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EDITORIAL

Rheumatoid arthritis and coronary atherosclerosis: two cousins engaging in a dangerous liaison

Roland Klingenberg[1]* and Thomas F. Lüscher[2]

[1]Department of Cardiology, Kerckhoff Klinik, Bad Nauheim, Germany; and [2]University Heart Center, Department of Cardiology, University Hospital Zurich, Zurich, Switzerland

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This editorial refers to 'Rheumatoid arthritis is associated with a more severe presentation of acute coronary syndrome and worse short-term outcome'†, by Ä. Mantel *et al.*, on page 3413.

Rheumatoid arthritis (RA) is a chronic inflammatory immune-mediated disease affecting the joints and several other organs. At a global prevalence of 0.24%, RA is ranked among the top 15% of diseases causing disability worldwide.[1] RA is associated with an increased risk of cardiovascular mortality.[2] Furthermore, post mortem[3] and coronary CT angiography data[4] indicate a higher prevalence of vulnerable coronary plaques in patients with RA compared with controls.

The article by Mantel *et al.*[5] in this issue of the journal adds an important piece to the puzzle, reporting their analysis of a large contemporary Swedish cohort study using national registries. The authors found an increased severity of disease at presentation with an incident acute coronary syndrome (ACS) and worse short-term all-cause mortality in patients with active RA compared with matched controls. Interestingly, worse outcome in patients with RA compared with matched controls persisted after adjustment for clinical covariates, including the type of ACS. Moreover, among deaths, the majority of cases had a cardiac cause (89.9% vs. 90.8%). Of note, all-cause mortality during the first 30 days after an ACS was quite high in patients with RA (15.7%) compared with matched controls (10.7%), likely attributable to the surprisingly advanced age in this cohort (median age 73.8 vs. 73.6 years). Altogether, these findings support the notion of an aggravated course of coronary atherosclerosis and ACS in patients with RA.

RA and atherosclerosis as the underlying cause of coronary artery disease share several features in pathophysiology, genetic predisposition and risk factors, assigning a central role to inflammation.[6] Indeed, like RA, atherosclerosis is a chronic inflammatory disease, specifically of the arterial wall. The dynamic nature of atherosclerosis is characterised by its evolution in several stages, culminating in plaque rupture or erosion with ensuing atherothrombosis and vascular occlusion as the pathophysiological culprit of an ACS.[7] Endothelial activation with expression of cell adhesion molecules occurs in arteries exposed to disturbed blood flow (i.e. bifurcations) and pro-inflammatory stimuli. Lipoprotein accumulation and oxidative modification in the subintimal space propagate expression of cell adhesion molecules and synthesis of pro-inflammatory cytokines and mediators by endothelial cells which, in turn, result in the recruitment and activation of various types of circulating leucocytes comprising neutrophils, monocytes and T cells (predominantly the T helper 1 subset). In the arterial intima, monocytes differentiate into macrophages and take up oxidised lipoproteins, converting them into foam cells. T cells can recognise specific antigens derived from these modified lipoproteins and orchestrate the immune response. Atherosclerotic lesion progression involves migration and proliferation of vascular smooth muscle cells in the intima and increased turnover of components of the extracellular matrix (i.e. collagen, elastin and proteoglycans) by matrix-degrading enzymes. Advanced stages of atherosclerotic plaques are characterised by a lipid core, an accumulation of extracellular lipids with cholesterol crystals derived from dead cells (i.e. foam cells and vascular smooth muscle cells), sealed on the luminal side by a fibrous cap separating it from circulating blood. These dynamic changes in plaque composition culminate in plaque rupture or erosion, followed by thrombus formation (*Figure 1A*).

In RA, the inflammatory process in the synovial joint is characterised by endothelial activation with increased expression of adhesion molecules and infiltration of immune cells comprising T cells of the T helper 1 subset and monocytes. Cartilage degradation in the synovial joint constitutes the hallmark of RA, mediated by persistently activated fibroblast-like synoviocytes (FLS) that express matrix-degrading enzymes. The combination of degradation products from the extracellular matrix exposing antigens that can be recognised by T cells and

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* Corresponding author. Department of Cardiology, Kerckhoff Klinik, Benekestr. 2-8, D-61231 Bad Nauheim, Germany. Tel: +49 (0) 6032 996 6463, Fax: +49 (0) 6032 996 2399, Email: r.klingenberg@kerckhoff-klinik.de

