The saga of atherothrombosis and T-cells: Looking for the lost prologue

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The vessel wall architecture remodels in arterial diseases, such as large vessel vasculitides and atherosclerosis. The process extends for years and multiple events combine in different ways in each given individual to determine vascular events, as in a Russian plot-oriented novel. Tobacco smoke, diabetes, hypertension and dyslipidaemia are all well-known characters [1]. Inflammatory players have also interested the scientific audience. Among the most popular villains, T cells have been paid a special attention [2], due to their apical function of master drivers of the immune response and to their involvement in vascular injury in a wide set of diseases. T cells cause inflammation in the systemic vasculitides, giant cell (GCA) and Takayasu’s arteritis [3]. Enhanced effector/reduced regulatory T-cell activation is coupled with the extent of inflammation and, notably, with accelerated atherosclerosis in autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis or psoriasis [4].

Experimental inflammatory lesions of the vessel wall in the absence of CD3+ lymphocytes or of specific T-cell populations fail to develop [5]. T-cells infiltrate human arterial vessel walls where they recognise locally expressed autoantigens [2]. Limited data from ex vivo assays suggest that accessibility of T lymphocytes to the vessel wall changes depending on the surrounding inflammatory microenvironment [5], while clonal amplification of T-cells in GCA is thought to occur ectopically, within the adventitial layer of large arterial vessel [3]. Senescent adventitial dendritic cells might fail to migrate to lymph nodes and to promote tolerogenic responses, eventually allowing intramural polarised T cell clonal amplification (Fig. 1). Immune senescence of T cells is also a well-characterised consequence of persistent antigen stimulation and energy deprivation [3]. It results in a progressively less diverse repertoire, a restricted pool of precursor cells and a relative failure to face infection/malignancies via T cell clonal amplification and functional differentiation. More prominently immune senescence, which has been previously described in patients with atherosclerosis and increased cardiovascular risk, results in defective deployment of anti-inflammatory, regulatory responses. Conversely, genome-wide association studies reveal a role of senescence genes in the risk of cardiovascular events.

T cells from the blood of patients with cardiovascular diseases have been extensively characterised and most studies have revealed peripheral accumulation of polarised T cells. T cells with putative cytotoxic action might contribute to plaque destabilisation, possibly via the regulation of innate immune cells effector actions in the arterial wall [2,5,6]. Pharmacological agents that target T-cells either directly or by modulating the permeability of vasa vasorum to leukocyte extravasation have clinically relevant effects on cardiovascular events [2]. Recent data on autopsied hearts from patients with acute myocardial infarction indicate that lymphocyte infiltration was associated with arterial inflammation, remodelling and destabilisation [7], while other studies have proposed that cell stress, a necessary outcome of T cell activation, reflects cardiovascular outcomes [8,9].

All together, we might have accumulated sufficient insight on the late maladaptive consequences of T cells recruited within damaged arteries. This however could only represent one side of the coin, the other being adaptive strategies relying on T cell homeostatic action leading to vessel healing and repair [10]. Conversely, understanding the prodromal events promoting a long-lasting T-cell response within large arterial vessels would be of paramount importance. Podolec and colleagues in this issue of the Journal aim at providing a “juvenile” portrait of T-cell-driven responses at the pre-lesional stage. They have investigated 114 patients who underwent coronary angiography, stratified based on the absence or the presence of atherosclerosis at a moderate or severe degree. Naïve (CCR7 + CD45RA+) CD8+ T cells were higher in the blood of patients with no evidence of coronary disease. In contrast, they were less numerous in atherosclerotic patients depending on lesion severity, possibly reflecting a prominent recruitment of CD8+ lymphocytes in atherosclerotic lesions. The relative reduction of naïve T-cells in elderly patients with high-grade atherosclerotic lesions might reflect the relative role of a restricted repertoire in the cardiovascular disease (Fig. 1).

Although convincing and well-controlled, the correlative nature of the clinical investigation and the lack of direct evidence from the arterial tissues make causes and repercussions of the redistribution of T cells in the blood of atherosclerotic patients tantalisingly obscure. Further studies involving larger groups from the general population are required to identify suitable naïve CD8+ cut-offs for the evidence to be valuable as a clinical biomarker. In addition, the specific determinants of CD8+ cells’ fate towards senescence remain elusive. Caution must also be paid to...
translating indirect phenotypic evidences from circulating cells into conclusions about their role in target tissues, such as vascular walls. Mechanistic studies, perhaps involving non-invasive cell tracking techniques, are necessary to identify the early events that connect the autoreactivity of T cells to the outcome of lesions of the arterial wall, thus recovering the prologue of a saga that has so far gone missing.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

References


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