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**Sublytic Complement Confers Tumor Cell Resistance to sTNF-α-induced Apoptosis and Necrosis**

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Promotionsfach: Immunologie
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Complement as well as soluble tumor necrosis factor-α (sTNF-α) are involved in the immune response to cancer cells. The complement system is activated with subsequent formation of the pore-like membrane attack complex (MAC), which inserts into cell membranes causing tumor cells death. Upon binding to TNF receptor 1 (TNFR1), sTNF-α induces tumor cells death either by apoptosis or necrosis. Although complement and sTNF-α potentially exert significant anti-tumor effects, increasing evidence indicates that complement as well as sTNF-α-induced tumor cell death is hampered by multiple protective mechanisms. It has been demonstrated that sublytic complement confers to tumor cells resistance to lytic doses of complement (and perforin, streptolysin O, melittin), and that low-dose sTNF-α even promotes the proliferation of some malignant cell lines. In this study, we wished to know if sublytic complement is able to interfere with sTNF-α-mediated tumor cell killing.

Our results clearly demonstrate that after pretreatment with either low-dose sTNF-α or sublytic complement, prostate cancer cells (DU145) significantly lose their susceptibility to sTNF-α-mediated cell death. In contrast to low dose sTNF-α, resistance to sTNF-α-mediated cell death conferred by sublytic complement was not associated with a downregulation of TNFR1 expression. Sublytic complement protected the tumor cells not only against sTNF-α-induced apoptosis but also against sTNF-α-induced necrosis, although with different mechanisms.

sTNF-α, in the presence of actinomycin D, mainly induced cell apoptosis with activation of caspase-8 and caspase-3. Pretreatment with sublytic complement led to an inhibition of sTNF-α-mediated caspase-8 and caspase-3 activation, inhibited cleavage of PARP-1 and induced the production of anti-apoptotic proteins (Bcl-2, Bcl-xL).

In the absence of actinomycin D, sTNF-α induced cells necrosis, characterized by lack of caspase-3 and caspase-8 activation. Here, the protective effect of sublytic C5b-9 went along

with inhibition of sTNF-α-mediated cleavage of PARP-1 and a significantly reduced production of reactive oxygen species (ROS).

These data extend our current view on the complex molecular mechanisms within the tumor microenvironment promoting cross-resistance of malignant cells against potentially dangerous effector molecules of the immune response.