DCC (deleted in colorectal carcinoma)

Sarah Derks, Manon van Engeland

Department of Internal Medicine, Maastricht University Medical Center, PO BOX 616, 6200 MD Maastricht, The Netherlands (SD); Department of Pathology, Maastricht University Medical Center, PO BOX 616, 6200 MD Maastricht, The Netherlands (MvE)

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### Identity

**Other names:** CRC18; CRCR1; IGDC1

**HGNC (Hugo):** DCC

**Location:** 18q21.2

**Local order:** Between RKHD2 and MBD2 genes.

### DNA/RNA

**Description**

The DCC gene is composed of 29 exons spanning in a region of 1.2 million bp. The promoter contains a CpG island located -72 bp to +217 bp relative to the transcription start site.

### Transcription

The complete transcribed mRNA is 5693 bp long. Splice variants: 13 splice variants have been documented.

### Protein

**Description**

DCC encodes a 158.5 kDa Type I membrane protein of 1447 amino acids with an extracellular (1100 amino acids), transmembrane and cytoplasmic (325 amino acids) domain. The extracellular domain includes four immunoglobulin-like domains and six fibronectin type III-like motifs.

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Diagram of chromosomal region 18q21.

Diagram of the DCC gene. Blue boxes represent exons.
The cytoplasmic domain is composed of three conserved domains named P1, P2 and P3.

**Expression**

Expression is detected in many tissues (testis, lung, colon, esophagus, skeletal muscle) but is highest in normal brain tissue. Most tissues express low levels of transcripts and proteins.

**Localisation**

Cell surface.

**Function**

DCC is a member of the immunoglobulin superfamily of cell adhesion molecules and acts as a transmembrane dependence receptor for netrins, key factors in the regulation of axon guidance during development of the central nerve system.

In response to netrin-1, DCC becomes tyrosine phosphorylated, localizes to lipid rafts and selectively interacts with the Src family kinases Fyn and Lck to mediate axon attraction.

Furthermore DCC induces apoptosis when unbound to its ligand netrin-1. The DCC cytoplasmic domain is required for the induction of apoptosis and contains a caspase cleavage site which is recognized by caspase 3 in vitro. Upstream of the caspase cleavage domain a proapoptotic domain named addiction dependence domain (ADD) is located, which interacts with caspase 9 in the absence of Netrin-1 and binds DCC-interacting protein-13a (DIP13-a) to mediate DCC-induced cell death.

DCCs downstream effects involve MAPK activation and subsequent activation of the transcription factor Elk-1 and SRE regulated gene expression.

**Homology**

DCC has a homolog in mammals named neogin and is conserved in chimpanzee, dog, cow, mouse, rat, zebrafish, Caenorhabditis elegans (UNC40) and Drosophila (Frazzled).

**Mutations**

**Somatic**

DCC mutations rarely occur in cancer. In colorectal cancer (CRC) the most common somatic mutations are 120 to 300 bp expansions in a dinucleotide repeat tract located in an intron region immediately downstream of exon 7. Expansions are present in 10-15% of CRCs which are cancers with microsatellite instability.

**Implicated in**

**Colorectal cancer**

**Note**

By regulating apoptosis in the absence of netrin-1, DCC is a conditional tumor suppressor. In normal conditions, DCC induced apoptosis limits cellular lifespan in the intestinal crypt and thereby inhibits the initiation of malignant transformation. Transfection of DCC cDNA into a human cell line lacking DCC expression suppresses tumor growth and results in apoptosis and cell cycle arrest.

DCC is located on chromosomal region 18q21-pter which is affected by loss of heterozygosity (LOH) which is associated with reduced DCC expression in approximately 70% of colorectal cancers.

Although DCC mutation is rare, DCC promoter CpG island methylation occurs in about 80% of CRCs.

**Prognosis**

Absent DCC expression is a strong predictor of poor survival in stage II and stage III CRCs. In patients with stage II disease decreased DCC expression is associated with a five-year survival rate of 61.6% versus 94.3% in DCC expressing stage II CRCs. In patients with stage III disease, the respective survival rates are 59.3 percent and 33.2 percent. LOH of 18q21 alone was also associated with poor prognosis and risk of metastasis in some studies although this association was not observed by others.

Furthermore 18q LOH is associated with decreases responsiveness to fluorouracil-based adjuvant chemotherapy in stage III CRC.

