Identity

Other names: MIC-1 (macrophage inhibitory cytokine-1); NAG-1; NRG-1; PDF (prostate derived factor); PLAB; PTGF-β; PTGFB
HGNC (Hugo): GDF15
Location: 19p13.11

Note

In the genome, the GDF15 gene is localized on chromosome 19 in the region p13.1-13.2. The macrophage inhibitory cytokine (MIC-1) DNA sequence is 2,746 bp long and consists of two exons separated by an intron. A conserved TATA-like motif (TATAAA) is present nearer to the start codon.

Transcription

The expression of GDF15/MIC-1 is upregulated by IL1β, TNFa, IL2, MCSF, TGFβ and p53. Androgen also regulates the expression of GDF15/MIC-1 in vitro and in vivo. In prostate cancer cells, calcitriol induces GDF15/MIC-1 expression. Furthermore, it has been shown that the basal transcription of MIC-1 gene is regulated by Sp1 and Sp3.

Protein

Description

The premature GDF/PDF/MIC-1 protein consists of 308 amino acids that contain a 29 amino acid signal peptide, a 167 amino acid propeptide, and a 112 amino acid mature protein. The mature protein is secreted as a homodimer linked by disulfide bonds and is released from the propeptide following intracellular cleavage at RXXR furine-like cleavage site. The mature peptide of GDF-1/MIC-1 contains two additional cysteine residues in addition to the seven conserved cysteines necessary for the cysteine knot, a structural hallmark of this TGF-β superfamily. The exact function of these two additional cysteine residues is still unknown. The propeptide has a consensus N-linked glycosylation site in it. Unlike all other TGF-β superfamily members, MIC-1 mature peptide can be correctly folded and secreted without a propeptide. The propeptide plays a novel role in proteosmal targeting of the monomeric precursor and ensures that only dimeric precursor exists in the endoplasmic reticulum.

Shows the genomic organization of GDF15 gene.
**Expression**
GDF15/PDF/MIC-1 is expressed at high levels in placenta, adult prostate, skin and at a low level in several other tissues including colon, kidney and fetal brain.

**Localisation**
MIC-1 is an extracellularly localized secretory protein.

**Function**
GDF15/MIC-1 plays diverse biological functions in varied cellular context. It has been proposed that GDF15/MIC-1 can regulate the late phase macrophage activation by inhibiting TNF-a as an autocrine/paracrine regulatory molecule. Its role in the early stages of endochondrial bone formation, hematopoietic development, embryonic implantation and placental function has been reported. Animal studies have shown the role of GDF15/MIC-1 as a central regulator of appetite and body weight. For midbrain dopaminergic neurons, GDF15/MIC-1 acts as a both neurotrophic and neuroprotective factor, in vitro and in vivo. A role of GDF15/MIC-1 in cancer progression has also been reported by impacting on cell signaling.

**Homology**
It shares a significant homology with the GDF15 gene of Pan troglodytes, Bos Taurus and Canis lupus familiaris. In addition, it is also similar to Gdf15 gene of Mus musculus and Rattus norvegicus.

**Implicated in**

### Various Cancers

**Disease**
GDF15/MIC-1 over expression is associated with different cancers, including gastric, pancreatic, prostate and colorectal cancer. It has been shown that measurement of serum GDF15/MIC-1 level aids in the diagnosis of prostate and pancreatic cancer.

**Prognosis**
Recently, a direct association of elevated serum GDF15/MIC-1 and metastatic prostate, colorectal, and breast cancer has been reported. Additionally, higher serum GDF15/MIC-1 level was correlated with higher incidence of lymph node metastasis and shorter relapse and shorter overall survival period.

**Oncogenesis**
The oncogenic property of GDF15/MIC-1 in different cancer has been reported. In prostate cancer, it promotes AR-positive prostate cancer cell proliferation through the activation of ERK1/ERK2 signal pathway. Additionally, GDF15 promotes the drug resistance property of prostate cancer cells. The role of GDF15/MIC-1 in promoting the invasive property of gastric cancer cells has been reported. This may be due to GDF15/MIC-1 mediated up-regulation of Uroki-nase-type plasminogen activator system. In contrast, some studies have reported an anti-tumorigenic role of GDF15/MIC-1 in colon, breast and glioblastoma cell lines. Most of these reports suggest a
role of GDF15/MIC-1 in the induction of apoptosis via both p53-dependent and independent mechanisms.

**Thalassemia**

**Disease**

Expanded erythroid compartment secrete high level of GDF15, which leads to iron overload in thala-ssemia syndromes by inhibiting hepcidin expression.

**References**


Chen SJ, Karan D, Johansson SL, Lin FF, Zeckser J, Singh AP, Batra SK, Lin MF. Prostate-derived factor as a paracrine and autocrine factor for the proliferation of androgen receptor-positive human prostate cancer cells. Prostate. 2007 Apr 1;67(5):557-71


This article should be referenced as such: