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EDITORIAL COMMENT

At its Heart, Homeostasis Is About T Cells*

Göran K. Hansson, MD, PhD

The human organism possesses an immense capacity to handle a broad variety of challenges. Its cardiovascular system can switch rapidly from maintaining basal organ perfusion in a sedentary position to supplying hard-working muscles with large amounts of oxygen during exercise. Its neurometabolic control system is able to maintain an even body temperature of 98.6°F/37°C irrespective of whether a patient is exposed to the heat of an Italian summer or the cold of a winter day in Sweden. The concept of an inner milieu that remains rather constant, thanks to counterbalancing activities, was first formulated 150 years ago by Claude Bernard, the great French physiologist (1). It was summarized in the word *homeostasis* and represents a central principle in life.

In the immune system, homeostasis is obtained by counterbalancing "killer" activities, such as cytotoxicity and inflammation, with immunosuppressive ones. This counterbalance is largely accomplished by different subsets of immune cells, such as cytotoxic $CD8^+$ T cells and proinflammatory $CD4^+$ T cells (Th1 cells), both controlled by anti-inflammatory regulatory T (Treg) and B cells. This homeostatic control operates in sets of antigen-specific cells; therefore, reactivity to antigens is tonically controlled by counterbalancing signals. An immunological challenge, such as an infection, disturbs this equilibrium. Innate immune stimuli prompt macrophages and dendritic cells to produce proinflammatory signals that favor the development of aggressive T and Th1 cells while inhibiting Treg development.

Atherosclerosis is a chronic inflammatory disease caused by a metabolic disturbance, such as cholesterol accumulation in the artery wall (2). Similar to other chronic inflammatory diseases, such as rheumatoid arthritis, psoriasis, and multiple sclerosis, adaptive as well as innate immune mechanisms operate in atherosclerosis (3). Proinflammatory Th1 cells and macrophages promote disease development, whereas Treg cells and certain B cells dampen it. Adaptive immune activation in atherosclerosis is driven, to a significant extent, by autoimmune reactions to low-density lipoprotein cholesterol and the intracellular protein heat shock protein-60.

Much less is known about the role of immune mechanisms in acute coronary syndromes (ACS), although they are usually caused by atherosclerosis. Animal models are lacking; therefore, mechanistic studies cannot readily be performed in ACS. However, careful clinical studies have revealed clonal expansions of T cells, some of which recognize low-density lipoprotein (4,5). T-cell effector populations are unbalanced, with expansion of the proinflammatory $CD4^+CD28^{null}$ cell type (4) and low levels of Treg (6). These data reflect a disturbed immune homeostasis and suggest that an immune reaction plays an important role in ACS.

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Some of the T-cell changes in ACS patients are clonal, indicating antigen-specific reactions, whereas others are general and may therefore reflect a general perturbation of cellular immunity. If the latter is the case, what level of immune homeostasis is perturbed? This question holds great interest not only for understanding pathogenesis but also as it may help to identify novel therapeutic targets. The paper by Flego et al. (7) in this issue of the *Journal* is a useful step forward in this research.

T cells are activated when dendritic cells present antigen, usually in the form of peptide fragments bound to major histocompatibility complex proteins,

