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The interaction of apoptotic cell material with monocytes and macrophages under the influence of interferon-alpha and its significance for the pathogenesis of systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is a systemic connective tissue disease characterised by autoantibody production towards nuclear molecules, the pathogenesis of which has remained largely unclear.
Apoptotic material has been implicated in the pathogenesis of SLE, as a high rate of circulating microparticles as well as a higher rate of apoptosis has been observed. Also, phagocytic function of professional phagocytes, such as macrophages has been reported to be impaired facilitating the accumulation of apoptotic debris, which poses a possible source of autoantigens. Apoptotic blebs are shedded from the plasma membrane as microparticles (AdMPs) during early stages of apoptosis. They have been shown to contain several nuclear antigens that are important targets of autoantibodies formed in systemic lupus. AdMPs have been implicated as conveyors of several immune functions and auto-adjuvants in the pathogenesis of SLE.
Monocytes and macrophages, as the main professional phagocytes responsible for clearance of apoptotic material, have been reported to be aberrant in patients with systemic lupus compared to healthy donors with regards to their cytokine secretion profile as well as their surface marker expression.
Another aspect of SLE is the observation of raised levels of IFNα in correlation with disease activity and a raised expression of IFN-induced genes, the “IFN signature”. Furthermore, long-term IFNα treatment elicits autoimmune reactions as well as autoantibody production in patients treated with this cytokine for other diseases that have no known autoimmune disorder. IFNα, which is normally foremost produced in reaction to viral infections, has numerous functions in the immune system. These include promotion of DC maturation and generation of distinct subset of monocyte-derived nondendritic antigen presenting cell as well as activation of T-cells and indirectly of B-cells.

In this study, I therefore focused on the interaction of these main pathogenetic factors associated with SLE: phagocytic and general function of monocytes and macrophages, excess of apoptotic material and raised levels of IFNα.
For this purpose, human monocytes or monocyte-derived macrophages were incubated with AdMPs, and in the case of monocytes also with apoptotic or necrotic cells, and phagocytosis of this material was examined in the presence or absence of IFNα. Also, cytokine secretion patterns and surface molecule phenotype were investigated for changes due to the presence of apoptotic material and IFNα.

I could show that uptake of AdMPs by monocytes was significantly increased in the presence of IFNα in a dose-dependent manner. Importantly, this effect was restricted to the interaction of IFNα with AdMPs, as uptake of apoptotic and necrotic cells by monocytes were observed to be no different in the presence of IFNα. Intriguingly, necrotic cells were taken up significantly more than apoptotic cells. No difference was observed between cells from NHD and SLE patients.
Engulfment of AdMPs led to a significant increase in the production of the pro-inflammatory cytokines IL-6, IL-8 and TNFα by monocytes. This effect was potentiated by the presence of IFNα and was not observed when IFNα was supplemented alone. Importantly, a generally higher presence of IL-8 and IL-10 in the supernatants of SLE patients than in those from NHD was observed.
Furthermore, phagocytosis of AdMPs induced an increase in the expression of the co-stimulatory molecules CD80 and CD86 as well as surface molecules important in the assembling of the phagocytic synapse such as CD44. Also, the maturation marker CD11c, CD16 and CD163 were significantly increased due to the presence of AdMPs. In contrast, IFNα supplementation was not able to induce significant increases of these markers by itself. Importantly, however, AdMP addition in the presence of IFNα led to an even higher expression of CD16, CD80, CD86 and CD163 compared to AdMPs alone.

In contrast, monocyte-derived macrophages incubated with AdMPs did not show any increase in phagocytosis in the presence of IFNα.
Importantly, the cytokine secretion of IL-6, IL-8 and TNFα as well as the expression of CD80 and CD86 were increased in M2 macrophages by the presence of AdMPs and/or IFNα.

In contrast, M1 macrophages were hardly influenced by the presence of IFNα and AdMPs with regards to their cytokine secretion and surface marker expression, as they already exhibited a highly pro-inflammatory phenotype.

These results indicate that IFNα and AdMPs act as auto-adjuvants on one another to promote auto-inflammatory reactions by increasing the uptake of autoantigens contained within AdMPs with possible subsequent presentation of these antigens to T-cells and elicitation of B-cell autoantibody production. They further promote differentiation of inflammatory macrophages in tissues, which could lead to a perpetuation of inflammatory reactions.