TNF-α MEDIATES INDUCTION OF A HIGH MOLECULAR WEIGHT TUMORICIDAL ACTIVITY (MTC 170) IN SERA OF MICE PRETREATED WITH P. ACNES OR INTERFERON-γ

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Sera of mice infected with certain bacteria and subsequently challenged with LPS promote hemorrhagic necrosis of some tumors *in vivo* and display tumoricidal activity against a variety of tumor cell lines *in vitro.* These activities have been associated with the induction of TNF-α, which is regarded as the central antitumor mediator both *in vitro* and *in vivo.* We have recently described the induction of a novel high molecular weight tumoricidal activity termed MTC 170, which is distinct from TNF-α in such sera as well as in culture supernatants of macrophages activated with IFN-γ and LPS. In the accompanying abstract we demonstrate induction of MTC 170 activity in culture supernatants of macrophages treated with IFN-γ and TNF-α, suggesting, that TNF-α, in contrast to its anticipated function as a direct tumor-cytotoxic factor, might play a more indirect role in tumor defense. We therefore tested, whether TNF-α can also induce MTC 170 activity and thus replace LPS *in vivo.* Sera of mice pretreated with heat-killed P. acnes and subsequently injected with TNF-α displayed strong antitumor activity against several TNF-resistant murine tumor cell lines *in vitro.* Maximal activity was detected about 8 hours after TNF-injection, while TNF-α activity was no longer detectable 1 hour after injection. Pretreatment of mice with P. acnes could be replaced by i.v injection of IFN-γ prior to TNF-challenge, while no antitumor activity was detectable in sera of unprimed mice injected with TNF-α, indicating that IFN-γ is a crucial mediator of priming by P. acnes. TNF-induced antitumor activity was indistinguishable from the LPS-induced factor MTC 170 with respect to molecular weight as well as other biochemical and functional criteria. In conclusion, our data demonstrate, that TNF-α in combination with IFN-γ is a strong inducer of an antitumor activity distinct from TNF-α, and thus suggest a novel pathway for TNF-induced tumor regression via induction of MTC 170.

Eur Cytokine Netw **7:**291. 1996