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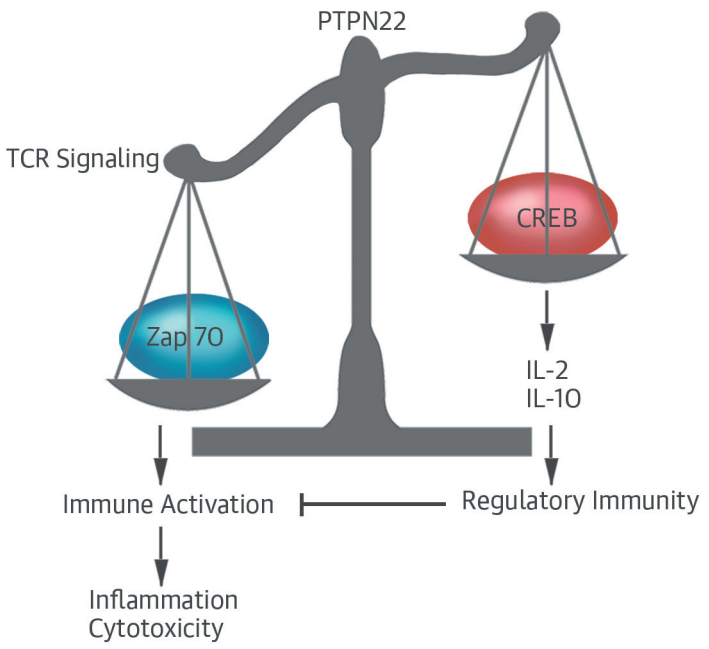
From the Department of Medicine and Center for Molecular Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden. Dr. Hansson has reported that he has no relationships relevant to the contents of this paper to disclose.

FIGURE 1 Signaling Cascades That Control Activation in T Cells



Ligation of the T-cell antigen receptor (TCR) initiates a signaling cascade that involves the kinase zeta-chain–associated protein kinase of 70 kDa (ZAP-70) and leads to immune activation. The outcome of this activation pathway is often inflammation. Counterbalancing this activity, intracellular signals, including the cyclic adenosine monophosphate response element–binding protein (CREB), promote the expression of the cytokines, interleukin (IL)-2 and IL-10, the latter of which is crucial for the regulatory immunity that dampens inflammation. Protein tyrosine phosphatase, nonreceptor type, 22 (PTPN22) modulates kinase cascade activities by removing phosphate groups from tyrosine residues.

to adjacent T cells. When the T-cell antigen receptor (TCR) forms an immunological synapse with the peptide-major histocompatibility complex, an intracellular signaling cascade is elicited, leading to activation of the T cell (**Figure 1**). Many different proteins participate in this cascade, but the general principle is straightforward. A number of proteins are phosphorylated, one after another, starting with the intracellular parts of the TCR complex. Phospholipid and calcium signals are called into action, ultimately leading to activation of 3 transcription factors: nuclear factor-kappaB, nuclear factor of activated T cells, and activator protein-1. When activated, these transcription factors occupy specific promoter elements that initiate deoxyribonucleic acid transcription, which, in turn, leads to the production of cytokines, such as interleukin-2, and to cell division.

The reacting T cell proliferates to form a clone of cells with identical TCR amplifying the capacity to react to antigen. In parallel, activated T cells help B cells to produce antibodies against the antigen, also promoting the activation of macrophages that trigger inflammation and help to remove infectious agents.

The T-cell activation cascade operates irrespective of the type of activating antigen. Therefore, reactive T cells expand clonally in infections and autoimmune diseases, and in response to allogeneic transplants. The activation cascade offers several targets for immunosuppressive therapy. Cyclosporine and tacrolimus target immunophilins, that is, protein-modifying enzymes that control nuclear factor of activated T-cell activation. A combination of sirolimus and rapamycin binds to mammalian target of rapamycin, a kinase enzyme involved in the pathway that activates activator protein-1 and causes cell division. The ultimate effect of all 3 drugs is to block T-cell activation, thus preventing the development of adaptive immunity and immunological memory. Treatment with this group of drugs has been successful in diseases ranging from transplant rejection and autoimmunity to vascular restenosis.

Flego et al. (7) examined the T-cell activation cascade in patients with non-ST-segment elevation myocardial infarction (NSTEMI) and compared it to the situation in patients with stable angina and in healthy controls. They observed increased expression and activity of tyrosine-protein phosphatase, nonreceptor type, 22 (PTPN22), an enzyme that attenuates signaling in the T-cell phosphorylation cascade. Remarkably, this increase persisted a year after the acute event, and the authors suggest that it reflects an intrinsic T-cell abnormality in ACS.

