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Gene Section
Review

ALOX5 (arachidonate 5-lipoxygenase)

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Identity

Hugo: ALOX5
Other names: 5-LO; EC 1.13.11.34; leukotriene A4 synthase; 5LPG; LOG5
Location: 10q11.2
Local order: Genes flanking ALOX5, in centromere to telomere direction on 10q11, are:
- OR6D1P 10q11.21 olfactory receptor, family 6, subfamily D, member 1 pseudogene.
- LOC643413 10q11.21 hypothetical protein LOC643413.
- OR13A1 10q11.21 olfactory receptor, family 13, subfamily A, member 1.
- ALOX5 10q11.2 arachidonate 5-lipoxygenase.
- MARCH8 10q11.21 membrane-associated ring finger (C3HC4) 8.
- LOC653306 10q11.21 similar to membrane-associated ring finger (C3HC4) 8.
- ANUBL1 10q11.21 AN1, ubiquitin-like, homolog (Xenopus laevis).

DNA/RNA

Diagram of the ALOX5 gene. Exons are represented by purple boxes (in scale). Exons 1 to 14 are from the 5' to 3' direction.

Description

ALOX5 gene spans a region of 71,88 kb and has 14 exons, the sizes being 192, 199, 82, 123, 107, 173, 147, 204, 87, 179, 122, 101, 171 and 606 bps. ALOX5 gene has 5CpG islands and 3' end of the gene for cellular modulator of immune recognition (c-MIR).

Transcription

ALOX5 gene promoter (H. sapiens) lacks the TATA box and has eight GC-boxes within 180 bp from the major transcription initiation site (at-65 in relation to ATG), five of which are in tandem (-176 to -147). Consensus-binding sites for the transcription factor serum protein 1 (SP1), and early growth-response protein 1(EGR-1) exists in this region. A Vitamin D receptor binding site has been located in a positive regulatory region (-779 to -229) of the ALOX5 promoter. Several other consensus-binding sites for transcription factors such as GATA, glucocorticoid receptors and NFKB also exist. DNA methylation and histone deacetylase are also strongly involved in ALOX5 expression.

Pseudogene

No pseudogenes have been reported for ALOX5.

Protein

Note: The ALOX5 gene encodes a member of the lipoxygenase gene family, 5-LOX, which catalyzes the synthesis of leukotrienes (LT) from arachidonic acid. Leukotrienes are responsible for a series of inflammatory and allergic conditions. 5-LOX is also unique in requiring the 5-LOX activating protein (FLAP), a nuclear trans-membrane protein that plays an essential role in the transfer of arachidonic acid to 5-LOX. FLAP can also bind to MK-886, a compound that blocks LT biosynthesis.

Description

5-LOX is a 77.9 kDa protein consisting of 673 amino acids. The enzyme requires calcium, iron and ATP as cofactors. The enzyme activity is also stimulated by the presence of microsomal membranes and trace amounts of lipid hydroperoxides. The protein has a catalytic domain and a regulatory domain. The regulatory domain, which controls leukotriene synthesis and binds calcium, nucleotides and phospholipids also has a PLAT (Polycystin-1, Lipoxygenase, alpha-Toxin) domain.

Expression

5-LOX protein is expressed in bone marrow derived cells such as monocytes/macrophages, mast cells, B-lymphocytes, polymorphonuclear leukocytes, dendritic cells and foam cells of human atherosclerotic tissues, as well as spleen, thymus brain, spinal cord, skeletal muscle, pancreas, prostate, kidney and lung in humans.

Localisation

Subcellular location of 5-LOX protein is the cytoplasm or nucleoplasm. 5-LOX is largely cytosolic in resting peritoneal macrophages, monocytes, neutrophils, monocytes and eosinophils. By contrast, alveolar macrophages and mast cells contain cytosolic and intranuclear fractions of the enzyme. Leukotriene synthesis capacity is determined by a calcium independent nuclear import of 5-lipoxygenase. Three nuclear localization sequence (NLS) exist, Leu-111 to Asp-121; Asp-156 to Asp-166 and Val-514 to Leu-535.

Function

5-LOX, a monomeric enzyme, catalyzes the conversion of arachidonic acid to 5(S)-hydroperoxy-6-trans-8, 11, 14-cis-eicosatetraenoic acid (5(S)-HETE), and further dehydration to the allylic epoxide 5(S)-trans-7,9-trans-11,14-cis-eicosatetrenoic acid (leukotriene A4). The LTA4 intermediate is then converted to LTB4 by LTA4 hydrolase. LTB4 attracts leukocytes and are important for the inflammatory response.

