Lymphocyte responses in acute coronary syndromes: lack of regulation spawns deviant behaviour

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This editorial refers to ‘Altered status of CD4⁺CD25⁺ regulatory T cells in patients with acute coronary syndromes’¹ by A. Mor et al., on page 2530

The inflammatory and immune systems are abnormally activated during the acute phases of coronary atherosclerotic disease.¹² In particular, an unusual population of effector cells, lacking costimulatory molecule CD28, is transiently expanded in parallel with the occurrence of the waxing phases of atherosclerotic coronary disease.³

The origin of the lymphocyte response in acute coronary syndromes has been a matter of debate in the last decade. Questions still overcome the answers. It has been demonstrated that the T-cell response can be directed to restricted antigens within the culprit lesions,⁴ and it was suggested that persistent antigenic stimulation could generate the unusual expansion of the aggressive CD28 negative effector cells that are characteristically expanded in autoimmune diseases such as rheumatoid arthritis.³ However, the putative target antigenic stimuli evoked in acute coronary syndromes can also be found in patients with chronic atherosclerotic disease. Indeed, self-reactive antibodies recognize similar antigenic epitopes in patients with acute or stable coronary syndromes and in the normal population.⁵ Altogether, these findings indicate that the repertoire of antigens targeted by the immune system cannot explain the deviant lymphocyte responses observed in acute coronary disease.

Recently, an interesting hypothesis has been raised, postulating that the cause of the pathological autoreactive immune response observed in acute coronary syndromes might reside in a tolerance break due to a defective regulation of the T lymphocyte compartment.⁶

In the latest years, the way in which the architecture of the immune system is envisioned has been amended to include a number of regulatory T cell populations committed to control the bunch of potentially autoaggressive T cells. Both ‘naturally occurring’ [the CD4⁺CD25⁺ regulatory T cells (Treg), the ambivalent NKT cells, and the immunoregulatory CD31⁺ T cell] and ‘induced’ regulatory T cells (the Tr1 and Th3 regulatory T lymphocytes) have been described (Figure 1). An emerging concept proposes that these various T cell populations interact within a hypothetic (and still poorly described) regulatory network (Figure 1). For instance, ‘unconventional’ NKT cells, endowed with both effector and regulatory capacities, are able to induce the generation of Treg, which, in turn, controls NK T cell activation and effector function.⁷

Interestingly, a pro-atherogenic role of effector NKT cells has been recently documented.⁸ Concomitantly, a defective Treg compartment has been reported to accelerate experimental atherogenesis.⁹ It is tempting to speculate that an imbalance of the NKT cell/CD4⁺CD25⁺ T cell regulatory axis would favour the activation of the pro-atherogenic effector NKT cells. Concerning the acute coronary syndromes, although murine atherosclerotic animal models do not reproduce acute coronary syndromes, it has been observed that aortic root plaque thrombosis can be detected more frequently in aged atherosclerotic mice in which systemic immunoregulatory CD31⁺ T cells are reduced.¹⁰

These recent findings suggest that the autoaggressive lymphocyte response observed in atherosclerosis and acute coronary syndromes might derive from a flawed regulatory lymphocyte network (Figure 1). This would explain the difference between stable and acute atherosclerotic clinical manifestation, in spite of common plaque structure and antigenic content.

Mor et al.,¹¹ are the first to demonstrate a defective Treg compartment in patients with acute coronary syndromes. The number and the suppressor efficiency of Treg were reduced in unstable patients. This is a crucial finding in this research area with important implications for possible future therapeutic strategies.

Oxidized (ox)LDL-specific T lymphocytes are activated in patients with unstable but not in patients with chronic stable angina.¹² In addition to activate the specific effectors, one would expect that oxLDL elicits antigen-specific Treg, because among mobilized antigen-specific T lymphocytes, some differentiate into Treg. Surprisingly, Mor et al. observed that the number of blood-derived Treg from patients with acute coronary syndromes was significantly reduced when cultured in the presence of oxLDL. Future studies are warranted in order to find out how oxLDL would be able to affect the regulatory network (Figure 1).
The cause of the regulation malfunction remains to be discovered. However, regardless of the cause, lack of regulation commonly spawns deviant behaviour. The work by Mor et al.\textsuperscript{11} suggests that this is true also for lymphocyte responses in acute coronary syndromes.

**Supplementary material**

Supplementary material is available at *European Heart Journal* online.

**Conflict of interest:** none declared.

**References**


Figure 1 The work by Mor et al.\textsuperscript{11} documents for the first time a Treg (CD4(+)CD25(+)) defect in the course of the acute phases of atherosclerotic coronary syndromes. These cells belong to a putative regulatory network including the ambivalent NKT cells, the immunoregulatory CD31(+) T cells, and the Tr1 and Th3-induced regulatory T lymphocytes. Such a network modulates the activation of autoimmune T cells that are abnormally active in acute coronary syndromes. It is conceivable that certain T cell populations of the regulatory network could act directly on the physiopathology of atherosclerotic disease (through cytokine-mediated effects, for instance). Mor et al.\textsuperscript{11} also propose a reciprocal relationship: oxLDL, a crucial component of the atherosclerotic plaque would be able to affect the regulatory network by decreasing the number of Treg. See online supplementary material for a colour version of this figure.