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Commentary

Inflammation: Friend and Foe

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Activation of inflammatory reactions by the immune system is of vital importance to the preservation of cellular and organ integrity in a hostile environment. It is a complex and fine-tuned mechanism. Insufficient response may cause immunodeficiency resulting in infection and cancer while overactivity may result in diseases like arthritis, diabetes, atherosclerosis, ischemic heart disease, heart failure, stroke, inflammatory bowel disease or Alzheimer's disease.

The inflammatory process is activated by different, not yet completely understood mechanisms, but factors such as age, race, gender, genetics, hypoxia, and antigens are involved. Stimulation of monocytes, macrophages, fibroblasts, and T-cells release numerous cytokines. Important are TNF-α and interleukin-1, which may activate several metalloproteinases (MMPs). Twenty-five MMPs have been defined; with specific proteolytic effects on extracellular matrix (ECM) collagen. Together with their endogenous tissue inhibitors (TIMP) they regulate the extracellular matrix (ECM).

In patients with rheumatoid arthritis, autoimmune stimulation of osteoclasts and chondrocytes activate MMPs, which target bone and cartilage destruction. In the heart, local MMPs stimulate the ECM degradation with breakdown of the collagen and elastin framework. Clinically the atherosclerotic plaque becomes unstable and with ventricular dilatation, rupture, and hypertrophy. In addition to local cellular effects, the hormonal and autonomic system interact with the inflammatory response and there is a spillover of inflammatory signal molecules to the systemic circulation with generalized effects.

Patients with rheumatoid arthritis have elevated levels of circulating cytokines that may affect other organs besides the joints (Avin-Zubieta et al., 2012). The additive effects of inflammatory expressions in two or more organ systems raise interesting possibilities regarding pathophysiology and treatment targets. People with rheumatoid arthritis have up to twice the risk of heart disease and development of heart failure than the general population, which is not explained by traditional cardiovascular risk factors (Crowson et al., 2013; Midtbø et al., 2014). Antigen induced arthritis in experimental rats activates proteolytic MMPs which release degradation product of different types of collagen (Siebuhr et al., 2012). Little is known of a common pathway that also may activate collagen degradation in other tissues. Degradation products of more than 20 different collagen molecules, neo-epitopes, have been described. In the present issue of the journal, Dragsbæk and co-workers (Dragsbæk et al., 2015) examined prospectively the long-time effects of disturbed homeostasis of ECM. The authors identified a type 1 collagen degradation fragment (C1M) among 5855 postmenopausal women and demonstrated that elevated levels (upper compared to the lowest quartile) were associated with 59% increase in mortality during an average of 9 year follow-up. The mortality curves diverged up to 9 years. Because C1M was obtained only at baseline, information beyond 9 years was confounded. When individuals in the high-risk group with elevated C1M die, the two curves will eventually converge.

Although the number of events was too small to analyze cause-specific events, except cancer and cardiovascular deaths, directional changes were similar for other events. The results therefore suggest that disturbed balance in the homeostasis of type 1 collagen is a general risk factor. The etiology is unknown. It is unclear if the elevated C1M in postmenopausal women represent a cause or an effect relationship to mortality. The inclusion of the women is vaguely described "as done by invitation ensuring no overrepresentation of subjects with a history of specific diseases". However, a history of hypertension, cancer, diabetes and underweight was clearly overrepresented among those who died (Dragsbæk et al., 2015). These are risk factors, which all cause a low-grade inflammatory activation. In addition, missing information on the occurrence of rheumatic arthritis and other autoimmune inflammatory diseases make it difficult to conclude about the mechanisms that contributed to the deregulated ECM.

Several MMPs may be responsible for the neo-epitope C1M from collagen type 1. In particular, MMP-2 and -9 are elevated acutely in infarcted tissue and are important for the tissue repair. However, elevated levels are also associated with increased incidence of cardiac rupture and portends a poor prognosis. MMP2 is closely related to left ventricular remodeling and to changes in proBNP. Lowering of MMP2 may predict reverse remodeling with high sensitivity and specificity (Morishita et al., 2015). Unfortunately, MMPs were not examined in the present study so which MMP was involved in these presumed healthy women remains unclear. Degradation of other collagens results in specific neo-epitopes. Cathepsin K is another specific protease with ability to catabolize elastin, collagen, and gelatin in bone and cartilage with release

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of the neo-epitope CTX-1. No association was observed between elevated CTX-1 and all-cause mortality in the present cohort. Underscoring the specificity of the MMP-collagen type 1 relationship as a risk factor (Dragsbæk et al., 2015).

Local activation of MMPs is also closely associated with progression of cancer although the decisive mechanism is unknown (Bauvois, 1825). However, it may explain the association between C1M and death from cancer (Dragsbæk et al., 2015).

Other protein molecules released from collagen like biglycan and mimecan are elevated in heart failure patients and have been shown to be associated with adverse outcome. They added, however, no extra information beyond conventional risk factors, when N terminal pro-BNP was included (Ueland et al., 2015). Dragsbæk and coworkers did not account for ProBNP, which weakens the claim that C1M was an independent risk factor.

The clinical implications of activated collagen degradation are unclear. MMP/TIMP system is important in tissue healing and repair as well as in tissue remodeling and disease progression. Patients with autoimmune diseases like rheumatic arthritis and inflammatory bowel disease benefit from treatments targeting molecules directly involved in the degradation of collagen. The data also suggest that inhibitors of inflammation attenuate the excess risk for heart failure development. However, these results contrast the disappointing results of randomized clinical trials in patients with established heart failure, NYHA class II–IV. TNF-α inhibitors in 3 trials resulted in no or increased number of deaths and hospitalization for heart failure (Anker and Coats, 2002; Chung et al., 2003). On the other hand, experiments in a rat model of heart failure demonstrated that MMP activity contributed to LV dilation and progression to LV dysfunction. Specific inhibitors of MMPs, including MMP-2 attenuated left ventricular dilatation and dysfunction. Unfortunately, prolonged exposure to MMP inhibitors stimulates a pro-fibrotic response and scar formation. This may convert systolic dysfunction into a diastolic dysfunction. Furthermore, fibromyalgia is a limiting side effect for the clinical use of MMP inhibitors.

It is interesting that angiotensin-converting enzyme may activate MMP and that part of the favorable effect of an ACE inhibitor in heart failure is reducing the MMP activity.

- The study by Dragsbæk and coworkers suggests that increased turnover of collagen type-1 is a general risk factor for all-cause mortality.
- The role of C1M as a ubiquitous risk marker of death is intriguing but needs to be confirmed.
- Inflammatory pathways may be additive and explain the excess mortality of ischemic heart disease in patients with autoimmune diseases.
- However, the response to anti-inflammatory treatment remains different for autoimmune disorders, cancer, and heart failure and suggests different specificity for treatment modalities.

Disclosure

The author declares no conflicts of interest.

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