Antigen-Dependent and Antigen-Independent Pathways Modulate CD4+CD28null T-Cells During Atherosclerosis

To the Editor:

We read with interest the article by Dumitriu et al1 that characterized the alternative costimulatory pathways of CD4+CD28null T cells, a terminally differentiated effector T-cell population, in patients with acute coronary syndromes (ACS). In this study, a significant increase in costimulatory receptors (OX40/CD134 and 4-1BB/CD137) was described in CD4+CD28null T cells from patients with ACS after stimulation with an anti-CD3 antibody (emulating T-cell antigen recognition). Furthermore, blocking of these costimulatory receptors was associated with reduced interferon-γ, tumor necrosis factor-α, and perforin release in CD4+CD28null T cells, thus affecting their proinflammatory and cytotoxic functions. Overall, these findings suggest a differential sensitivity to costimulation in activated CD4+CD28null T cells in the context of ACS.

During ACS we recently observed that in addition to CD28 activation, the classical immunologic synapse mediated by antigen-T-cell receptor (TCR) engagement is perturbed also.2 Of the TCR subunits, the ζ (ζ) chain (CD247 or CD3ζ) has a key role in receptor assembly and antigen recognition by coupling the engaged TCR-CD3 complex to downstream intracellular signal transduction pathways through phosphorylation and intracellular protein recruitment. Downregulation of the TCRζ chain generally occurs after antigen engagement or in response to inflammatory stimuli as a feedback mechanism aimed at tuning the immune response. Together with CD28 downregulation, TCRζ-chain reduction was observed in T cells isolated in several chronic pathologies, including cancer, and autoimmune (ie, systemic lupus erythematosus) and infectious diseases.3

Downregulation of TCRζ-chain expression and impairment of T-cell function, such as loss of TCRζ-chain expression, defines a population of effector T cells (TCRζdim T cells) that migrate to inflamed tissues.4 We have shown that the TCRζdim T-cell subset, although refractory to TCR-induced proliferation, paradoxically displays features of antigen-experienced effector T cells, produces elevated levels of interferon-γ and tumor necrosis factor-α, and has a prevalence of memory CD45RO+ cells.4 We further demonstrated that antigen-experienced effector memory T cells (CD3+CD4+CD45RO+CCR7−),5 but not regulatory T cells (CD3+CD4+CD25highCD127low),6 are associated with the extent of atherosclerosis and symptomatic coronary artery disease in humans.

In the latter setting, we observed a significant increase in TCRζdim T cells and, more importantly, a highly correlation with CD4+CD28null T cells (r=0.62; P=0.002).5 Furthermore, a majority of CD4+CD28null T cells in ACS (>65%) were TCRζdim T cells compared with chronic stable angina patients (approximately 30%) and controls (approximately 20%).5 This indicates a potential correlation, in the context of ACS, between impairment in the TCR pathway (signal 1) and in the costimulatory CD28 pathway (signal 2). Given that intact TCR signaling is critical to maintain immune homeostasis through the generation or function of regulatory T-cell subsets, alterations in signal 1 pathway could result in increased TCRζdim T cells, which in turn could dampen modulator feedback signals, thus potentially limiting CD4+CD28null T-cell responsiveness to inhibitory signals.

However, CD4+CD28null T cells can respond to stimuli independent of antigen-mediated TCR pathway. Circulating or plaque CD4+CD28null T cells from ACS patients express interleukin-12 receptors, even in the absence of antigenic stimulation, and upregulate the expression of the chemokine receptor CCR5 and the C-type lectin receptor CD161, both implicated in regulating tissue homing of effector T cells after interleukin-12 stimulation.7 This suggests that CD4+CD28null T cells functionally could also resemble natural killer cells, with proinflammatory activity even in the unprimed state and increased tissue trafficking and homing after interleukin-12–inducing host infection associated with accrual in inflammatory lesions.

Both antigen-dependent and antigen-independent mechanisms therefore are critical to elicit response in CD28 and/or TCRζ-chain defective memory T-cell subsets, thus promoting a proinflammatory and proatherosclerotic response. Therefore, a further step in the characterization of CD4+CD28null T cells in the context of cardiovascular disorders should be the investigation of their antigen-dependent–mediated and antigen-independent–mediated responses (in terms of costimulatory activities and of TCRζ-chain impairment), with the aim of defining potential therapeutic targets to inhibit their proinflammatory and proatherosclerotic activities.

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Disclosures

None.

Enrico Ammirati
San Raffaele Scientific Institute and Vita-Salute University
Milan, Italy
Heart Transplantation Division
Ospedale Niguarda Ca' Granda
Milan, Italy

Claudia Monaco
Kennedy Institute of Rheumatology Division
Imperial College School of Medicine
London, UK

Giuseppe Danilo Norata
Department of Pharmacological Sciences
Università degli Studi di Milano
Milan, Italy
Center for the Study of Atherosclerosis
Bassini Hospital

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References


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