Mode of Tumor Cell Death in Macrophage-Mediated Tumor Cytotoxicity - Apoptosis or Necrosis ?

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Background: We have recently shown that exposure of macrophages to apoptotic or necrotic tumor cells differentially affects macrophage-mediated tumor cytotoxicity (MTC) in a suppressive or enhancing way, respectively. Likewise, apoptotic as compared to necrotic cells have recently been proposed to induce immunological tolerance rather than specific immunity. Thus, the mode of tumor cell death may critically influence the efficacy of further tumor destruction by the immune system. Since macrophages are supposed to constitute an early defense mechanism leading to destruction of tumor cells, we have analyzed the mode of tumor cell death brought about by MTC. **Methods:** In vitro culture of murine bone marrow-derived macrophages; Cellular cytotoxicity assays on TNF-resistant tumor target cells; Analysis of cell death via Annexin-V/Propidium Iodide staining and fluorimetric caspase detection. **Results:** Despite morphological features consistent with apoptosis, interaction of activated macrophages with TNF-resistant tumor cells primarily resulted in a rather necrotic type of tumor cell death, characterized by early loss of plasma membrane integrity combined with low phosphatidylserine exposure on the surface of dying cells. Nevertheless, caspase activation as well as nuclear fragmentation typical for apoptotic cell death was observed, indicating triggering of the apoptotic cascade within dying cells. Interestingly however, neither the extent nor the kinetics of cytotoxicity was affected by the broad spectrum caspase inhibitor AcDEVD-CHO, whereas nuclear fragmentation was almost completely inhibited. **Conclusions:** Our data suggest, that MTC primarily initiates a necrotic type of tumor cell death, while induction of the apoptotic machinery in dying cells likely constitutes an epiphenomenon, which however does not appear to be required for actual tumor cell death. This mode of cell death, which we would like to term "pseudoapoptosis" may thus allow to discriminate "executed" dangerous tumor cells from innocent normal cells undergoing truly apoptotic self demise during tissue restructering or termination of immune reactions. Given the impact of the mode of cell death on antitumor immune responses this may lead to local amplification of tumor cytotoxicity at sites of macrophage-mediated tumor destruction and may as well constitute a prerequisite for the induction of specific tumor immunity.

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