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Gene Section
Review

IL1RN (interleukin 1 receptor antagonist)

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Abstract

Review on IL1RN, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: DIRA, ICIL-1RA, IL-1RN, IL-1ra, IL-1ra3, IL1F3, IL1RA, IRAP, MVCD4

HGNC (Hugo): IL1RN

Location: 2q13

Local order

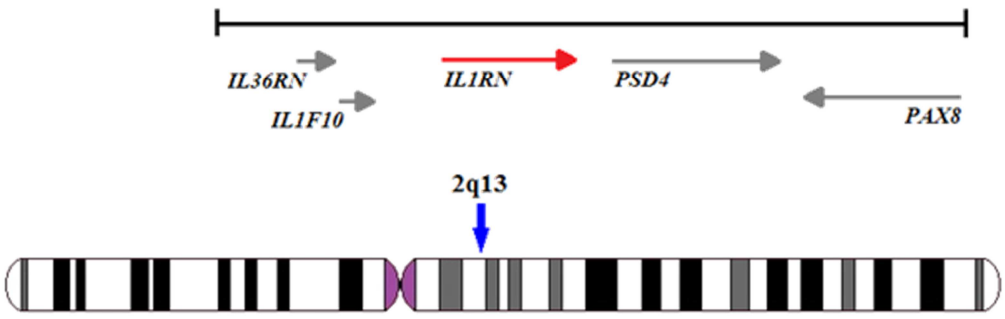
IL1RN is located between PSD4 gene (pleckstrin and Sec7 domain containing 4) and IL36RN (interleukin 36 receptor antagonist) and IL1F10 (interleukin 1 family, member 10 (theta)) genes (NCBI).

DNA/RNA

Note

IL1RN (interleukin 1 receptor antagonist) was identified in 1990 by Carter and cols (Carter et al., 1990).

It codes a protein that binds to interleukin 1 receptor (IL1R1) and inhibits the binding of interleukin 1 alpha and beta (IL1A and IL1B), blocking the biological activity of these two cytokines, this is the first interleukin 1 family member described that has antagonist function (Arend, 1991; Arend and Gabay, 2000).



IL1RN locus is 2q13. The gene length is 22901 bp (starts at 113868692 - ends at 113891592, according NCBI 08-Jul-2013). In this region is located along with IL36RN, IL1F10 and PSD4 and PAX8.

Linear diagram of IL1RN gene with their 6 exons (pink boxes).

This gene is overexpressed in different infectious diseases and immune conditions.
The IL1RN gene has a length of 22901 base-pairs, and is constituted by 6 exons; there are four isoforms described to date that are produced by alternative splicing: one isoform is secreted and the other three are cytoplasmic (Gabay et al., 1997; Arend and Guthridge, 2000).

Description

The IL1RN gene has a length of 22901 base-pairs, encodes a member of the interleukin 1 cytokine family. The gene is located on 2q13.

Transcription

6 exons; mRNA linear (NM_173842.2) with 1794 bp. IL1RN mRNA does not contain the AUUUA sequence that has been implicated in shortening the half-life of several cytokine mRNAs (Carter et al., 1990).

Pseudogene

No pseudogenes have been identified.

Protein

Note

The IL1RN precursor protein consists of 177 amino acids and has a molecular weight of 20055 Daltons. The IL1RN cDNA encodes a 152 amino acid protein preceded by a 25 amino acid secretory leader sequence indicating that this protein takes a more straightforward pathway out of the cell than IL1.
IL1RN is found extracellularly in its mature form without requiring extracellular cleavage to its mature form. The mature protein consists in ~159 amino acids (Arend, 1991; Haskill et al., 1991).

The IL1RN gene produces two forms of IL1RN: intracellular (icIL1RN) and secreted (sIL1RN) which are controlled by different promoter regions (Redlitz et al., 2004).

Description

The protein consists of 177 amino acids, and a molecular weight of 20KDa. The amino acid sequence homology is 26-30% to IL1β and 19% to IL1α. The mature protein is a single nonglycosylated polypeptide of 150 amino acids approximately, further, this protein contains a 25 amino acids leader sequence (Eisenberg et al., 1990).

