AIREG (amphiregulin (schwannoma-derived growth factor))

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Identity

Other names: AR; CRDGF; MGC13647; OTTHUMP00000160473; SDGF; amphiregulin
HGNC (Hugo): AREG
Location: 4q13.3
**Description**

The AR/AREG human gene spans 10 kb in the genomic DNA and it is composed of six exons.

**Transcription**

The transcription of the AR gene produces a 1.4 kb mRNA. AR gene shows broad constitutive expression, being more prevalent in human ovary and placenta although it is also expressed in pancreas, cardiac muscle, testis, colon, breast, lung, spleen and kidney, whereas it is undetectable in liver.

**Protein**

**Description**

AR is synthesized as a 252-amino acids transmembrane glycoprotein, also known as transmembrane precursor or pro-form (Pro-AR). Pro-AR consists of a hydrophilic extracellular N-terminus (or ectodomain), a hydrophobic transmembrane domain (TM) and a hydrophilic cytoplasmic C-terminus (CT-tail). In the extracellular N-terminus we can distinguish an N-terminal pro-region containing glycosylation sites followed by a heparin-binding domain and an epidermal growth factor EGF-like region. The EGF-like region is shared by other members of the EGF family of ligands. At the plasma membrane Pro-AR undergoes proteolytic cleavage to release the mature soluble factor in a process known as “ectodomain shedding”. Cleavage of Pro-AR at two N-terminal sites gives rise to two major soluble forms of ∼19 and ∼21 kDa. Alternatively Pro-AR cleavage can produce a larger 43-kDa soluble protein corresponding to the entire extracellular domain. Cleavage of Pro-AR at the cell surface can be mediated by tumor necrosis factor-alpha converting enzyme (TACE), a member of the disintegrin and metalloproteinase (ADAM) family also known as ADAM17. Shedding of AR allows the autocrine or paracrine interaction of the mature ligand with its cognate receptor, the EGFR (also known as ErbB1), a transmembrane protein endowed with tyrosine kinase activity, although juxtacrine interaction between membrane-bound Pro-AR and the EGFR has also been observed.
Expression
AR is constitutively expressed in human ovary and placenta, in pancreas, cardiac muscle, testis, colon, breast, lung, spleen and kidney, whereas it is undetectable in liver. AR gene overexpression has been frequently demonstrated in cancerous tissues like colon, breast, bladder, prostate, pancreas, lung, ovary, squamous cell carcinomas, hepatocarcinoma and myeloma cells. Besides changes in AR gene expression, different stimuli can also influence the availability of this growth factor through the stimulation of Pro-AR cleavage at the cell membrane. This is achieved by the activation of TACE/ADAM17 in response to agonists acting through G-proteins coupled receptors (GPCRs) in a process termed EGFR transactivation.

Localisation
AR is synthesized as a transmembrane precursor which is proteolytically cleaved to produce the soluble factor.

Function
Binding of AR to the epidermal growth factor receptor (EGFR/ErbB1) triggers key intracellular signaling pathways, such as the mitogenic MAPK and survival PI3K/Akt pathways, which have been demonstrated to participate in the transduction of AR-effects. AR was originally identified as a factor capable of inhibiting the growth of certain carcinoma cell lines, while stimulating the proliferation of normal cells, a fact that motivated its denomination. Actually, depending on its concentration and the nature of the target cell AR promotes the growth and survival of most cell types, both normal and transformed.

Homology
The EGF-like region characterized by a six-cysteine consensus motif, $X_nCX_7CXC_4CX_{10}CX_5GX_2CX_n$, is shared by other members of the EGF family of ligands. Mature HB-EGF and AR also have N-terminal extensions, composed of predominantly basic residues which are thought to confer their heparin-binding abilities.

Implicated in Various cancers
Note
AR gene overexpression has been demonstrated in a large variety of human cancerous tissues such as colon, breast, liver, prostate, pancreas, lung, squamous cell carcinoma, bladder, ovary, skin and myeloma cells. The genetic or epigenetic alterations responsible for this overexpression are unknown. However it has been documented that the expression of AR can be induced by hormones such as androgen or 17beta-estradiol, EGF-family growth factors, such as TGF-alpha or AR itself, pro-inflammatory cytokines, such as TNF-alpha or interleukin-1 beta, prostaglandins, aryl hydrocarbon receptor agonists, bile acids, or hypoxic conditions. In addition to these changes in AR gene expression the availability of this growth factor may be increased through the stimulation of pro-AR cleavage at the cell membrane, which result in a process termed EGFR transactivation. This is achieved through the activation of TACE/ADAM17 in response to agonists acting through GPCRs.

Figure 4: Cladogram
Figure 5: from Sanderson et al., 2006.
This process has been shown in different cancer cells upon treatment with lysophosphatidic acid, gastrin-releasing peptide, cigarette smoke, or the activation of cannabinoid receptors. In vitro studies performed in tumour cell lines upon treatment with AR, or conversely with specific siRNAs to silence AR gene expression, have shown that AR plays an important role in the proliferation and survival of transformed cells. These assays have also demonstrated that AR participates in the maintenance of the metastatic and oncogenic properties of these cells as well as in their resistance to chemotherapy.

The role of AR in cancer development and progression is also supported by clinical data. It has been established a significant correlation between elevated AR mRNA levels in bladder tumour tissue and poor patient survival. In patients with advanced non-squamous non-small cell lung cancers increased levels of circulating AR in serum are predictors of poor response to gefitinib.

Psoriasis

Note
AR is an autocrine growth factor for keratinocytes and the expression of AR is significantly induced in psoriatic epidermis. Transgenic mice which overexpress AR in the epidermis develop a psoriasis-like cutaneous phenotype and psoriatic arthritis. These results show that AR contributes to the pathogenesis of psoriasis and present AR as a target for anti-psoriatic therapy. Indeed the use of heparin, which binds and inhibits AR activity or the administration of glucosamine which induces the synthesis of heparan sulfates, physiological AR antagonists, provide therapeutic benefits in psoriasis.

Rheumatoid arthritis

Note
The expression of AR is increased in rheumatoid arthritis patients. AR induces the proliferation of fibroblast-like synoviocytes and the production of proinflammatory cytokines such as interleukin-8 and vascular endothelial growth factor.

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**AREG (amphiregulin (schwannoma-derived growth factor))**

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*This article should be referenced as such:*