PTPN22 is an interesting enzyme because genetic variants are associated with an increased risk for several chronic inflammatory diseases; it is therefore considered an important nonhuman leukocyte antigen autoimmunity gene (8). However, the finding of *increased* PTPN22 is seemingly contradictory to the increased T-cell activity and TCR phosphorylation events in ACS patients reported here and in previous studies (9). The fine specificity of the enzyme with regard to its attack on phosphorylated tyrosine residues in the target proteins may perhaps explain this paradox.

NSTEMI patients also showed transiently reduced phosphorylation of the transcription factor cyclic adenosine monophosphate response element-binding protein in NSTEMI T cells. This reduction was associated with reduced cyclic adenosine monophosphate response element-binding protein binding to the promoters of interleukin-2 and -10, 2 cytokines important for Treg, and with reduced numbers of Treg.

All of these data point to a dysregulated T-cell homeostasis in NSTEMI. The delicate homeostasis of immune activation appears to be disturbed in

these patients, leading to an imbalance between proinflammatory and regulatory immune cells. Such a situation would justify treatment of NSTEMI, and possibly other forms of ACS, with T-cell–modulating strategies. Experimental studies showing the benefit of immunomodulatory therapy in atherosclerosis could provide helpful clues for this work (10,11). However, the present study was based on small patient groups, as pointed out by the authors, and several questions linger with regard to the phosphorylation-dephosphorylation state in the patients' cells. Therefore, larger immunological studies should be performed and genomic databases scrutinized in order to clarify the state of T-cell homeostasis in ACS.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Göran K. Hansson, Center for Molecular Medicine L8:03, Karolinska University Hospital, SE-17176 Stockholm, Sweden. E-mail: goran.hansson@ki.se.

REFERENCES

1. Bernard C. Lessons on the phenomena of life common to animals and plants [in French]. Paris: J.B. Baillière and Son; 1878.

2. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352:1685–95.

3. Libby P, Lichtman AH, Hansson GK. Immune effector mechanisms implicated in atherosclerosis: from mice to humans. Immunity 2013;38:1092–104.

4. Liuzzo G, Goronzy JJ, Yang H, et al. Monoclonal T-cell proliferation and plaque instability in acute coronary syndromes. Circulation 2000;101:2883–8.

5. Caligiuri G, Paulsson G, Nicoletti A, Maseri A, Hansson GK. Evidence for antigen-driven T-cell response in unstable angina. Circulation 2000;102:1114–9.

6. Mor A, Luboshits G, Planer D, Keren G, George J. Altered status of CD4(+)CD25(+) regulatory T cells in patients with acute coronary syndromes. Eur Heart J 2006;27:2530–7.

7. Flego D, Severino A, Trotta F, et al. Increased PTPN22 expression and defective CREB activation impair regulatory T-cell differentiation in non-ST-segment elevation acute coronary syndromes. J Am Coll Cardiol 2015;65:1175–86.

8. Stanford SM, Bottini N. PTPN22: the archetypal non-HLA autoimmunity gene. Nat Rev Rheumatol 2014;10:602–11.

9. Pryshchep S, Goronzy JJ, Parashar S, Weyand CM. Insufficient deactivation of the protein tyrosine kinase lck amplifies T-cell responsiveness in acute coronary syndrome. Circ Res 2010;106:769–78.

10. Groyer E, Nicoletti A, Ait-Oufella H, et al. Atheroprotective effect of CD31 receptor globulin through enrichment of circulating regulatory T-cells. J Am Coll Cardiol 2007;50:344–50.

11. Zhang L, Ovchinnikova O, Jonsson A, et al. The tryptophan metabolite 3-hydroxyanthranilic acid lowers plasma lipids and decreases atherosclerosis in hypercholesterolaemic mice. Eur Heart J 2012;33:2025–34.

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