

Insight Receptor activation of nuclear factor κ B ligand (RANKL) increases the release of neutrophil products associated with coronary vulnerability

RANK(L)-ing biomarkers as surrogates for coronary calcium score

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Coronary calcium deposition, expressed as the coronary calcium score (CCS), is a precisely quantifiable and reproducible measure of underlying coronary artery disease which has been shown in large prospective studies to be strongly associated with the risk of future cardiovascular events (1).

Despite the strong predictive value of CCS, radiation exposure and financial costs remain significant concerns. Therefore, discovery of biomarkers as surrogates for CCS would be highly beneficial. Classical biomarkers for cardiovascular disease such as high sensitivity C-reactive protein (hsCRP), FVIIIc, fibrinogen and soluble intercellular adhesion molecule (sICAM), were found to be associated with CCS (2). Other inflammatory markers like interleukin-6 and tumour necrosis factor- α often

failed to show a correlation, suggesting that the inflammatory markers used to predict coronary heart disease fail to predict coronary artery calcification.

In the present issue of *Thrombosis and Haemostasis*, Quercioli et al. describe the highly relevant finding that serum levels of receptor activation of nuclear factor κ B ligand (RANKL), together with age, hypertension and serum matrix metalloproteinase (MMP)-8 and -9 levels are positively correlated with CCS. RANK, RANKL together with other bone matrix regulatory proteins like bone morphogenetic protein (BMP)-2 and BMP-4, as well as osteopontin (OP) and osteonectin (ON), are highly expressed in calcified atherosclerotic lesions, and play an important role in mediating plaque calcification (3). In addition, some of these bone matrix regulatory proteins, especially RANKL have also been identified as important players in the immune system and in inflammation.

Not surprisingly, Quercioli et al. found that RANKL was able to activate the degranulation of MMP-8 and -9 from neutrophils in culture, via the signalling intermediates ERK1/2 and Akt signalling, but only in suspension, which corresponds to neutrophils in the circulation.

These data show that RANKL is a promising surrogate marker for CCS. The biomarker has a good potential to improve cur-

rent CHD risk prediction models, since RANKL is involved in bone and matrix turnover within atherosclerotic plaques, is able to induce MMP-8 and -9 in neutrophils and plays an important role in inflammation, all processes crucial in the pathogenesis of atherosclerosis. However, the population studied in this paper is small, and larger clinical trials should be initiated to unequivocally prove that serum levels of RANKL are a reliable surrogate marker for CCS.

Conflict of interest

None declared.

References

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