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International Mining, 1990-07 **Autocar**, 2001 *NETosis 2: The Excitement Continues* Mariana J. Kaplan, Marko Radic, Martin Herrmann, 2017-12-28 NETosis is a form of cell death that manifests by the release of decondensed chromatin to the extracellular space provides valuable insights into mechanisms and consequences of cellular demise Because extracellular chromatin can immobilize microbes the extended nucleohistone network was called a neutrophil extracellular trap NET and the process of chromatin release was proposed to serve an innate immune defense function Extracellular chromatin NETs were initially observed in studies of neutrophils and are most prominent in these types of granulocytes Subsequent studies showed that other granulocytes and in a limited way other cells of the innate immune response may also release nuclear chromatin following certain kinds of stimulation Variations of NETosis were noted with cells that remain temporarily motile after the release of chromatin Numerous stimuli for NETosis were discovered including bacterial breakdown products inflammatory stimuli particulate matter certain crystals immune complexes and activated thrombocytes Fundamental explorations into the mechanisms of NETosis observed that neutrophil enzyme activity PAD4 neutrophil elastase proteinase 3 and myeloperoxidase and signal transduction pathways contribute to the regulation of NETosis Histones in NET chromatin become modified by peptidylarginine deiminase 4 PAD4 and cleaved at specific sites by proteases leading to extensive chromatin externalization In addition NETs serve for attachment of bactericidal enzymes including

myeloperoxidase leukocyte proteases and the cathelicidin LL 37 NETs are decorated with proteases and may thus contribute to tissue destruction. However, the attachment of these enzymes to NET-associated supramolecular structures restricts systemic spread of the proteolytic activity. While the benefit of NETs in an infection appears obvious, NETs also participate as key protagonists in various pathologic states. Therefore, it is essential for NETs to be efficiently cleared; otherwise, digestive enzymes may gain access to tissues where inflammation takes place. Persistent NET exposure at sites of inflammation may lead to a further complication. NET antigens may provoke acquired immune responses and over time could initiate autoimmune reactions, serve as antigen for nuclear autoantibodies, and foster DNA immune complex-related inflammation. Neutrophil products and deiminated proteins comprise an important group of autoantigens in musculoskeletal disorders. Aberrant NET synthesis and/or clearance are often associated with inflammatory and autoimmune conditions. Recent evidence also implicates aberrant NET formation in the development of endothelial damage, atherosclerosis, and thrombosis. Intravital microscopy provides evidence for conditions that induce NETosis in vivo. Furthermore, NETs can easily be detected in synovial fluid and tissue sections of patients with arthritis and gout. NETosis is thus of interest to researchers who investigate innate immune responses, host-pathogen interactions, chronic inflammatory disorders, cell and vascular biology, biochemistry, and autoimmunity. As we enter the second decade of research on NETosis, it is useful and timely to review the mechanisms and pathways of NET formation, their role in bacterial and fungal defense, and their importance as inducers of autoimmune responses.

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