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Gene Section
Short Communication

MCC (mutated in colorectal cancers)

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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.

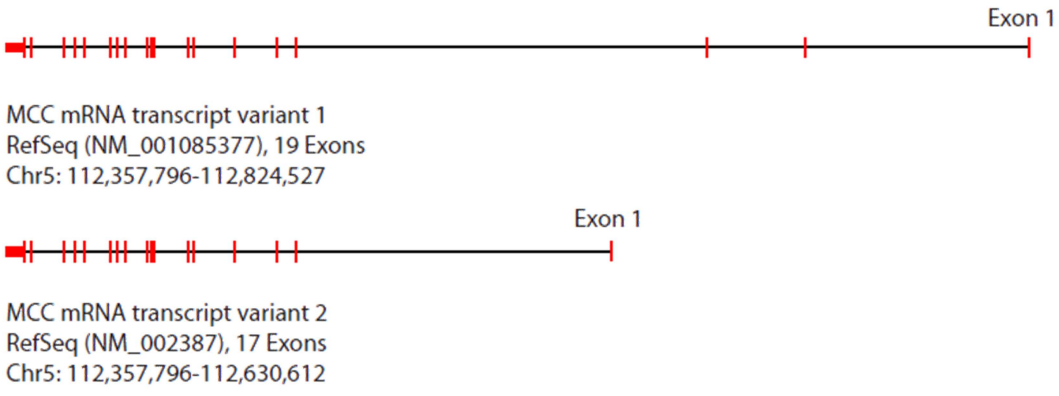
Transcription

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MCC protein is most highly expressed in the colon, heart, lung and brain (Pangon et al., unpublished).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 NFkB 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 leukemia. Lack of induction of MCC expression is associated with poorer responsiveness to cytarabine (Gamazon et al., 2013).

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