TNF-α INDUCES SECRETION OF A HIGH MOLECULAR WEIGHT TUMORICIDAL ACTIVITY (MTC 170) BY MURINE BONE MARROW-DERIVED MACROPHAGES

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Macrophages selectively destroy a variety of tumor cells in a reaction termed Macrophage-Tumor-Cytotoxicity (MTC). This effector function has been associated with the induction of TNF-α, which is regarded as a central cytotoxic mediator of MTC. However, discrepancies exist concerning the role of TNF-α as a direct cytotoxic effector molecule in MTC, since the *in vitro* cytotoxic activity of TNF-α has been shown to be restricted to a small number of highly sensitive tumor cell lines, which is in marked contrast to the results obtained in MTC. Recently, we have described the secretion of a novel high molecular weight tumoricidal activity distinct from TNF-α (termed MTC 170) with broad antitumor specificity by activated murine bone marrow-derived macrophages (BMMΦ). Since TNF-α is known to activate macrophages for a variety of functions, we investigated, whether it might play a more indirect role in MTC by activating macrophages for secretion of MTC 170. In the present study we show, that stimulation of BMMΦ with recombinant TNF-α induced a dose dependent activation for cytotoxic activity against TNF-resistant tumor cells as well as secretion of MTC 170 as evidenced by functional activity in BMMΦ conditioned culture supernatants. TNF-induced activation of BMMΦ for tumor cytotoxicity and MTC 170 secretion were synergistically enhanced by IFN-γ. In contrast, the functionally related monokines IL-1 and IL-6 were not effective as inducers of macrophage antitumor activity or MTC 170 secretion, regardless of the addition of IFN-γ. In conclusion, our data suggest, that while TNF-α may play only a restricted role as a direct cytotoxic effector molecule in MTC, it constitutes a central endogenous mediator of macrophage activation for tumor cytotoxicity via induction of MTC 170 secretion, which likely represents the ultimate antitumor effector mechanism of MTC.

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