

Serpins as Players in Autoimmune Diseases

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Serpins (serin protease inhibitors) are a superfamily of evolutionary old, structurally conserved molecules that are widespread among all branches of life. They might have derived from a common ancestor, were lost throughout evolution in simpler organisms but gained important features among metazoans [1,2]. Beyond inhibition of serine proteases, serpins have several functions in homeostasis of living organisms [1], particularly regarding regulation of apoptosis and cellular survival [3].

All serpins share a common tertiary structure that is cored around the reactive center loop, driving serpin specificity and function [1,2]. To date, 37 serpins have been characterized in humans, mainly acting at the extracellular level and belonging to separate clades (termed A-I) according to their phylogenetic relationship. Serpins belonging to clade A (alpha-1 antitrypsin-like) and B (ovalbumin-serpins) represent the largest groups [2]. Unlike the majority of serpins, those belonging to clade B are localized intracellularly and their major task appears to be cellular protection against cytotoxic molecules which can leak into the cytoplasm [4], thereby exerting a direct cytoprotective effect. Moreover, clade B serpins and particularly SERPINB3 are endowed with an anti-apoptotic capability, further contributing to cellular survival [1,3].

The prosurvival role of SERPINB3 had previously emerged due to detection of high levels of SERPINB3 in the presence of squamous cell carcinomas [5] and more recently in liver carcinoma [6], though the mechanisms exploited in apoptosis modulation have not been fully unraveled. SERPINB3 was initially suggested to interfere either with mitochondrial release of cytochrome C or with caspase 3 activation or upstream proteins, due to decrease in caspase 3 activity following cellular transduction with SERPINB3 cDNA [7]. Interestingly, SERPINB3 may exert a double-faced effect regarding modulation of cell death as it was proven to promote endoplasmic reticulum stress and eventually apoptosis [1]. Whether a cell is driven toward uncontrolled survival or stress-induced death may depend on persistence of stressing stimuli. Hence, SERPINB3 is likely to modulate apoptosis following environment influxes as well.

SERPINB3 expression is displayed by several kinds of cells, including mononuclear cells and particularly B lymphocytes [1].

Recently, expression of SERPINB3 on peripheral blood mononuclear cells (PBMC) was analyzed in patients affected either with hepatitis C virus (HCV)-chronic liver disease or systemic lupus erythematosus (SLE) [8]. Interestingly, surface levels of SERPINB3 on PBMC were significantly lower in HCV-carriers than in healthy controls and the lowest levels were found on B lymphocytes of patients with SLE [8]. These findings led the authors [8] to propose a unifying role for interferon type I (IFN-I) and IFN-I-induced genes in dampening SERPINB3 expression on mononuclear cells both in HCV hepatitis and lupus.

In fact, reduced SERPINB3 expression in SLE and possibly in other systemic autoimmune disorders may account for alterations in apoptosis, which may intervene in the exposition of autoantigens in the extracellular space, thereby evoking an aberrant autoimmune response. Early data collected by our group on SERPINB3 administration in murine models of lupus suggested that lupus-like glomerulonephritis could be hindered by increased SERPINB3 levels [9]; however, exogenous administration of SERPINB3 may diverge from its intracellular function. Hence, more experiments investigating the potential of SERPINB3 restoration in lupus models either as a preventive or therapeutic strategy are being carried out.

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