Expression

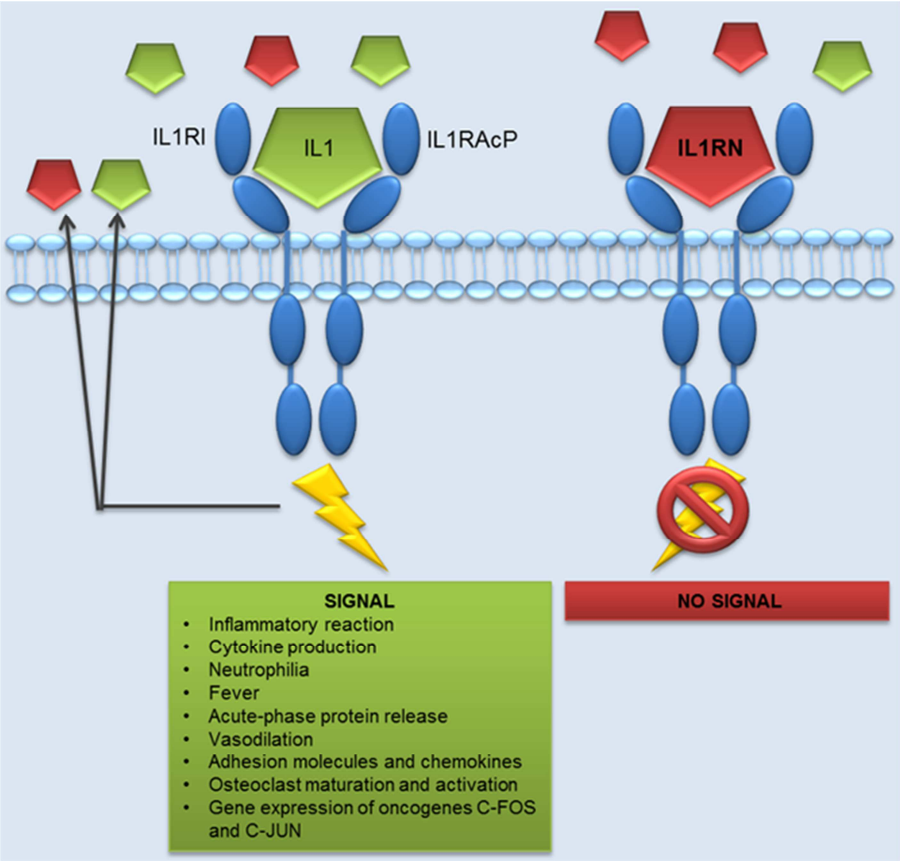
Practically, IL1RN is expressed in whole organism, in both adult and embryonic stages. IL1RN is expressed physiologically in different tissues like lymph node, brain, heart, colon, adipocyte, kidney, liver, lung, thyroid, adrenal gland, skin, placenta, ovary, prostate and testis (GeneCards). Furthermore, IL1RN is present in numerous cancers such as gastric cancer (Iizuka et al., 1999), cervical cancer (Fujiwaki et al., 2003), lymphoblastic (Hulkkonen et al., 2000) and myelogenous (Estrov et al., 1992) leukemias, breast cancer (Miller et al., 2000), endometrial cancer (Van Le et al., 1991), bladder cancer (Ahirwar et al., 2009), colorectal cancer (Viet et al., 2005), lung cancer (Lind et al., 2005) and brain tumors (Oelmann et al., 1997; Ilyin et al., 1998).

Localisation

There are four isoforms of IL1RN. The IL1RN isoform 1 is secreted, and the other three, IL1RN2, IL1RN3 and IL1RN4 have localization into cytoplasm (Arend and Guthridge, 2000).

IL1RN isoform	Number of Exons	Length	Protein Sequence	Size
1	4	1794pb	MEICRGLRSH LITLLLFLFH SETICRPSGR KSSKMQAFRI WDVNQKTFYL RNNQLVAGYL QGPNVNLEEK IDVVPIEPHA LFLGIHGGKM CLSCVKSGDE TRLQLEAVNI TDLSENRKQD KRFAFIRSDS GPTTSFESAA CPGWFLCTAM EADQPVSLTN MPDEGVMVTK FYFQEDE	177aa
2	6	1865pb	MALETICRPS GRKSSKMQAF RIWDVNQKTF YLRNNQLVAG YLQGPNVNLE EKIDVVPIEP HALFLGIHGG KMCLSCVKSG DETRLQLEAV NITDLSENRK QDKRFAFIRS DSGPTTSFES AACPGWFLCT AMEADQPVSL TNMPDEGVMV TKFYFQEDE	159aa
3	5	1802pb	MALADLYEEG GGGGGEGEDN ADSKETICRP SGRKSSKMQA FRIWDVNQKT FYLRNNQLVA GYLQGPNVNL EEKIDVVPIE PHALFLGIHG GKMCLSCVKS GDETRLQLEA VNITDLSENR KQDKRFAFIR SDSGPTTSFE SAACPGWFLC TAMEADQPVS LTNMPDEGVM VTKFYFQEDE	180aa
4	6	1973pb	MQAFRIWDVN QKTFYLRNNQ LVAGYLQGPN VNLEEKIDVV PIEPHALFLG IHGGKMCLSC VKSGDETRLQ LEAVNITDLS ENRKQDKRFA FIRSDSGPTT SFESAACPGW FLCTAMEADQ PVSLTNMPDE GVMVTKFYFQ EDE	143aa

