MCC (mutated in colorectal cancers)

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Published in Atlas Database: September 2013
Online updated version: http://AtlasGeneticsOncology.org/Genes/MCCID330ch5q22.html
DOI: 10.4267/2042/53537
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Abstract

Review on MCC, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: MCC1
HGNC (Hugo): MCC
Location: 5q22.2

DNA/RNA

Note
The MCC gene was discovered in 1991 due to its linkage with the APC gene (Kinzler et al., 1991; Nishisho et al., 1991). APC was quickly recognised as a key tumour suppressor gene and MCC is now also emerging as an important gene in cancer. MCC has multiple cellular functions and is frequently altered in colorectal cancer.

Description

Three isoforms of MCC have been identified: MCC-001 (17 exons), MCC-003 (19 exons) and MCC-011 (17 exons). MCC-001 and MCC-003 are known protein coding isoforms and MCC-011 is a putative protein coding isoform.

Transcription

In addition to the three protein coding transcripts, there are at least six non-coding transcripts (splice variants) of varying length.

Protein

Description

MCC-001, 829 aa, known protein, predicted 93 kD; observed at 105 kD.
MCC-003, 1019 aa, known protein, predicted 113 kD.
MCC-011, 766 aa, putative protein, predicted 86 kD.
**Expression**

Limited protein expression data are available but it appears that MCC expression is variable in different tissues. MCC protein is most highly expressed in the colon, heart, lung and brain (Pangon et al., unpublished).

**Localisation**

Cytoplasm, membrane cortex, nucleus.

**Function**

MCC is a tumour suppressor gene in colon and liver cancer. It regulates multiple cellular processes in epithelial cells, such as proliferation (Matsumine et al., 1996), DNA damage response (Pangon et al., 2010), lamellipodia formation (Pangon et al., 2012) and cell migration (Arnaud et al., 2009). MCC can suppress Wnt and NFκB signalling pathways (Bouwmeester et al., 2004; Fukuyama et al., 2008; Sigglekow et al., 2012) but the exact mechanisms remain poorly understood.

The function of MCC itself can be regulated through post-transcriptional modifications, of which site-specific serine phosphorylation has been best studied (Pangon et al., 2010; Pangon et al., 2012).

**Mutations**

**Germinal**

There are hundreds of SNPs in the coding region of MCC. Most are missense variants although short in-frame indels or protein-truncating mutations have also been detected. No disease associations have been described for these germline variants or mutants. However, germline retrotransposition events have been identified in the MCC locus which ablate MCC expression and are associated with virally-induced hepatocellular carcinoma (Shukla et al., 2013).

**Somatic**

Despite its name, mutations of the MCC gene are found in only ~5% of colorectal cancers but MCC gene is silenced through promoter methylation in up to 50% of colorectal cancers (Kohonen-Corish et al., 2007; Fukuyama et al., 2008). For other cancers promoter methylation data are only available for lung cancer where MCC is not methylated (Poursoltan et al., 2012). MCC mutations have also been detected in 2-5% of other cancers, such as endometrial, melanoma, bladder urothelial, gastric, lung and prostate. Homozygous deletions have been detected in 2-4% of bladder urothelial carcinomas, ovarian serous cystadenocarcinomas, acute myeloid leukemias, prostate and gastric adenocarcinomas. MCC expression is downregulated in a subset of hepatocellular carcinomas possibly through several mechanisms, including LINE-1 insertion (Shukla et al., 2013) and targeting by oncogenic miRNA-494 (Lim et al., 2013).

**Implicated in**

**Sporadic colorectal cancer**

**Oncogenesis**

Mouse experiments have shown that MCC is a tumour suppressor gene in colorectal cancer (Starr et al., 2009). In vitro experiments indicate that loss of MCC expression can impact on multiple signalling pathways but most strikingly on the activation of β-catenin directed transcription (Fukuyama et al., 2008). Aberrant activation of Wnt signalling is widely accepted as a major event in colorectal carcinogenesis and is mostly caused by APC mutations. It has been suggested that MCC silencing is also important in activating β-catenin, particularly in the context of the 'serrated neoplasia pathway' where APC mutations are less common but MCC methylation is frequent (Kohonen-Corish et al., 2007; Fukuyama et al., 2008; Li et al., 2013). Other possible tumour promoting mechanisms of MCC silencing include impaired DNA damage response to single-strand DNA breaks (Pangon et al., 2010). Site-specific phosphorylation of MCC regulates G2/M cell cycle arrest and loss of MCC is thus expected to promote proliferation of damaged cells. MCC also regulates lamellipodia formation in epithelial cells which suggests that MCC silencing could affect epithelial restitution in the colon (Pangon et al., 2012).

**Hepatocellular carcinoma**

**Oncogenesis**

Loss of MCC expression in hepatocellular carcinoma is associated with aberrant activation of β-catenin (Shukla et al., 2013). MCC knockdown in vitro causes increased proliferation of hepatocellular cancer cells and is accompanied by increased G1/S transition (Lim et al., 2013).

**Acute myeloid leukemia**

**Prognosis**

Loss of MCC expression has been studied in relation to chemotherapy responsiveness in acute myeloid leukaemia. Lack of induction of MCC expression is associated with poorer responsiveness to cytarabine (Gamazon et al., 2013).

**References**


of chromosome 5q21 genes in FAP and colorectal cancer patients. Science. 1991 Aug 9;253(5020):665-9


Pangon L, Sigglekow ND, Larance M, Al-Sohaily S, Miadenova DN, Selinger CI, Musgrove EA, Kohonen-Corish MR. The "Mutated in Colorectal Cancer" Protein is a Novel Target of the UV-Induced DNA Damage Checkpoint. Genes Cancer. 2010 Sep;1(9):917-26


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