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#3661 Restoration of TFPI-2 in a human glioblastoma cell line triggers caspase mediated pathway and apoptosis. Joseph George, Christopher S Gondi, Dzung H Dinh, Meena Gujrati, Jasti S Rao. University of Illinois College of Medicine, Peoria, IL.

The induction of apoptotic pathways in cancer cells offers a novel and potentially useful approach to improve patient responses to conventional chemotherapy. Tissue factor pathway inhibitor-2 (TFPI-2) is a protease inhibitor that is abundant in the extracellular matrix (ECM) and highly expressed in non-invasive cells, but absent or undetectable in highly invasive human glioblastoma cells. Using a recombinant adeno-associated viral vector carrying human TFPI-2 cDNA (rAAV-TFPI-2), we stably expressed TFPI-2 in U-251 cells, a highly invasive human glioblastoma cell line. Our previous studies demonstrated that restoration of TFPI-2 in glioblastomas effectively prevents cell proliferation, angiogenesis and tumor invasion. In the present study, we determined whether TFPI-2 restoration could induce apoptosis through the caspase mediated signaling pathway. The results of caspase 9 and caspase 3 activity assays showed increased activity, which indicates enhanced apoptosis. Immunofluorescence for cleaved caspase 9 and 3 depicted increased expression and co-localization of both molecules. Western blot analysis demonstrated increased transcriptional activities of FasL, TNF-α, BAX, FADD and TRADD, as well as elevated levels of cleaved caspases and PARP. Semiquantitative RT-PCR depicted increased expression of TNF-α and FasL and the related death domains, TRADD and FADD. Taken together, these results demonstrate that restoration of TFPI-2 activates both intrinsic and extrinsic caspase-mediated, pro-apoptotic signaling pathways and induces apoptosis in U-251 cells. Furthermore, our study suggests that rAAV-mediated gene expression offers a novel and potential tool for cancer gene therapy.

Citation Format

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