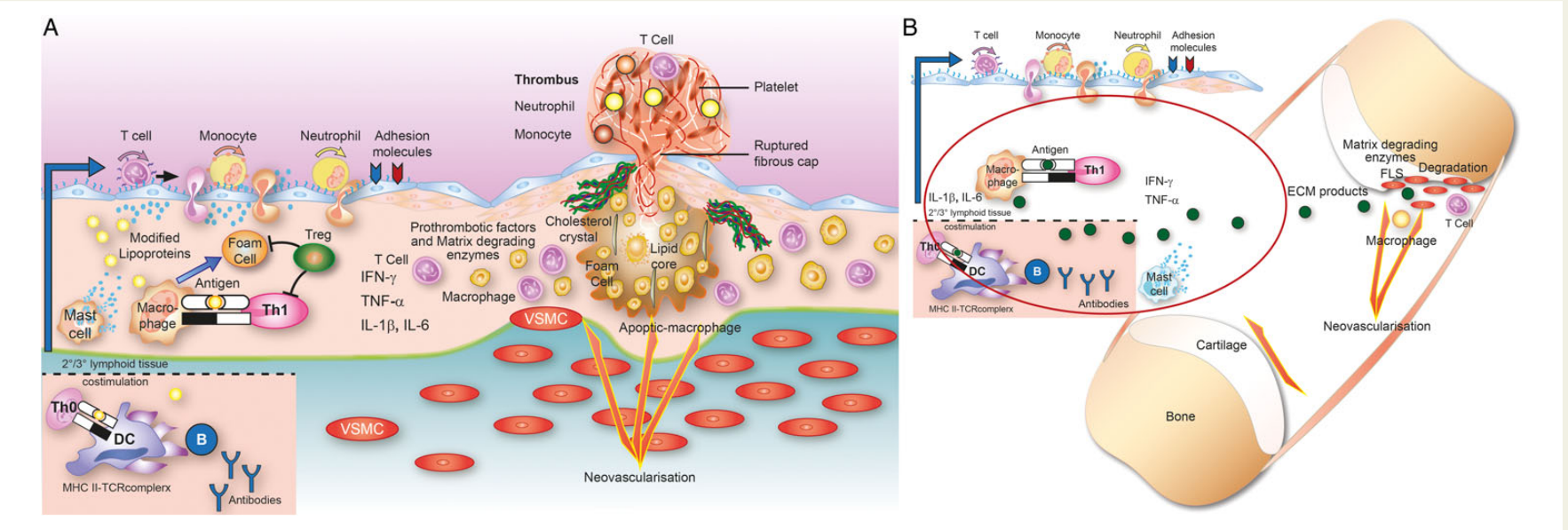

Figure 1 (*A*) Atherosclerosis: lesion progression culminating in atherothrombosis. (*B*) Rheumatoid arthritis: cartilage degradation in the synovial joint. B, B cell producing antibodies; DC, dendritic cell; ECM, extracellular matrix; FLS, fibroblast-like synoviocytes; IFN, interferon; IL, interleukin; MHCII-TCR, major histocompatibility complex class II–T cell receptor; Th, T helper cell subset; Treg, regulatory T cell subset; TNF, tumour necrosis factor; VSMC, vascular smooth muscle cell.

inflammatory signals from adjacent cells lead to perpetuation of the inflammatory process, including neovascularisation[6,8] (*Figure 1B*).

Increased numbers of a distinct T cell subset—$CD4^{+}CD28^{null}$ T cells—were detected in blood from patients with an ACS[9] as previously described in patients with RA.[10] $CD4^{+}CD28^{null}$ T cells are characterised by clonal restriction indicative of a reduced repertoire of antigens recognised by the T cell receptor complex in both patients with RA[10] and patients with an ACS[11] when compared with controls. In line with this, T cells in coronary thrombi aspirated from the culprit lesion in the epicardial vessel in patients with an ACS are profoundly clonally restricted compared with circulating T cells.[12] Moreover, circulating T cells from patients with an ACS[12] and patients with RA[13] showed clonal restriction when compared with controls. These findings indicate similar autoimmune responses against specific antigens in ACS and RA alike.

Anti-inflammatory drugs have been used for a long time in patients with RA and the anti-metabolite methotrexate was associated with a reduction in cardiovascular events in a recent meta-analysis.[14] Among the novel anti-inflammatory biologic agents used in patients with RA, it will be interesting to learn about the effects on cardiovascular outcomes during long-term follow-up of therapeutic inhibition of tumour necrosis factor-α, inhibition of interleukin-1β or antagonism of the interleukin-6 receptor, respectively. In turn, in patients with coronary artery disease, ongoing trials are evaluating the effects on cardiovascular events of methotrexate and inhibition of interleukin-1β.[7,15] It will be of great interest whether these trials confirm or refute the inflammatory hypothesis presented.

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