Zap70 = zeta-chain-associated protein kinase of 70 kDa

rheumatoid arthritis (RA) and inflammatory vascular diseases (6). The importance of TH1 and IFN-γ in atherosclerosis progression is well described in animal models (2), whereas their role in plaque destabilization is suggested by numerous studies, which show a marked increase in TH1 frequency and increased expression of TH1-related effectors, such as IFN-γ, signal transducer and activator of transcription-4, and T-bet in patients with ACS (9–13). IFN-γ can contribute to plaque destabilization in several ways: by the recruitment and activation of macrophages in the atherosclerotic lesions; by reducing collagen synthesis; by increasing the production of extracellular matrix-degrading proteins; and by activating APCs (14). Furthermore, the increased IFN-γ expression induces a positive feed-forward loop of TH1 induction, keeping a proinflammatory state.

When activated in the intima, TH1 cells produce proinflammatory cytokines and enhance the expression of CD40 ligand. Ligation of CD40 on APCs by CD40 ligand induces release of extracellular matrix-degrading metalloproteinases and the expression of tissue factor, the key initiator of the coagulation cascade, which has been well documented in experimental models (14).

$CD4^+CD28^{null}$ T cells are distinct from classic helper T cells in several respects. This terminally differentiated subpopulation shows an increased resistance to apoptosis and a wide range of proinflammatory properties (7). The proinflammatory functions of $CD4^+CD28^{null}$ T cells include the production of high levels of IFN-γ, tumor necrosis factor alpha (TNF-α), and IL-2 (9) to direct cytotoxic ability (15). Indeed, they express killer immunoglobulin (Ig)-like receptors and directly kill endothelial cells in vitro by cytolytic enzymes, such as perforin, granzyme A, and granzyme B, which usually are present in killer T cells and natural killer cells. Several studies showed the association of $CD4^+CD28^{null}$ T cells with infections and chronic inflammatory diseases, particularly RA. $CD4^+CD28^{null}$ T cells are present preferentially in unstable ruptured atherosclerotic plaques (4), and their frequency significantly increases the risk of ACS (8,16), particularly in patients with diabetes (17).

In patients with ACS, CD4+$CD28^{null}$ T cells circulating in the peripheral blood and infiltrating the unstable atherosclerotic plaque show high levels of the costimulatory receptors OX40 and 4-1BB, which mediate IFN-γ and TNF-α production, and modulate cell degranulation (18), as well as increased resistance to apoptosis (19). Overall, these molecular abnormalities could enhance the inflammatory and cytotoxic function of $CD4^+CD28^{null}$ T cells and could contribute to atherosclerotic plaque destabilization. One study failed to replicate the differences in $CD4^+CD28^{null}$ T cells from ACS and controls in patients treated with high-dose statins (20).

TH17 CELLS. TH17 cells are characterized by the expression of retinoid-related orphan receptor γt, the master regulator transcription factor responsible for IL-17 production. This T-cell subset, implicated in several autoimmune disorders, is important in the immune responses against fungi and extracellular bacteria (6). The precise role of IL-17 in atherosclerosis and ACS remains controversial, as discussed in detail in a recent editorial (21). On the one hand, experimental studies in mouse models have provided direct evidence that IL-17 is predominantly proatherogenic. On the other hand, these cells promote procollagen expression, which might reduce the risk of fibrous cap fissure (22).

Similarly, in the clinical setting, the TH17 subset is expanded in patients with ACS (8,23), and the TH17/Treg balance might play a role in the development of inflammatory disorders, including atherosclerosis, and autoimmune diseases; however, in a cohort of patients with ACS, lower serum levels of IL-17 were associated with a higher risk of major cardiovascular events (24). The issue of whether TH17 cells are protective or detrimental in ACS remains unsettled.

REGULATORY T CELLS. Tregs are a subset of $CD4^+$ T cells capable of suppressing the immune response. These lymphocytes are characterized by expression of the transcription factor Foxp3, by high levels of the IL-2 receptor CD25, and by down-regulation of the surface molecule CD127 (6). Tregs induce immunosuppression through multiple mechanisms, including production of the anti-inflammatory cytokines IL-10 and transforming growth factor-beta, direct cytolysis, and inhibition of dendritic cell maturation and function (6). In experimental atherosclerosis, the role of Tregs is well appreciated. Indeed, this T-cell subpopulation inhibits atherosclerosis development and progression by suppressing effector T-cell responses (25). Recently published data have consistently demonstrated a defective Treg compartment in the peripheral blood of patients with ACS. Patients with ACS show low levels of circulating Tregs, a reduced suppressive efficiency of Tregs, and increased Treg susceptibility to apoptosis (26–29).

B CELLS. The contribution of B cells in autoimmunity is well recognized, and their function has been evaluated in various animal models of atherosclerosis (30).