1. Autoantibodies

A1 HMGB1 CONTAINING NUCLEOSOMES FROM APOPTOTIC CELLS INDUCE INFLAMMATION AND IMMUNE ACTIVATION VIA TLR2 – IMPLICATIONS FOR THE ETIOPATHOGENESIS OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Nucleosomes (NCs) are the major primary autoantigens in systemic lupus erythematosus (SLE) and autoantibodies against dsDNA and NCs are a serological hallmark of SLE. However, it is still unknown why NCs, which are ubiquitous and abundant self-components, become immunogenic in SLE. Impaired phagocytosis of apoptotic cells with consecutive release of modified nuclear antigens may crucially contribute to the immunopathogenesis. High Mobility Group Box protein 1 (HMGB1), a nuclear DNA-binding protein and an extracellular pro-inflammatory mediator gets tightly attached to hypoacetylated chromatin during apoptosis. Normally, it is not released, since apoptotic cells are immediately engulfed by phagocytes. Conversely, in conditions of clearance deficiency, which is observed in a subset of patients with SLE, non-ingested apoptotic cells, may undergo secondary necrosis, thereby releasing NCs containing the endogenous adjuvant HMGB1. Here the authors investigated if these HMGB1-containing NCs may contribute to the breakdown of immunological tolerance against dsDNA and nucleosmes. The authors found that HMGB1 in fact remains bound to NCs released from apoptotic cells in vitro. Also the blood of some patients with SLE, but not in controls, complexes of HMGB1 and NCs were detected. Importantly, HMGB1 containing NCs from apoptotic cells induced secretion of cytokines IL-β, IL-6, IL-10 and TNFα as well as expression of costimulatory molecules on human and murine macrophages and dendritic cells (DC), respectively. Both, cytokine release from murine peritoneal macrophages and DC activation upon stimulation by 'apoptotic' NCs were dependent on the presence of MyD88 and Toll-like receptor 2 (TLR2). Neither HMGB1-free NCs from living cells nor from apoptotic HMGB1- or HMGB1/2-deficient cells induced marked cytokine production or DC activation. Additionally, specific inhibition of HMGB1 activity by antagonistic A box domain significantly reduced capacity of 'apoptotic' NCs to induce TNFα and IL-10 release by macrophages. Intravenous injections of HMGB1-containing NCs from apoptotic cells induced anti-dsDNA and anti-histone IgG responses in a TLR2-dependent manner, whereas NCs from living cells did not. In addition, the induction of anti-dsDNA and anti-histone IgG antibodies in pristane-treated TLR2 deficient mice was delayed compared to pristane-treated wild type controls.

The authors conclude that HMGB1 in complex with NCs activate antigen presenting cells via TLR2 thereby contributing to breaking of the immunological tolerance against nucleosomes/dsDNA and, hence, to the immunopathogenesis of SLE.