Universität Basel

Research Project

NETosis and mitochondrial DNA in the pathogenesis, diagnosis and activity of systemic lupus erythematosus and ANCA-associated vasculitis.

Third-party funded project

Project title NETosis and mitochondrial DNA in the pathogenesis, diagnosis and activity of systemic lupus erythematosus and ANCA-associated vasculitis.
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Activated neutrophils have been implicated in the pathogenesis of Systemic Lupus Erythematosus (SLE) and the ANCA-associated vasculitides (AAV). Upon activation with various stimuli, neutrophils release DNA and chromatin material into the extracellular space, a process coined neutrophil extracellular trap (NET) formation. Toll-like receptor (TLR) 9 can recognize double stranded (ds)DNA and initiate the characteristic type I interferon (IFN) signature that has been implicated in the breakdown of peripheral tolerance and generation of autoreactive T- and B-cells. Recent data suggests that subjects with SLE are characterized by impaired NET degradation, disseminating the availability of extracellular DNA as a proinflammatory stimulus to the innate immune system. NETs may also contain mitochondrial DNA (mtDNA), a dsDNA molecule which is phylogenetically evolved from bacteria and rich in hypomethylated CpG sequences, thus especially suited to trigger TLR9 signaling and disease flares. Working Hypothesis: SLE and AAV patients have increased plasma concentrations of circulating extracellular mtDNA, possibly released by NET formation. Elevated mtDNA concentrations are associated with disease flares. NET formation on the one hand contributes to overt mtDNA release, and on the other hand is modulated by circulating mtDNA or nDNA, as well as by hormones and cytokines.Overall objectives and specific aims: We aim to analyse the extent and nature of circulating extracellular DNA species (mtDNA vs. nuclear DNA) in SLE and AAV and determine if mtDNA plasma concentrations can serve as a marker for diagnosis and disease activity. Furthermore, we aim to determine which factors promote, modulate and inhibit the NETotic release of mtDNA in comparison to nuclear DNA.Experimental methods and design: Using quantitative PCR, we will determine circulating DNA concentrations (mtDNA and nuclear DNA) in centrifuged plasma samples from patients with SLE and AAV and compare them with those of healthy controls and patients with rheumatoid arthritis (RA). Uni- and multivariate statistics will correlate circulating DNA plasma concentrations with disease activity, using known disease activity markers as covariates. In vitro work will examine the triggers and inhibitors of NETosis in AID derived neutrophils and plasma and analyse their presence in patients plasma in comparison with that from healthy controls. Expected value of the proposed project: Manifest mtDNA release is likely to contribute to the pathology of SLE and AAV by feeding back to neutrophil activation and thereby to disease activity and systemic inflammation. An increased understanding of how this aberrancy is brought about will facilitate new targeted therapeutic approaches. An immediate benefit of this study is that it will indicate whether or mtDNA quantification in patient plasma can serve as the basis for a novel test for disease screening and activity.

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