**MME (membrane metallo-endopeptidase)**

**Emina E Torlakovic**

Department of Pathology, The Norwegian Radium Hospital, University of Oslo Montebello, Oslo 0310, Norway

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### Identity

**Hugo:** MME

**Other names:** common acute lymphocytic leukemia antigen (CALLA); CD10; DKFZp686O16152; MGC126681; MGC126707; Kidney-brush-border neutral proteinase; Nepriyisin (NEP); Enkephalinase; Atriopeptidase; Endopeptidase-2; Neutral endopeptidase

**Location:** 3q25.2

**Note:** Membrane metallo-endopeptidase (MME) is a 100-kD type II transmembrane glycoprotein originally described on human acute lymphoblastic leukemia cell lines and therefore it was originally designated as common acute lymphocytic leukemia antigen (CALLA). MME is a neutral endopeptidase that cleaves peptides at the amino side of hydrophobic residues and inactivates several peptide hormones including atrial natriuretic factor, glucagon, enkephalin, substance P, neurotensin, oxytocin, and bradykinin. It is also a major enzyme for degradation of beta-amyloid.

### DNA/RNA

**Note:** Gene: on chromosome 3 at location: 156284651-156384186; length: 99536; type: protein coding.

**Description**

MME gene spans a region of 99536 bases and has 24 exons. Exons 1 and 2 encode 5' untranslated sequences. Initiation codon and transmembrane and cytoplasmic domain are encoded by exon 3, which has 170 bp. 20 short exons (exons 4-23) range in size from 36 to 162 bp. They encode large part of the extracellular portion of the enzyme. Exon 24 which has about 3400 bp encodes the COOH-terminal 32 amino acids and contains the entire 3' untranslated region (UTR). Exon 19 encodes the pentapeptide sequence associated with metallocproteinase zinc binding and substrate catalysis (His-Glu-Ile-Thr-His).

The sequence is nearly identical to rat and rabbit NEP. Transcriptional regulation: MME is constitutively expressed in some tissues (kidney, adipose tissue, brain) and at some developmental stages in other (T- and B-lymphocytes, neutrophils). Its gene transcription is regulated by at least two alternative regulation regions including type 1 and type 2 promoter. Both regulatory regions are characterized by the presence of multiple transcription initiation sites and the absence of classic TATA boxes and consensus initiator elements. The purine-rich type 1 regulatory region, which includes 5’ UTR exon 1 sequence, is characterized by multiple putative PU.1-binding sites and consensus ets-binding motifs. In marked contrast, the GC-rich type 2 regulatory region contains multiple putative Sp1-binding sites, a potential consensus retinoblastoma control element (RCE); and an inverted CCAAT box. Type 2 promoter has a wide tissue distribution, a low constitutive level of expression, and multiple transcription initiation sites. However, normal and malignant lymphoid progenitors (fetal thymocytes and pre-B ALL) as well as fetal kidney and glioblastoma cell line A172 showed significantly higher levels of type 1 transcripts.

**Transcription**

The 5' untranslated region of this gene is alternatively spliced, resulting in four separate mRNA transcripts. The coding region is not affected by alternative splicing. The transcript variants 1, 1bis, and 2a contain an alternate 5' UTR exon, compared to variant 2b. The 2b variant is the longest transcript and includes alternate exon 2b. Variants 2b, 2a, 1bis and 1 all encode the same protein. Transcript variant 1 mRNA has 5643 bp. Transcript variant 1bis mRNA has 5619 bp. Transcript variant 2a
mRNA has 5665 bp. Transcript variant 2b mRNA has 5710 bp.
In normal human tissues, the highest mRNA levels were found in kidney, prostate, liver, and lung. Other tissues with high levels include whole blood, bone marrow, thymus, skeletal muscle, brain, ovary, testis, and placenta. Levels in lymph nodes and other secondary lymphoid tissues are dependent on the content of CD10+ B-cells in secondary germinal centers.

**Protein**

**Note:** MME belongs to peptidase family M13, which belongs to a peptidase superfamily known as the metzincins. These are zinc-dependent metalloproteases. Family M13 also includes endothelin-converting enzyme 1 (ECE-1), Kell blood group glycoprotein, and peptidase O from Lactococcus lactis (gene pepO).

**Description**

MME protein contains 750 amino acids, and is a type-II membrane anchored enzyme known to inactivate oligopeptides. It has a single 24-amino acid hydrophobic segment that could function as both a transmembrane region and a signal peptide. The COOH-terminal 700 amino acids compose the extracellular protein segment, whereas the 25 NH2-terminal amino acids remaining after cleavage of the initiation methionine form the cytoplasmic tail.

**Function**

Thromolysin-like specificity, but is almost confined on acting on polypeptides of up to 30 amino acids. Biologically important in the destruction of opioid peptides by cleavage of a Gly-Phe bond. Involved in the degradation of atrial natriuretic factor. Preferential cleavage of polypeptides between hydrophobic residues, particularly with Phe or Tyr at P1'. Inhibited in a dose dependent manner by opiorphin. Inhibited by phosphoramidon and thiorphan.

**Mutations**

**Note:** Truncating mutations in the MME gene in mothers are the cause of alloimmunisation during pregnancy (1342 C to T nonsense mutation and 446delC). The absence of the MMP protein in pregnant women induces an alloimmunisation against MMP presented by fetus. Maternal antibodies attack fetal podocytes ensuing nephron loss, which could lead to chronic renal failure in early adulthood. This is the first model of idiopathic renal failure in early adulthood, which appears to be caused by immune-mediated fetal nephron loss.

