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Regulation of synovial cell apoptosis by proteasome inhibitor

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Keywords

Apoptosis, proteasome, synovial cell

Context

Proliferative and apoptotic homeostasis in various types of cells is regulated by different cytokines and involves Fas-mediated activation of caspase-3 by caspase-8 for programmed cell death. The proteasome is an essential proteinase complex that is involved in the degradation of caspase-3. In RA, progressive destruction of cartilage and bone is associated with pronounced synovial tissue hyperplasia. To investigate whether inhibition of proteasome function induces apoptosis of cultured synovial cells *in vitro* and whether this process is modulated by cytokines.

Significant findings

Proteasome inhibitor Z-Leu-Leu-Leu-aldehyde induced the apoptosis of synovial cells in a dose dependent manner in samples from patients with RA as well as patients with osteoarthritis. This process was significantly enhanced by pretreatment of cultured cells with TNF-a, whereas addition of TGF?1 shows an anti-apoptotic effect. Addition of a caspase-8 or -3 inhibitor markedly reduced the Z-Leu-Leu-Leu-aldehyde effect on apoptosis. The expression of apoptosis-related proteins in synovial cells was influenced by TNF-a as well as TGF?1, but was not clearly associated with a susceptibility to apoptosis due to proteasome inhibitor.

Comments

This study analyzed the stimulatory effect of a proteasome inhibitor on the apoptosis ratio of human synovial cells *in vitro*. Interestingly, the induction of apoptosis due to the inhibition of proteasomal function was augmented by the pro-inflammatory cytokine tumour necrosis factor (TNF)-a, which is involved in the pathogenesis of rheumatoid arthritis (RA). In fact, the proteasome represents a central

proteinase machinery essential for cellular viability, and as such might be a candidate therapeutic target in rheumatic disorders.

Methods

Type B (fibroblast like) synovial cells were isolated from tissue samples of patients with RA. Apoptosis of cultured cells was induced by addition of the proteasome inhibitor Z-Leu-Leu-Leu-aldehyde under the influence of TNF-a or recombinant transforming growth factor ?1 (rTGF?1) and subsequently quantified using Hoechst 33258 dye staining and ^{51}Cr release assay. Activity of caspase-3 was measured using a fluorescent substrate in an enzyme assay. Expression of apoptosis-related proteins (pro-caspases-3 and -8, Bcl-2, Bax, Bcl-xL and XIAP) was analyzed in immunoblot analysis using monoclonal and polyclonal antibodies.

References

1. Kawakami A, Nakashima T, Sakai H, Hida A, Urayama S, Yamasaki S, Nakamura H, Ida H, Ichinose Y, Aoyagi T, Furuichi I, Nakashima M, Migita K, Kawabe Y, Eguchi K: Regulation of synovial cell apoptosis by proteasome inhibitor. Arthritis Rheum . 2000, 42: 2440-2448.