GENE THERAPY FOR THE TARGETED APOPTOSIS OF TRANSITIONAL CELL CARCINOMA CELLS.

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The process of apoptosis is mediated by aspartate-specific cysteine proteases (caspases) that include initiators (caspases 2, 8, 9, and 10) and executors (caspases 3, 6, and 7). By engineering the expression of caspase intermediates through gene delivery, apoptosis-resistant carcinoma cells were successfully driven into apoptosis.

One method used by cancer cells to achieve apoptosis resistance is the expression of genes in the inhibitor of apoptosis protein (IAP) family. Survivin, an IAP, is expressed in many carcinomas but not in normal, untransformed tissues. By using expression-targeted gene delivery with the polycation poly(ethyleneimine) as the gene delivery vector, directed production of an inducible form of caspase 9 in survivin over-expressing cancer cells was achieved, which in turn initiated the apoptosis cascade from an intermediary point. The murine bladder tumor cell lines MB49 and MBT2, which both over-express survivin, were selected because of their positive survivin expression levels, which are common to many carcinomas. Targeting of the gene therapy was achieved at the transcriptional level.

The effect of the targeted gene therapy was that, following activation of the resulting caspase pro-forms, survivin-positive cells underwent apoptosis in vitro. Experiments in an orthotopic murine model of bladder cancer are ongoing. Such directed apoptosis could eventually serve as a treatment for survivin over-expressing carcinomas.

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