**Implicated in**

**Alzheimer disease and normal aging**

**Note:** Decreased MME expression in cerebral cortex correlates with amyloid-beta deposition but not with degeneration and dementia.

**Enkephalin metabolism in anxiety**

**Note:** A dinucleotide polymorphism in the 5’ region of the MME gene was linked to type of anxiety.

**T-cell apoptosis**

**Note:** Both, CD8+ and CD4+ T-cells express MME upon induction of apoptosis in vitro as well as in apoptotic T-cells in vivo.

**Low amplitude of the P300 evoked potential waves (linked to substance abuse)**

**Note:** Based on the association of MME gene polymorphisms with P300 wave amplitudes of the parietal and coronal leads, it is suggested that MME plays a significant role in the regulation of the amplitude of the P300 wave. It is presumed that lower molecular weight alleles of the MME polymorphism are associated with increased levels of NEP and thus lower CNS enkephalin levels.

**Recessive dystrophic epidermolysis bullosa**

**Note:** In recessive dystrophic epidermolysis bullose, MME activities were considerably increased in the skin and blister fluid samples compared with values found in normal control skin and in blister fluid from a patient with a burn.

**Acute lymphoblastic leukemia**

**Note:** MME is expressed in majority acute lymphoblastic leukemias, in which MME was originally described as common acute lymphocytic leukemia antigen (CALLA). The role of MME in acute leukemia is not clear.

**Burkitt lymphoma**

**Note:** Burkitt lymphoma/leukemia was originally misclassified with acute lymphoblastic leukemia due to its expression of CD10 and blastic cytologic appearance. However, now it is correctly classified as mature B-cell neoplasm and expression of MME (referred as to CD10 in this context) is secondary to its germinal center stage of development. In normal B-cell development MME transitory reappears on B-cells in germinal centers.
**Follicular lymphoma and other malignant lymphomas**

**Note:** Follicular lymphomas originate from mature B-cells with germinal center stage of differentiation. Majority of follicular lymphomas typically express MME (referred to in this context as CD10) and its expression positively correlates with survival and negatively with the grade of follicular lymphoma. Other B-cell malignant lymphomas that typically express MME (CD10) are some diffuse large B-cell lymphomas (DLBCL) which are than subtyped as so-called germinal center type (GC-type DLBCL). Of T-cell lymphomas, angioimmunoblastic T-cell lymphoma typically shows expression of CD10.

**Carcinoma**

**Note:** MME is expressed in some carcinomas that originate in organs, which normally express high levels of MME, which is best illustrated in renal cell carcinoma. MME detection is important for identification of bile canaliculi, which appear by neogenesis in hepatocellular carcinoma. This feature is diagnostically useful in hepatocellular carcinoma. It is also expressed in many other carcinomas including prostate carcinoma, urothelial carcinoma, colorectal carcinoma, and others in which expression of higher levels of MME were associated with more aggressive tumors.

**Melanoma**

**Note:** Higher expression levels were associated with more aggressive disease.

**Stromal cells**

**Note:** Various benign stromal cells express MME. In particular, adipose tissue, endometrial stroma, and dendritic stromal cells in the bone marrow are known to express significant levels of MME. The role of MME in these tissue is not known. However, it possibly contributes to functional changes of the endometrial stromal in the secretory phase when its levels are highest in this tissue. It is also known that dendritic MME+ stromal cells of the bone marrow provide maturational niche for development of B-cells. Other MME+ benign stromal cells are induced by invasion of malignant tumors like melanoma, breast carcinoma, and others. In malignant stromal lesions MME has been found expressed in rhabdomyosarcoma, leiomyosarcoma and other sarcomas.

**Juvenile idiopathic arthritis (JIA) and rheumatoid arthritis (RA)**

**Note:** Circulating MME levels were lower in JIA patients than in controls, while synovial fluid values were higher than those found in circulation, which might reflect a reactive effort to control synovial proliferation. RA patients have higher levels of MME in plasma and synovial fluid than patients with osteoarthritis.

**Acne**

**Note:** Sebaceous glands in acne patients express high levels of MME. In addition, in vitro experiments using an organ culture system demonstrated that substance P induced expression MME in sebaceous glands in a dose dependent manner.

**Idiopathic diffuse hyperplasia of pulmonary neuroendocrine cells (IDHPNC)**

**Note:** MME expression in patients with IDHPNC was compared with MME expression in patients with idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, and normal lung by using immunohistochemistry, ELISA, activity assay, and Western blot analysis. MME expression was highest in IDHPNC. Increased MME expression in lung tissue from patients with IDHPNC may reflect a compensatory increase that partly counteracts abundant neuropeptides, including BLP, present in this disorder.

**Pathophysiology of ischemia/reperfusion myocardial injury**

**Note:** MME expression was increased in the neutrophils from patients with early phase of acute myocardial infarction (AMI) by 5.2- and by 4.2-fold of the neutrophils from patients with late phase of AMI, respectively. ANP and BNP, which increase in AMI, modulate the neutrophil functions and exert protective effects against the neutrophils-induced endothelial cytotoxicity at the physiological concentrations. But the effects are suppressed due to their degradation by the neutrophil own MME. Thus, neutrophil MME, which also increases in AMI, may play a role in the pathophysiology of ischemia/reperfusion myocardial injury.

**References**


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