CARD8 (caspase recruitment domain family, member 8)

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Identity

Hugo: CARD8
Other names: CARDINAL; DACAR; DKFZp779L0366; KIAA0955; MGC57162; NDPP1; TUCAN
Location: 19q13.32

DNA/RNA

Description
The CARD8 gene contains 13 exons spanning over approximately 30 kb of genomic DNA.

Transcription
At least 5 transcripts have been identified generated by alternative splicing that together with different start codon usage yield different CARD8 isoforms. Gene products encoded by exons 1 to 13 and 5 to 13 yield TUCAN/CARD8-54-kDa and TUCAN/CARD8-48-kDa, respectively.

Protein

Description
The CARD8 gene encodes different CARD8 isoforms that contain the caspase-associated recruitment domain (CARD) in their carboxy-termini that acts as a protein-protein interaction interface. A 431 amino acids CARD8 protein of 48-kDa (TUCAN-48) has been best studied and more recently a 54-kDa isoform (TUCAN-54, 487 amino acids) was identified sharing the same CARD motif but with a different stretch of 80 amino-terminal residues. In the amino terminal part of the protein a NAC/DEFCAP/CARD7 homology domain is present.

Expression
Normal tissue: wide and differential expression at mRNA level in tissues; present in heart, brain, lung, muscle, spleen, ovary; high in kidney, testis and spinal cord; absent in liver.

Cancer: the CARD8 (48 kDa) protein is differentially expressed in cancer. High levels of CARD8 expression were found in tumor cell lines, including breast, prostate, ovarian and colon cancer cells as well as high expression in non-small cell lung cancer (NSCLC) cells and with hardly detectable expression in normal lung, in contrast to a lack of expression in small-cell lung cancer cell lines. In tumor specimens from patients CARD8 expression has been demonstrated in colon cancer and non-small cell lung cancer.

Schematic representation of two CARD8 variants. The CARD domain, the NAC/DEFCAP/CARD7 homology domain, and the amino-terminal residues that differ between the isoforms are indicated.
The 54-kDa CARD8 isoform has a different expression profile when compared to TUCAN/CARD8-48. For example a number of breast cancer cell lines do not express TUCAN/CARD8-54, although some of them express TUCAN/CARD8-48. Expression also varies widely among different tumor cell lines with high levels in colon cancer cells.

**Localization**

In MCF-7 cells overexpressed CARD8 localized to both the cytoplasmic and nuclear compartment. In specimens derived from colon cancer cells a predominant cytoplasmic expression was found, whereas in NSCLC tumor samples CARD8 was either exclusively nuclear or cytoplasmic or present in both compartments.

**Function**

CARD8 belongs to the CARD family of proteins that play a role in apoptosis regulation and NF-kB signaling associated with the innate or adaptive immune response. For example the binding of CARDs present in caspase-9 and Apaf-1 mediate the assembly of the apoptosome in which caspase-9 is activated. CARD motifs have different binding selectivity towards each other and the presence of additional structural/functional domains in the various CARD-containing proteins may also determine the choice of interaction partner.

In literature there is some controversy on the function of CARD8. Some reports mention an apoptosis inhibitory function of CARD8 involving its CARD-dependent binding to procaspase-9, whereas others did not find an association between CARD8 and caspase-9 and instead found either pro-apoptotic activity of CARD8 and associations with the inflammatory caspase-1 or the regulatory subunit of IkB kinase (NEMO) thereby suppressing NF-kB activation. Also an interaction between the p53-responsive gene DRAL (FLH2) and CARD8 has been reported resulting in the suppression of NF-kB activation. Furthermore, TUCAN/CARD8-54 was found to inhibit chemotherapay-induced caspase-9 activation and Fas ligand-induced caspase-8 activation. Based mainly on its proposed anti-apoptotic activity CARD8 is considered as a possible therapeutic target for cancer.

**Homology**

CARD family proteins.

**Mutations**

**Somatic**

Ten single nucleotide polymorphisms (SNPs) across TUCAN/CARD8 have been identified in healthy persons and patients suffering from inflammatory bowel disease.

**Implicated in**

**Colon cancer**

**Prognosis**

TUCAN/CARD8 expression has been analyzed by immunohistochemistry in paraffin-embedded colon cancer specimens (N=102) derived from patients with clinical stage II that were surgically treated. TUCAN/CARD8 staining was stronger in colon cancer cells when compared to normal cells in 64% of the 102 specimens examined. Scoring staining intensity revealed a significant correlation between high TUCAN/CARD8 expression in tumor cells and shorter patient survival.

**Non-small cell lung cancer (NSCLC)**

**Prognosis**

The expression of TUCAN/CARD8 has been determined by immunohistochemistry in tumor specimens derived from NSCLC patients (N=49, stage III and IV) that received neoadjuvant or palliative chemotherapy. TUCAN/CARD8 expression was detected in 69% of the samples, showing exclusively cytoplasmic (27%) or nuclear (11%) staining, or in both compartments (31%). No correlation between response to chemotherapy or expression/localization was found, although, cytoplasm-only staining NSCLC samples predicted shorter survival, suggesting a possible prognostic value.

**Inflammatory bowel disease (IBD)**

**Disease**

Crohn’s disease and ulcerative colitis.

**Prognosis**

Patients with IBD (Crohn’s disease (CD) and ulcerative colitis) and healthy individuals were genotyped for SNP. A significant association between a TUCAN SNP and CD was found. However, in other reports this association was not confirmed, rejecting TUCAN/CARD8 as a possible susceptibility gene for IBD.

**References**


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