Table of four IL1RN isoforms, showing the amino acid sequences and other protein characteristics.



When IL1 binds to IL1-receptor induces proinflammatory reaction and gene expression. Blocking of the receptor by IL1RN prevents this response.

Function

The protein binds to interleukin 1 receptor (IL1R1) and inhibits the binding of interleukin 1 alpha and beta (IL1A and IL1B) (Arend, 1991; Arend and Gabay, 2000), modulating the immune response (Dinarello, 2011).
IL1RN competes with IL1 for binding two IL1 cell surface receptors type I and type II (IL1RtI and IL1RtII), however, when it occupies the receptor it does not trigger the cellular responses typical of IL1 which includes the production of secondary substances that mediate inflammatory responses and tissue remodeling (Dinarello, 2011).

Homology

Homologs of IL1RN protein are highly conserved in different species (NCBI).
Rattus norvegicus: Il1rn (178 amino acids).
Mus musculus: Il1rn (159 aa).
Equus caballus: IL1RN (177 aa).
Bos taurus: IL1RN (174 aa).
Canis lupus familiaris: IL1RN (176 aa).
Tursiops truncatus: IL1RN (177 aa).
Gallus gallus: IL1RN (163 aa).
Macaca fascicularis: IL1RN (177 aa).

Mutations

Note
Allelic variants

Germinal

The most common variation in the IL1RN gene is the penta allelic variable number of tandem repeat of 86 base pair located in intron 2 which results in a short allele with two repeats (IL1RN*2), and long alleles (IL1RN*L): allele 1 (four repeats), allele 3 (five repeats), allele 4 (three repeats) and allele 5 (six repeats).
The most frequent allelic form is allele 1 followed by allele 2, the rest of the alleles are very rare.
It has been reported that the allele 2 causes a 10-fold increased seric IL1RN (Danis et al., 1995). Furthermore, Redlitz and cols, found that allele 1 has a 4-fold increase of the production of icIL1RN compared to allele 1 (Redlitz et al., 2004).
Two other germline mutations: Gln57Ter (rs121913162) and Glu80Ter (rs121913161) have been associated with the deficiency of IL1RN leaning to an autoinflammatory (Aksentijevich et al., 2009).

Somatic

The somatic mutation rs148026279 producing the protein change Phe148Val has been associated with malignant melanoma (Wei et al., 2011).

Implicated in

Various cancers

Note

The IL1 cluster has been strongly associated with different types of cancer. Multiple studies have shown that IL1RN, included in this cluster is altered in cancer development. IL1RN plays a central role in the response to pathogens associated with cancer etiopathogenesis (Roberge et al., 1996; Hurme and Helminen, 1998; Wang et al., 2003; Queiroz et al., 2004; Rocha et al., 2005) and chronic inflammation, well described as an important risk factor in cancer development (Hanahan and Weinberg, 2011; Baniyash et al., 2014; Khatami, 2014), thus, cytokines such as IL1RN could be used as risk and progression markers in the future.

In the meta-analysis performed by Zhang and cols., which included 71 studies of multiple cancers, with 14854 cases and 19337 controls, the research group found a consistent association with gastric cancer. IL1RN polymorphisms frequency is significantly different across ethnicities; the frequency of allele 2 is significantly lower in Asian controls (11.14%) compared to Caucasian controls (26%) (Zhang et al., 2011).

Gastric cancer

Note

Gastric cancer after H. pylori infection susceptibility has been linked with IL1RN gene. Studies of genetic association have shown an increased risk of gastric cancer with the allele IL1RN*2 across different populations (El-Omar et al., 2000; Furuta et al., 2002; Alpizar-Alpizar et al., 2005; Garza-Gonzalez et al., 2005; Palli et al., 2005; Morgan et al., 2006; Oliveira et al., 2012). However, IL1RN*2 has been also been associated independently of H. pylori infection (Mattar et al., 2013).

