Targeting T Cell Costimulation to Prevent Atherothrombosis

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Inflammation plays a key role in atherogenesis and precipitation of atherothrombosis. Immune cells, including macrophages and T cells, infiltrate the affected vascular wall, and inflammation drives build-up of atherosclerotic plaques. This concept of immune activation in atherosclerosis has become accepted, but specific therapy directed at inflammatory mechanisms is yet lacking. T cell activation regulated by costimulatory molecules plays an important role in experimental atherogenesis. Mounting evidence show that CD4+CD28null T cells have unique capabilities that potentially promote plaque vulnerability and atherothrombosis. In this issue of Circulation Research, Dimitriu et al identify alternative costimulatory molecules that regulate CD4+CD28null T cells and associate this mechanism with the process of plaque rupture.

To understand the implications of these novel findings, it is useful to consider that CD4+CD28null T cells, T cells deficient in the key costimulatory molecule CD28, have a distinctly different phenotype than do their CD4+CD28+ T helper cell counterparts. CD4+CD28null T cells produce cytotoxic agents that can destroy vascular endothelial cells and release large amounts of IFN-γ, a cytokine that robustly stimulates activity of inflammatory macrophages and promotes development of atherosclerosis. They are highly resistant to apoptosis and accumulate gradually throughout life. In addition, CD4+CD28null T cells from acute coronary syndrome (ACS) patients express a killer immunoglobulin-like receptor-variant that can elicit activation and degranulation without antigen recognition by the T cell receptor, a mechanism that might compromise self-tolerance. Taken together, the transition of CD4+CD28+ T helper cells to CD28null cells makes them more like “killers” than “helpers.”

Intriguingly, CD4+CD28null T cell reactivity to cytomegalovirus and heat shock protein 60, both antigens implicated in atherogenesis, has been shown. The CD4+CD28null population is small in young and healthy individuals, but may represent a substantial proportion of T helper cells in patients suffering from chronic inflammatory disease, especially in cytomegalovirus-infected individuals, raising the possibility that repeated activation by a resident pathogen promotes expansion of the CD4+CD28null population.

Liuzzo et al found a positive correlation between CD4+CD28null T cell frequency and recurrence of acute coronary events in a prospective study. Dumitriu et al now expand the understanding of CD4+CD28null T cells in atherosclerosis by examining samples from normal controls and patients with stable angina or ACS. These new data reveal that stimulation with an anti-CD3 antibody (emulating T cell antigen recognition) induces expression of costimulatory molecules on CD4+ T cells in cultured peripheral blood mononuclear cells (PBMC) from patients with stable angina. Stimulation of PBMC from patients with ACS induced significantly higher levels of the costimulatory receptors Tumor Necrosis Factor Receptor Superfamily (TNFRSF) 4 (OX40, CD134) and TNFRSF9 (4–1BB, CD137) on CD4+CD28null T cells than on their CD28+ counterparts. This finding suggests a differential sensitivity to costimulation in activated CD4+CD28null T cells (Figure 1) associated with ACS.

Dumitriu et al confirmed that the CD4+CD28null T cell fraction was increased in ACS-patients in comparison with individuals with stable angina or healthy controls and that the stimulation-induced cytokine production and release of perforin and granzyme B in this cell population was augmented. Blocking either of the costimulatory receptors TNFRSF4 or TNFRSF9 in PBMC from ACS-patients in vitro reduced degranulation and intracellular levels of TNF and IFN-γ in CD4+CD28null T cells, thus inhibiting known proatherogenic activities of CD4+CD28null T cells. Furthermore, the local availability of the T cell costimulatory ligands TNFRSF4/9 in atherosclerotic lesions may promote inflammation and plaque destabilization.

What do these new insights into the regulation of CD4+CD28null T cells tell us about potential new bio-markers and therapeutic targets in atherothrombosis? We know that the analysis of individual cardiovascular risk is improved by the addition of markers of inflammation, eg, hs-CRP, to the classical Framingham variables. Since CD4+CD28null T cells accumulate in a range of conditions associated with increased cardiovascular risk and up-regulation of TNFRSF4/9 on CD4+CD28null T cells was observed in samples from ACS patients, it is possible that their frequency and receptor repertoire represent integrated information on risk, but this remains to be investigated. If so, it may be feasible to develop a simple diagnostic assay to determine the ratio of inducible TNFRSF4/9 levels on CD4+CD28null versus CD4+CD28+ T cells.

TNFRSF costimulation has been suggested to play a prominent role for effector responses in CD28null cells, and manipulation of TNFRSF4/9 signaling has profound effects on the course of experimental inflammatory diseases. Therefore, targeting costimulation to reduce inflammation in atherosclerosis...
and prevent destabilization of lesions is a reasonable approach. However, the in vivo dynamics, regulation, and activity of TNFRSF4/9 expression on CD4+CD28null T cells in ACS patients are currently not known, and further studies of circulating and plaque-resident cells are warranted to understand the influence of TNFRSF4/9 costimulatory mechanisms in detail. Available experimental data indicates that the response to costimulatory agonists may differ substantially depending on the specific context, and timing of intervention can be pivotal. Because in vivo models for mechanistic studies of the CD28null populations are currently unavailable, it will be a challenge to accreu the comprehensive understanding of alternative costimulation needed for therapeutic targeting of TNFRSF4/9 in atherosclerosis.

Interestingly, increased TNF levels reduce CD28 expression on CD4+ T cells. Reciprocally, in vitro treatment with the TNF inhibitor infliximab increases the fraction of CD4+CD28null T cells. Therefore, therapeutic reduction of TNF may be a method to restore CD28 expression, reduce the CD28null T-cell population, potentially rehabilitate “killers” to “helpers,” and normalize immune function. This possibility warrants further evaluation. In the future, it is likely that additional T cell subsets will be found to play a role in the atherogenic immune response. For example, the recently defined acetylcholine-producing T cells under neural control that regulate TNF production may represent a novel opportunity to control immune cells in cardiovascular disease.

Although much has been learned about inflammation in atherogenesis, atherosclerosis is a complex and multifactorial disease. Accumulating evidence indicates unique capabilities of CD4+CD28null T cells that potentially promote plaque vulnerability and atherothrombosis. These new data on costimulatory regulation of CD4+CD28null T cells in ACS represent a significant advance. As we understand more about this multifaceted biology, we are poised to acquire new tools to diagnose and treat cardiovascular disease.

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