Apoptosis and autoantibodies in systemic lupus erythematosus

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Chapter I

Introduction
**Systemic lupus erythematosus**

Systemic lupus erythematosus (SLE) is the prototype of a systemic autoimmune disease and is characterised by the presence of multiple autoantibodies. Especially antibodies to dsDNA are specific for the disease, and changes in their levels are a sensitive tool for the detection of disease activity [1-3]. A rise in the level of these antibodies precedes the development of a clinical relapse in many cases [1] suggesting a particular role of these antibodies in the pathogenesis of the disease. This concept is supported by the presence of antibodies to dsDNA in affected kidneys [4,5]. Furthermore, antibodies to dsDNA in SLE patients, in contrast to those found in healthy controls, are high-affinity antibodies of the IgG subclass carrying T cell-dependent somatic hypermutations [6-8]. The rise of antibody levels preceding a clinical relapse is associated with an increase in the proportion of B cells and T-helper cells expressing activation markers [9]. Taken together, these data are consistent with the concept that the anti-dsDNA response in SLE is an antigen driven, T cell-dependent process [10].

Although the presence of antibodies to nuclear (and cytoplasmic) antigens and their levels have been shown to be of value for the clinician in diagnosing and monitoring SLE patients, it is poorly understood why these antibodies develop. However, in recent years some intriguing new concepts concerning the development of autoantibodies and the etiopathogenesis of SLE have emerged.

**Apoptosis**

Every day billions of cells are eliminated by a very tightly orchestrated process called programmed cell death or apoptosis. In contrast to cell death by necrosis, apoptosis is characterised by a stereotypical pattern of morphological changes, irrespective of the initiating event [11]. These changes include cellular and nuclear condensation and fragmentation, flip flop, (that is, negatively charged phosphatidylserine moves from the inner to the outer surface) and blebbing of the cell membrane [12]. In these blebs autoantigens are exposed. It has been shown that in apoptotic keratinocytes many nuclear and cytoplasmic antigens, that are characteristic targets for autoantibodies, are clustered in high concentrations in the cell membrane [13]. The presentation of nuclear antigens at the outer surface of the cell might give a clue to the question why in autoimmunity antibodies are produced that are directed towards intracellular antigens. It does, however, not answer the question why antibodies arise anyhow as apoptotic cells are phagocytosed very rapidly [14].
**Phagocytosis**

Phagocytosis of apoptotic cells is a complex process in which many cells, membrane receptors and serum molecules are involved [15]. The involvement of receptors like CD14 on professional phagocytes insures a non-inflammatory process because apoptosis via this receptor leads to the production and release of TGFβ, a potent anti-inflammatory cytokine [16]. The phagocytosis of apoptotic cells is a self regulating process [17] as previous uptake of apoptotic cells downregulates the phagocytic capacity of macrophages. It can be speculated that the increased presence of apoptotic cells thereby results in a declining phagocytic capacity of macrophages, and so introduces a vicious circle leading to the persistence of non-ingested apoptotic cells presenting intracellular antigens on their surface.

**Inflammation**

The presence of apoptotic cells in sufficient amounts can break tolerance characterised by the production of autoantibodies [18]. As this production is probably T cell dependent a proper T and B cell interaction is necessary. A proper interaction means that, next to binding of the T cell receptor (TCR) with the major histocompability complex (MHC) molecule complexed with the antigen, additional signalling through costimulatory molecules occurs. The autoantibodies produced play a central role in the initiation of inflammation, as has been shown in the kidney in particular [19,20]. Autoantibodies can bind to the antigenic structures that are presented on the surface of apoptotic cells during the apoptotic process [21,22]. In stead of the normal opsonization with serum components like CRP, SAP and complement proteins [23,24] the apoptotic cell now will be opsonised with autoantibodies. The constant domain of these antibodies will allow Fcγ-receptor bearing cells to interact. Interaction with Fcγ-receptors will lead to secretion of pro-inflammatory cytokines, resulting in attraction of neutrophils and monocytes, eventually leading to inflammation that is characteristic for autoimmune diseases like SLE. The important role of Fcγ-receptors is strongly supported by studies performed in γ-chain knock out mice in which it was shown that, despite the presence of autoantibodies in the kidneys, no inflammation occurred [25].

**Aim of the thesis**

The general objective of the studies in this thesis is to elucidate the role apoptotic cells play in the etiopathogenesis of SLE. First, we focus on the function of soluble Fas (sFas), a molecule which has been described to interfere with the induction of Fas-mediated apoptosis. It has been suggested that elevated levels of sFas hamper apoptosis of
(autoreactive) lymphocytes, subsequently resulting in autoimmunity. In chapter II we analyse the fluctuations in sFas levels in the serum of SLE patients in time, in relation to disease activity. In addition, to evaluate whether increased sFas levels are associated with lymphocyte activation, we cross-sectionally analysed sFas levels in relation to the activation status of the respective peripheral blood lymphocyte populations. Results are presented in chapter III. The interference of sFas with the induction of Fas-mediated apoptosis is only one possible mechanism accounting for the presence of apoptotic cells in the peripheral blood of lupus patients. The susceptibility of peripheral blood lymphocytes (PBL) in SLE patients for Fas-mediated apoptosis is further dependent on the expression of membrane Fas. In chapter IV we describe the results of Fas expression on PBL of SLE patients. As a spin off, in chapter V we evaluate the effects of cigarette smoking on Fas expression in healthy subjects. Finally, the question whether there are intrinsic defects in the Fas-mediated apoptosis in SLE patients is subject of investigation in chapter VI.

The development of an inflammatory process is one of the hallmarks of SLE. The T cell-dependent production of autoantibodies plays a central role in the initiation of inflammation. We measured the expression of costimulatory molecules on PBL in SLE patients in conjunction with disease activity to evaluate whether expression of these molecules in SLE is increased, a factor which might facilitate the production of autoantibodies. In chapter VII the results of this analysis are described. Autoantibodies are primarily of the IgG isotype. Of the different IgG subclasses, IgG1 and IgG3 activate complement more efficiently than IgG2 while IgG4 does not activate complement at all. The IgG subclass distribution of autoantibodies therefore can be of relevance in the development of inflammation, in lupus nephritis in particular. In chapter VIII we studied IgG subclass profiles of autoantibodies to nucleohistone and to dsDNA in patients prior to a renal relapse in comparison to patients developing an extra-renal relapse. Finally, we analysed whether the Fcγ receptor polymorphism, by their differential interaction with the respective IgG autoantibodies, has influence on the course of the disease. Results are presented in chapter IX. This study was conducted because it was shown that the different Fcγ-receptor isotypes described have different affinity for the several IgG subclasses. An overview of the current ideas about the pathogenesis of SLE is given in chapter X. The results of this thesis are summarised in chapter XI.

References

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