Oncogenesis

The inflammatory response after H. pylori infection has been linked to the IL1 gene cluster. The infection induces the synthesis of IL1B which binds to its target receptor and starts the inflammatory response against the pathogen (Sierra et al., 2008). The IL1RN competitively binds to the IL1 receptor with the same affinity as IL1 without activating the inflammation cascade, modulating the effects of IL1B. The severity of damage caused by inflammatory response in mucosal tissue is regulated by the balance between these cytokines. The short allele IL1RN*2, is associated with increased levels of IL1B, which could probably have a significant effect on increased inflammatory damage (Santtila et al., 1998).

It has also been described that IL1B inhibits gastric secretion (Sugimoto et al., 2009), and it is 100 times more potent than proton pump inhibitor (Wolfe and Nompleggi, 1992), which favors the corpus colonization, causing atrophic gastritis that may evolve to gastric carcinoma. El-Omar and cols., demonstrated an increased risk of hypochlorhydria when IL1RN*2 allele is present in homozygous form (El-Omar et al., 2000).

Cervical cancer

Oncogenesis

Cervical cancer is associated with the infection by human papillomavirus (HPV), however, although millions of women are infected with high-risk HPV subtypes, only a subset of them develop cervical cancer, reveling an important role of host immunity in cervical carcinogenesis. Various studies have observed a significant contribution of IL1RN*2 allele to increase risk of cervical cancer (Sehouli et al., 2002; Mustea et al., 2003; Tamandani et al., 2008; Sousa et al., 2012). Moreover, Sousa and cols, found that IL1RN*2 correlated not only with cervical cancer but with cervical lesions and earlier onset of cases with cervical lesion and cancer in patients homozygous IL1RN*2 (Sousa et al., 2012). Tamandani and cols, showed a protective association of heterozygous IL1RN*1*2 and homozygous IL1RN*2 and HPV 16 and 18 subtypes but a risk association with adenocarcinoma (Tamandani et al., 2008).

Breast cancer

Prognosis

In Caucasian women it has been described that IL1RN*2 is associated with shortened disease free survival and overall survival (Grimm et al., 2009). In this study, Grimm and cols reported that only 80% of women positive to IL1RN*2 survived after 12 months, and 30% had died after 48 months; the disease-free survival was only of 40% in women with IL1RN*2 compared with 80% in women with the wild allele (Grimm et al., 2009). In respect to the long alleles of IL1RN gene, allele *2 has been reported to be modify the binding on the IL1 receptor, leading to less efficient inhibition of IL1a and IL1b (Tarlow et al., 1993), this might result in a proinflammatory status and enhanced tumor aggressiveness, which is likely to result in a shortened survival of women with breast cancer (Grimm et al., 2009).

Oncogenesis

Breast cancer oncogenesis has been associated with polymorphisms in different cytokines (Gomez-Flores-Ramos et al., 2013; Dinarello, 2006) and it

has been widely discuss the participation of chronic inflammation in breast carcinogenesis (Honma et al., 2002). Different research groups have studied the association of IL1RN and breast cancer risk. Lee and cols, found a decreased breast cancer risk with the short allele (*2) and a higher risk of cancer in women with the long allele and higher body mass index (Lee et al., 2006). Zhang and cols, performed a meta-analysis study and found a similar trend with allele IL1RN*2 (Zhang et al., 2011), however, with this apparent diminish in risk for breast cancer, other studies have found an elevated risk of earlier recurrence of breast cancer in women with IL1RN*2 allele (Grimm et al., 2009).

Bladder cancer

Oncogenesis

Significant association with higher risk of bladder cancer has been described to Il1RN*2 allele (Bid et al., 2006; Ahirwar et al., 2009). This allele has been proposed as a potential marker for genetic susceptibility to bladder cancer (Ahirwar et al., 2009). Studies have showed that IL1RN*2 increases the production of IL1B significantly (Santtila et al., 1998; Nazarenko et al., 2008) and it can induce angiogenesis via upregulation of COX-2 or inducible nitric oxide and vascular endothelial growth factor which may contribute to tumor growth (Rahman et al., 2001).

