**Editorial**

*Footprints of Neutrophil Extracellular Traps as Predictors of Cardiovascular Risk*

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Cardiovascular events, such as myocardial infarction and stroke, are leading causes of mortality and morbidity in Western societies. Biomarkers could help to predict the risk of a patient and to advance the treatment of people at risk by allowing fine-tuning of the intensity of therapy.1 Although more recent studies have used proteomic, metabolomic, and genetic approaches to identify biomarkers, Borissoff et al2 here investigate the importance of double-stranded DNA, nucleosomes, thrombin-antithrombin complex complexes, and myeloperoxidase (MPO)–DNA complexes in predicting the severity of atherosclerosis and the risk of future cardiovascular events. Their data indicate that these markers were elevated in patients with severe coronary ath erosclerosis or calcified coronary arteries. Furthermore, plasma nucleosome levels were found to be associated with an increased risk of coronary stenosis, whereas MPO–DNA complexes predicted the occurrence of major adverse cardiac events. Double-stranded DNA, nucleosomes, and MPO–DNA complexes are all markers of neutrophil extracellular traps (NETs), a mesh of DNA released from activated neutrophils (Figure).

**NETs as Biomarkers or Mediators of Atherosclerosis?**

Neutrophils have just recently emerged as important contributors to atherosclerosis.3 Depletion studies revealed that neutrophils primarily contribute to atherogenesis by mechanisms involving the release of alarms, such as cathelicidin, that promote arterial recruitment of classical monocytes.4,5 In addition, NETs were identified in murine and human atherosclerotic lesions, as well as in myocardial thrombi.6,7 Hence, the study by Borissoff et al8 does not only point toward a possible role for NET components in the prediction of cardiovascular risk but also raises the question whether NETs are mediators of the disease process per se. Mechanistically, complexes of self-DNA and neutrophil-derived granule proteins are potent activators of plasmacytoid dendritic cells in the vessel wall, thus promoting atherosclerotic lesion formation.9,10 At later stages, luminal NETs may contribute to the activation of platelets, resulting in thrombus formation as was shown in models of venous thrombosis.11,12 Although these stand out as possible mechanisms of NET-driven atherothrombotic complications, it remains unclear to what extent neutrophils and neutrophil-derived NETs contribute to plaque destabilization.13

**Are NET Components Superior in Predicting Cardiovascular Risk?**

Before the work presented here, several proteins typically expressed and released by neutrophils emerged as possible biomarkers for cardiovascular events. Plasma levels of MPO, an enzyme stored in neutrophil primary granules and partially released on neutrophil activation, positively correlate with the risk of coronary artery disease.13 Alternatively, the clinical value of MPO to predict acute myocardial infarction and adverse events during a follow-up period in patients presenting with signs of acute coronary syndrome has been established.14 Similarly, matrix metalloproteinase-2 and matrix metalloproteinase-9, abundantly expressed in neutrophil secondary and tertiary granules, are elevated in patients with acute coronary syndrome.15 These observations are further extended by studies indicating a positive correlation between circulating neutrophil counts and the risk of cardiovascular events.16,17 However, it is important to note that NET components, namely DNA complexes and nucleosomes, may also be released during other programs of cell death, for example, during endothelial cell apoptosis or macrophage necrosis in advanced atherosclerotic plaques.18 Despite the potential clinical value, this imposes an important caveat for attempts to extrapolate a causative role of clinically detectable NET components in the pathogenesis of atherosclerosis and for the notion that such DNA constituents are necessarily or exclusively neutrophil- and NET-derived. Nevertheless, given the possible mechanistic implications of MPO and matrix metalloproteinases in plaque destabilization, future work needs to clearly define a clear role for NETs and their fragments in the prediction of atherosclerosis as well as in the process of atherothrombosis.

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**References**

Figure. Potential new biomarkers in atherosclerosis and atherothrombosis. The study by Borissoff et al identifies a novel set of predictors, namely nucleosomes and their complexes, for atherosclerosis and severe coronary artery disease. Mechanistically, these complexes may not just stand out as biomarkers but also as mediators of vessel wall inflammation and thrombotic events within arteries. Plasma markers defined as predictors by Borissoff et al are underlined and marked in red, and potential proatherogenic and atherothrombotic mechanisms initiated by these mediators are highlighted in boxes. DC indicates dendritic cell; EC, endothelial cell; IFN, interferon; IL, interleukin; MMPs, matrix metalloproteinases; MPO, myeloperoxidase; NET, neutrophil extracellular trap; ROS, reactive oxygen species; TNFα, tumor necrosis factor-α; and VSMC, vascular smooth muscle cell.

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