5-LOX migrates to the nuclear membrane upon cellular activation leading to LTB4 biosynthesis. This function depends on calcium dependent binding of the N-terminal C2 domain of 5-LOX to phospholipids resulting in the release of fatty acid substrates for enzyme action.

Phosphorylation of 5-LOX on Ser-271 by MAPK-activating protein (MAPKAP) kinase 2, Ser-663 by extracellular signal-regulated kinases (ERK-2) and Ser-523 by protein kinase A (PKA) catalytic subunit has been shown to stimulate 5-LOX activity.

In addition, overexpression of 5-LOX was shown to promote senescence-like growth arrest in human and mouse embryo fibroblasts via a p53/p21-dependent pathway, by regulating reactive oxygen species production, independent of telomerase activity. Thus, a senescence-like growth arrest may be of significance in the pathogenesis of 5-LOX-associated disorders.

Homology

C. familiaris: LOC477753, similar to Arachidonate 5-lipoxygenase;
R. norvegicus: ALOX5, arachidonate 5-lipoxygenase;
M. musculus: ALOX5, arachidonate 5-lipoxygenase;
A. thaliana: AT3G22400 iron ion binding/ lipoxygenase;
O. sativa: OSJNBb0017F17.2, putative lipoxygenase.

Mutations

Note: A family of mutations in the G+C-rich transcription factor binding region of ALOX5 has been identified in which several Sp1 and Egr-1 binding motifs are altered in the region of 176 to 147 bp upstream from the ATG translation start site. These mutations alter transcription factor binding and may play a role in 5-LOX gene expression in vivo. A haplotype containing polymorphisms in a negative regulatory region of the ALOX5 promoter (G-1752A and G-1699A) may influence colon cancer risk in Caucasians. In addition, the genetic variant of tandem repeat (GGGCGG; Sp1-binding motif) in ALOX5 promoter in group of Korean aspirin intolerant asthma patients has been associated with the severity of airway hyper-responsiveness.

Implicated in

Esophageal cancer

Disease

Immunohistochemistry analyses of 5-LOX expression in 161 esophageal tissue indicated that the enzyme was expressed in 79% (127/161) of cancer tissues but in only 13% (4/32) of normal esophageal mucosa. 5-LOX was also expressed in 8 esophageal cancer cell lines examined. In addition, 5-LOX inhibitors AA861 and REV5901 increased cell viability and apoptosis in the esophageal cancer cell lines.

Pancreatic cancer

Disease

5-LOX expression is upregulated human pancreatic cancer cells. The 5-LOX metabolite 5(S)-HETE was shown to stimulate proliferation, as well as the proliferation of the mitogenic intracellular tyrosine kinases, MEK/ERK and PI3 kinase/AKT.

Colorectal cancer

Disease

Exposure to cigarette smoke extract (CSE) was shown to enhance 5-LOX protein expression in the inflammation-associated colonic adenomas. The effects of CSE on colon cancer cells were mediated by 5-LOX DNA demethylation. In addition, an up-regulation of matrix metalloproteinase-2 (MMP-2) and vascular endothelial growth factor (VEGF), key angiogenic factors for tumorigenesis, were also observed. These effects were reversed by treating the colon cancer cells with dual 5-LOX and COX-2 inhibitors.

Atherosclerosis

Disease

5-LOX, known to generate proinflammatory LTs, is

highly expressed in the arterial walls of atherosclerotic patients, with the number of enzyme expressing lesion leukocytes increasing during disease progression. All constituents of the 5-LOX pathway are significantly expressed in human diseased arteries, thereby supporting a model of atherogenesis, whereby 5-LOX pathway dependent inflammatory circuits composed of leukocytes, smooth muscle cells and endothelial cells evolve within blood vessels during late stages of lesion development.

Asthma

Disease

LTs and their receptors play an important role in the pathogenesis of asthma. Th2 cytokines, interleukins-4 and -13 can upregulate cysteinyl leukotriene 1 receptor expression. In addition, cysteinyl LTs favour an allergic phenotype by upregulating type 2 cytokine expression and decreasing type 1 cytokine expression. Polymorphisms of the 5-LOX promoter have also been associated with the development of asthma.

Immune response and tissue homeostasis

Note: The products of the ALOX5 pathway, particularly LTs, are lipid messengers that act on the immune response system and tissue homeostasis. Their abnormal production can induce several diseases such as asthma, inflammation, atherosclerosis, basophilic leukaemia, oedema, exercise-induced asthma, anaphylaxis, psoriasis, bronchial spasms and allergic rhinitis.

Oncogenesis

Alterations in the 5-LOX pathway can result in the aberrant formation of its products, hydroxyeicosatetraenoic acids or leukotrienes. This can, in turn, increase cellular proliferation and survival and suppress apoptosis of human cells and thereby play a significant role in human carcinogenesis.

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