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Gene Section
Mini Review

GPNMB (glycoprotein (transmembrane) nmb)

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Identity

Other names: HGFIN; NMB; osteoactivin

HGNC (Hugo): GPNMB

Location: 7p15.3

DNA/RNA

Description

The GPNMB gene maps (Homo sapiens) on the plus strand of chromosome 7p15 between 23,252,841 and 23,281,254 bp from the promoter and spans 28,414 bp.

Transcription

2 transcript variants:
Variant 1:
- 2775bp, accession #: NM_001005340.1
- the longer transcript
- encodes the longer isoform (isoform a)
- open reading frame from bp 162 to 1880
- 11 exons.

Variant 2:
- accession #: NM_002510.2
- undergoes alternative splicing and uses an in-frame splice site
- conserved N- and C-terminals compared to isoform a, but decreased in length.

Protein

Note
The GPNMB gene, which is the human homolog of murine osteoactivin, encodes a type I transmembrane glycoprotein. It has homology to the melanocyte specific protein precursor pMEL17. GPNMB expression is inversely correlated with aggressiveness of melanoma cell lines. GPNMB is thought to be inversely correlated with metastatic potential, although limited data is available.

Description

Two protein isoforms exist: isoform a: 572 aa; isoform b: 560 aa.

Expression

GPNMB is expressed in osteoclasts, dendritic cells, macrophages, and breast epithelia. Its expression is nearly undetectable in monocytes but increases upon conversion of monocytes to macrophages.

Localisation

GPNMB localizes to the plasma membrane, as it is a type I transmembrane glycoprotein. It is also found in melanosomes and membrane-bound vesicles in the cytoplasm.

Function

GPNMB is involved in binding to heparin sulfate and integrins. It functions in mineralization of bone and differentiation of osteoblasts. It also functions in cellular adhesion. It is thought to reduce inflammation involving macrophages.

Homology

Homo sapiens GPNMB shares sequence homology with mouse and rat sequences. GPNMB shares structural homology with neurokinin 1 (NK1) and can interact with the NK ligand substance P.

Implicated in

Breast cancer

Note
It is unclear to date whether GPNMB plays a tumor

suppressive role or oncogenic role in breast cancer.

Disease

In a murine model, osteoactivin (OA) has been associated with enhanced invasiveness of breast cancer cells in vivo, and forced overexpression of OA in weakly bone metastatic cells lines resulted in increased migratory and invasive characteristics in vitro (Rose et al., 2007). Furthermore, analysis of 51 breast cancer cell lines revealed higher osteoactivin expression than normal breast MCF-12A cells and in estrogen receptor negative breast tumors (Rose and Siegel, 2007). However, other studies with non-tumorigenic human breast cancer cells have shown that there was increased migration and evidence of transformation and loss of contact dependency in the absence of GPNMB/HGFIN (Metz et al., 2007).

Glioblastoma multiforme (GBM)

Note

In immunocompromised mice, glioma cells expressing osteoactivin and osteonectin (two strucurally bone-related genes) developed a highly invasive phenotype and invaded the brain along blood vessels when implanted intracranially (Rich et al., 2003).

Disease

Evaluation of 50 GBM patient tumor samples revealed that 35 out of 50 samples (70%) were positive for GPNMB wild-type and splice variant transcripts while the remaining 30% were positive for wild-type only (Kuan et al., 2006). This is in contrast to normal brain samples that expressed little or no GPNMB mRNA (Kuan et al., 2006).

Prognosis

Detection of GPNMB mRNA and surface membrane protein in glioma cells may potentially be used as a tumor-associated antigen for targeting by therapeutic treatment (Kuan et al., 2006).

Melanoma

Note

Analysis of a cDNA library between lowly and highly metastatic human melanoma showed the preferential expresion of GPNMB in low-metastatic cell lines (Weterman et al., 1995). Additionally, transfection of partial GPNMB cDNA into highly-metastatic melanoma cell line resulted in slower subcutaneous tumor growth in nude mice (Weterman et al., 1995).

Disease

A potential therapeutic agent in the treatment of malignant melanomas is an antibody-drug conjugate tartgeting GPNMB (Pollack et al., 2007). Intravenous administration of the immunoconjugate in athymic mice with human melanoma xenografts showed inhibition of tumor growth and complete regression of the tumor (Pollack et al., 2007).

End-stage kidney disease

Note

Macrophages involved in uremia have elevated levels of GPNMB expression. Its role in end-stage kidney disease may relate to its role in soft tissue calcification and arteriosclerosis (Pahl et al., 2009).

Acute liver injury

Note

In normal rat livers, OA was found to be expressed in high levels in Kupffer cells and peritoneal macrophages (Haralanova-Ilieva et al., 2005). Upon induction of acute liver injury after carbon tetrachloride administration, OA expression was upregulated after 2 days and returned to normal levels after 7 days (Haralanova-Ilieva et al., 2005). In normal human liver, OA RNA was not detected while fulminant hepatitis B and C infections, paracetamol intoxication, and liver cirrhosis all resulted in positive OA RNA levels (Haralanova-Ilieva et al., 2005).

Osteopetrosis

Note

OA cDNA was found to be overexpressed 3- to 4-fold in rats with osteopetrotic bones when compared to normal rat long bones (Safadi et al., 2001). Furthermore, OA mRNA was primarily localized in cuboidal osteoblasts lining bone surfaces (Safadi et al., 2001).

Disease

Osteopetrosis, also known as marble bone disease, is a rare hereditary disease which results in thickening and hardening of bones due to deficient osteoclast activity (Kumar et al., 2003). OA is expressed at highest levels in primary osteoblasts and thus, may account for the imbalance in activity of osteoblasts and osteoclasts in osteopetrosis (Sadafai et al., 2001).

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