Triggering of Transient Receptor Potential Vanilloid Type 1 (TRPV1) by Capsaicin induces Fas/CD95-mediated apoptosis of urothelial cancer cells in an ATM-dependent manner.

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The transient receptor potential vanilloid type-1 (TRPV1) channel plays an important role in urothelial cancer (UC) biology, and it represents a potential target for molecular therapy in urogenital tumors. We provided evidence on the expression of TRPV1 on human urothelial cancer cells (UC), and its involvement in the apoptosis induced by the selective agonist capsaicin (CPS).

We analyzed TRPV1 mRNA and protein expression on human UC cell lines demonstrating its progressive decrease in high grade UC cells. Treatment of RT4 cells with CPS induced cell cycle arrest in G0/G1 phase and apoptosis. These events were associated with rapid coordinated transcription of pro-apoptotic genes including Fas/CD95, Bel-2 and caspase families and ATM/CHK2/p53 DNA damage response pathway. CPS induced Fas/CD95 up-regulation, but more importantly Fas/CD95 ligand independent, TRPV1-dependent death receptor clustering and triggering of both extrinsic and intrinsic mitochondrial dependent pathways. Moreover, we observed that CPS activates ATM kinase that is involved in Ser15, Ser20 and Ser392 p53 phosphorylation as shown by the use of the specific inhibitor KU55933. Notably, ATM activation was also found to control up-regulation of Fas/CD95 expression and its co-clustering with TRPV1 as well as RT4 cell growth and apoptosis. In addition we evaluated the expression of TRPV1 mRNA and protein levels in normal bladder (NB) and UC tissues, to correlate TRPV1 expression with clinicopathological parameters and disease-specific survival. Our results show that the progression of UC of human bladder is associated with a marked decrease of TRPV1 expression, with a progressive loss in high-grade muscle invasive UC. Down-regulation of TRPV1 mRNA expression may represent an independent negative prognostic factor for the survival probability of bladder cancer patients.