

Increased levels and cytoplasmic accumulation of DWNN in human cancers

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DWNN, domain with no name, is a novel cell death related gene that has been shown to be involved in apoptotic cell death. This gene is located on chromosome 16p21 and is 36 kb long with three main transcripts i.e. 1.1kb and 6.1kb transcripts whereby the former is translated to the DWNN domain (DWNN-13) and the latter giving rise to DWNN domain associated with other domains (DWNN-200). The 6.1 kb transcript is alternatively spliced giving rise to two 6.1 kb transcripts with one lacking exon 16, hence there are three transcripts.

Cancers were formerly regarded as a result of disorders in mitosis but currently it is a view that cancers are as a result of failure of apoptosis. Identification of genes and their products involved in the regulation of apoptosis is very important for cancer drug development.

The aim of the study was to determine the expression pattern and tissue distribution of the DWNN in a wide range of human cancers and to determine whether there is correlation between the DWNN expression levels and apoptosis. This might contribute towards the determination of the role of DWNN in apoptosis. Cancers that were investigated include adenocarcinomas of the stomach, ovary, pancreas, prostate, transitional cell carcinoma of the bladder, hepatocellular carcinoma, kidney clear cell carcinoma, papillary carcinoma of the thyroid, astrocytoma, squamous cell carcinoma of the skin, infiltrating duct carcinoma of the breast and endometrioid carcinoma of the ovary.

Tissue arrays for the above-mentioned human cancers from multiple organs were obtained from Cybrdi, USA. These were used for the localization of the DWNN at both mRNA and protein levels. Immunocytochemistry (ICC) was used to localize the DWNN proteins while fluorescent in situ hybridization (FISH) was done for the localization of the DWNN mRNA transcripts. TUNEL based method was used to detect apoptosis in these cancers so as to correlate apoptotic and DWNN expression levels.

Our results show that DWNN is localising to the cytoplasm in most human cancers. ICC results show that all the protein species of DWNN localize to the cytoplasm. This is not any different for the mRNA because FISH shows that DWNNs mRNAs are localizing in the cytoplasm as their protein counterparts, DWNN 13 and DWNN-200. In contrast, normal tissues demonstrated nuclear localisation for both the ICC and FISH. In most cancers, using TUNEL, apoptosis was detected where there was DWNN expression.

The cytoplasmic localization correlates to mutated p53 localization that has been shown in oesophageal carcinoma. If DWNN is involved in apoptosis, it might be in a p53 dependent pathway. The cytoplasmic localization of the DWNN in all these cancers can be targeted for therapeutic development.