Extracellular DNA and histones as thrombus stabiliser

Bernd Engelmann
Institut für Laboratoriumsmedizin, Ludwig-Maximilians-Universität, München, Germany

Recent work suggests that extracellular (cell-free) nucleic acids, both DNA and RNA species, as well as extracellular nucleosomes can activate blood coagulation and promote thrombosis in vitro and in vivo (1, 2). Indeed, they substantially contribute to the development of microvascular thrombosis which can act as an intravascular immune response to circulating bacteria and has been termed immunothrombosis (3). However, they also foster pathological vessel occlusions as shown in animal models of large vessel thrombosis including deep-vein thrombosis and arterial thrombosis. Large filaments of extracellular nucleosomes that are released from activated neutrophils (neutrophil extracellular traps, NETs) and isolated extracellular nucleosomes support fibrin formation and platelet adhesion/activation via different mechanisms. These include for example stimulation of fibrin formation by degradation of the endogenous anticoagulant tissue factor pathway inhibitor and via activation of proteins involved in the contact pathway of blood coagulation such as factor XII (2, 3). The study by Varjú et al. (4) adds a new aspect to the procoagulant role of nucleosome components and NETs. These authors show that isolated eukaryotic DNA and histone proteins such as HIIIS enhance the diameter of thrombus-forming fibrin fibers under in vitro conditions. Moreover, they are found to decrease the permeability of fibrin clots and to enhance the overall stability of such clots. Mechanistically, these effects are mediated by regulation of endogenous anticoagulant and fibrinolytic pathways. Indeed, histone proteins prevented the inactivation of thrombin by antithrombin and DNA reduced plasminogen activation. Furthermore, NETs released from isolated neutrophils suppressed t-PA-promoted fibrinolysis. Together with earlier work, these results further corroborate the conclusion that extracellular nucleosomes and their major components target the coagulation system at different levels and that their overall effect is to enhance fibrin formation. It will be of interest to clarify in the future whether the stabilization of fibrin clots by histones, DNA and nucleosomes as shown in (4) contributes to the prothrombotic role of NETs and extracellular nucleosomes in vivo.

Conflicts of interest
None declared.

References
4. Varjú I, Longstaff C, Szabo L, et al. DNA, histones and neutrophil extracellular traps exert anti-fibri-