**Oncogenesis**

LOH of chromosome 18q21 profoundly occurs in progressed adenomas and colorectal carcinomas and is present in about 100% of hepatic metastasis but rarely occurs in early stage lesions. The same accounts for DCC promoter CpG island methylation which is present in 80% of adenomas and carcinomas and in only 23% of normal colon tissues.

**Gastric cancer**

**Note**

Reduced DCC mRNA expression is observed in 52% of gastric cancers, being present in 72% of intestinal type gastric cancers and in 17% of infiltrative type gastric cancers.

LOH of 18q21 occurs in 30% of intestinal type gastric cancers and is an infrequent event in early or advanced gastric cancer.
Oncogenesis

All liver metastasis of gastric carcinomas showed reduced DCC expression.

**Head and neck squamous cell carcinoma (HNSCC)**

**Note**
DCC promoter CpG island methylation occurs in 75% of HNSCC. Restoration of DCC expression (by transfection) led to inhibition of cell growth in HNSCC cell lines.

**Prognosis**
LOH of chromosomal region 18q21 occurs in 40% of HNSCC and is associated with poor patient survival.

**Esophageal cancer**

**Note**
18q21 LOH occurs in 23% of esophageal squamous cell carcinomas (ESCC). DCC promoter CpG island methylation occurs in 74% of primary ESCCs in a cancer-specific manner. Sixty-nine percent of esophageal adenocarcinomas show LOH of 18q21.

**Oncogenesis**
18q21 LOH occurs in 32% of barrets mucosae, 42% of low-grade dysplastic lesions, 73% of high grade dysplastic lesions and 69% of adenocarcinomas.

**Glioma**

**Note**
DCC expression is reduced in 66% of high-grade astrocytomas, 53% of secondary glioblastomas (progressed for low-grade astrocytomas) and 23% of de novo glioblastoma.

DCC expression is reduced in 88% of glioblastoma multiforme.

**Oncogenesis**
Only a minority (6%) of low-grade astrocytomas show reduced DCC expression, whereas high-grade tumors show reduces DCC expression in 66% of cases.

**Neuroblastoma**

**Note**
Reduced DCC expression and 18q21 LOH occurs in 25-40% and 31% of primary neuroblastomas respectively.

**Oncogenesis**
In neuroblastomas decreased DCC expression increases from 25% in stage 1-3 to 72% in stage 4 disease to 81% in metastatic disease.

**Hematologic malignancies/Lymphoma**

**Note**
DCC is inactivated in 30% of acute leukemias in 25% of chronic myelogenous leukemias (CML) and in 53% of non Hodgkins lymphoma.

In 18% of follicle centre cell lymphoma LOH of DCC is observed.

**Bladder cancer**

**Note**
LOH of 18q21 occurs in 36% of bladder carcinomas and 33% of human bladder transitional cell carcinomas (TCCs).

**Prognosis**
DCC expression is reduced in 40-55.6% of primary breast cancer.

**Oncogenesis**
DCC expression is associated with longer relapse free and overall survival.

**Prostate cancer**

**Note**
Eighty-five percent of prostate cancers exhibit decrease DCC expression compared to normal tissue. 18q21 LOH occurs in 26-31% prostate cancers.

**Renal cancer**

**Note**
DCC protein expression is reduced in 40% of clear cell renal cell carcinomas (cRCC) and LOH of 18q21 occurs in 19% of cRCC.

18q21 LOH is observed in 20% of nephroblastomas.

**Prognosis**
Decreased DCC protein expression occurred more frequently in patients who died from the disease (63%) compared to patients who did not (36%). 18q21 LOH in nephroblastomas is associated with poor prognosis.

**Ovarian cancer**

**Note**
DCC mRNA expression is reduced in 60% of epithelial ovarian cancer and in 50% of serous ovarian cancers.

**Prognosis**
Reduced DCC expression is associated with poor patient outcome in epithelial ovarian cancer which is also observed in a cohort treated with combined chemotherapy platinum-paclitaxel.

**Oncogenesis**
Reduces DCC mRNA expression is reported in only 10% of ovarian adenomas and 6% of borderline tumors compared with 60% in ovarian carcinomas.

**References**


Porfiri E, Secker-Walker LM, Hoffbrand AV, Hancock JF. DCC tumor suppressor gene is inactivated in hematologic...


Ren XR, Hong Y, Feng Z, Yang HM, Mei L, Xiong WC. Tyrosine phosphorylation of netrin receptors in netrin-1 signaling. Neurosignals. 2008;16(2-3):235-45


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