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Apoptosis inhibitors and lupus

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Keywords

Animal model, antinuclear antibodies, apoptosis, caspase inhibitors, keratinocytes, systemic lupus erythematosus, therapy

Context

Recent evidence suggests that nucleosomes and nucleoproteins processed during apoptosis may act as primary autoantigens in systemic lupus erythematosus (SLE) autoimmunity. Abnormal clearance of apoptotic debris by macrophages can drive a T-cell-dependent immune response against nuclear autoantigens specifically modified by the apoptosis enzymatic machinery and processed by professional antigen presenting cells. Decreased nonspecific clearance of apoptotic cells or excessive apoptosis of keratinocytes has been linked to murine and human SLE.

Significant findings

The authors use a previously described transgenic model of SLE expressing IFN-? in keratinocytes, leading to excessive keratinocyte apoptosis, systemic autoimmunity and nephritis (see Additional information). Treatment of this model with the broad-spectrum caspase inhibitor ZVAD-fmk daily for 21 days led to a significant decrease in the number of apoptotic keratinocytes without gross adverse responses. ZVAD-fmk-treated mice showed a significant decrease in the severity of renal disease evaluated as glomerular cellularity and interstitial infiltration when compared to saline-treated mice. No consistent changes in the levels of anti-dsDNA and antihistone antibodies were observed in ZVAD-fmk-treated mice.

Comments

Different murine models of SLE have shown a dual role for apoptotic mechanisms in the pathogenesis of autoimmunity. The *lpr* and *gld* SLE models are characterized by a primary defect in the Fas pathway of lymphocyte apoptosis leading to an abnormal expansion of autoimmune responses. In contrast, other

SLE models display excessive apoptosis or defective clearance of apoptotic debris suggesting that autoimmunity against autoantigens generated by apoptotic pathways may contribute to the pathogenesis of SLE. Both kinds of models share with human lupus a similar pattern of autoantibodies. The contribution of both pathogenetic mechanisms to human SLE is not known.

The use of systemic inhibitors of apoptosis in SLE appears as a double-edged sword, on the one hand decreasing the release of autoantigens and, on the other, decreasing the ability of the immune system to limit its responses. The reported study demonstrates that short-term therapy with a caspase inhibitor has beneficial effects on nephritis, presumably by decreasing the release of autoantigens generated by apoptosis. This therapy was not accompanied by consistent changes in the titer of antihistone or anti-dsDNA antibodies, precluding conclusions on the direct effects of caspase inhibitors in the autoimmune response. The use of a similar strategy in other SLE models may help to better answer these questions.

Methods

IFN-? transgenic mice (CBA X C57/BL10 F1s), daily subcutaneous administration of carbobenzoxy-valyl-alanyl-aspartyl-(?-*o-methyl*)-fluoromethylketone (ZVAD-fmk), TUNEL, ELISA, histological assessment of kidney disease

Additional information

Seery JP: **IFN-? transgenic mice: clues to the pathogenesis of systemic lupus erythematosus?** *Arthritis Res* 2000, **2**:437-440.

References

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