Colorectal cancer

Prognosis

IL1B and IL1RN have been shown to play an important role in angiogenesis of early onset tumors, Viet and cols, found that allele *1 was more frequent in patients with localized disease compared with disseminated disease, being allele *2 associated with dissemination of the disease (Viet et al., 2005). The study of Lurje and cols, showed that patients with IL1RN VNTR had a significant six-fold increment in relative risk of developing tumor recurrence compared to those patients with the wild allele. The IL1RN homozygous *2/*2 genotype had a median time-to-recurrence of 5.7 years, compared with 10.7 years for those with *1/*1 genotype (Lurje et al., 2009).

Serum levels of IL1Ra have been studies as prognostic factors as well, in colorectal cancer patients, low preoperative IL1Ra was associated with postoperative infection (Miki et al., 2005).

Oncogenesis

Colorectal cancer has been widely associated in epidemiological and experimental studies with chronic inflammation. Viet and cols, found that the allele IL1RN*3 of VNTR variant was significantly increased in patients compared with controls, and the allelic distribution of this VNTR differed between colon and rectum, being allele *3 more abundant in colon (Viet et al., 2005). Other polymorphic sites have been associated with colorectal oncogenesis. Burada and cols, linked the polymorphism IL1RN +2018C>T with colorectal cancer, allele C was found to be enriched in patients with cancer compared to controls. This study described that this association was limited to early stage I and II (Burada et al., 2013).

In attempt to find markers for colorectal cancer disease, serum cytokines levels have been studied; Iwagaki and cols, found that patients with colorectal cancer present reduced level of IL1Ra relative to normal controls, indicating that cancer patients have an immunologic disorder (Iwagaki et al., 1997).

Lung cancer

Oncogenesis

Tobacco smoking is the main risk factor for lung cancer, however, only 10-15% of smokers develop lung cancer, suggesting that genetic factors are important in individual susceptibility for this disease (Ridge et al., 2013). Lind and cols, found that individuals homozygous for IL1RN*1 in combination with the allele IL1B-31T had an increased risk of non-small cell lung cancer and a two-fold higher level of bulky/hydrophobic DNA adducts in the long in patients with IL1RN*1 (Lind et al., 2005). These data were confirmed in Chinese patients, with a decreased risk of 32% in patients with IL1RN*2 allele (Hu et al., 2006). On the other hand, Lim and cols, found a 5-fold-time increased risk in lung cancer in never-smokers patients with the IL1RN*2 (Lim et al., 2011), but these results are not consistent, since Hu and cols, found a reduced risk in non-smokers with squamous cell carcinoma (Hu et al., 2006).

Brain cancer

Oncogenesis

Inflammatory status of brain tumors has been studied, and it has been shown that IL1 cluster is important in development and progression of neoplasia. Ilyin and cols, investigated the levels of IL1 and IL1Ra in pediatric astrocytomas, ependymomas and primitive neuroectodermal tumors. The results demonstrated a significant different profile among tumors. Pilocytic, nonpilocytic and anaplastic astrocytomas had a significant increase of mRNA of IL1 beta and its receptor, but low levels of IL1Ra mRNA, suggesting an imbalance between stimulatory and inhibitory cytokines in brain tumors growth and development via autocrine/paracrine mechanisms (Ilyin et al., 1998).

Oelmann and cols, performed a study in cell lines of glioblastoma showed that IL1Ra modulates glioblastoma growth. Experimental addition of neutralizing antibody against IL1Ra down-

regulated growth of IL1 and IL1Ra producing glioblastoma, the authors suggest that an autocrine production of IL1Ra can counteract IL1 function and represent a basic escape mechanism malignant growth in some glioblastomas (Oelmann et al., 1997).

Septic shock in pediatric population with acute lymphoblastic leukemia

Prognosis

The presence of IL1RN*2 allele was associated with significant susceptibility to septic shock in pediatric patients with acute lymphoblastic leukemia by (Zapata-Tarres et al., 2013). The patients studied by Zapata-Tarres and cols, were susceptible to septic shock.

The association between sepsis and IL1RN*2 has been reported previously, Fang and cols, reported an increased relative risk of sepsis in patients homozygous IL1RN*2 as well heterozygous patients (Fang et al., 1999). Arnalich and cols reported a significant increase in the risk of death after severe sepsis in patients with IL1RN*2 and that the allele is associated with decreased production of IL1Ra in culture but higher concentrations of the protein in serum (Arnalich et al., 2002).

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