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The role of interleukin-2 in regulating the sensitivity of natural killer cells for Fas-mediated apoptosis.

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The Fas/Fas-ligand (FasL) system seems to play a key role in regulating immunoresponses. Highly purified CD56+CD3- natural killer (NK) cells were found to be resistant to the apoptosis-inducing Fas mAb CH11 in the absence or in the presence of interleukin-2 (IL-2) for up to 3 days. However, NK cells activated with IL-2 for 3 days became apoptotic following combined treatment with CH11 and actinomycin D, suggesting the presence of an intact apoptotic machinery. In contrast, NK cells cultivated in IL-2 for 6 days became sensitive to CH11-induced apoptosis without addition of actinomycin D. At this time, a pronounced up-regulation of the Fas protein on the NK cell membrane was detected. By using reverse transcription/polymerase chain reaction it was found that the anti-apoptotic gene FLIP was strongly expressed in NK cells for up to 6 days of IL-2 stimulation. After day 6, a time-dependent decrease in the expression of FLIP was observed concomitantly with increased sensitivity for Fas-mediated apoptosis. The amount of apoptotic and necrotic NK cells in the presence of IL-2 increased in a time-dependent manner, reaching 40% at day 6 of culture. The amount of apoptotic and necrotic NK cells was reduced in the presence of Fas-Fc protein. In addition, IL-2 stimulated the NK cells to release soluble FasL in a time-dependent manner, whereas membrane FasL did not seem to increase in a similar manner. These results indicate that Fas/FasL interactions are involved in the down-regulation of IL-2-activated human NK cells.

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