

## Gene Section

### Review

# IL6 (interleukin 6 (interferon beta 2))

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### Identity

**Hugo:** IL6

**Other names:** interleukin 6; interferon beta 2; IL-6; HSF; HGF; CDF; BSF2; IFNB2

**Location:** 7p15.3

**Local order:** cen. - RAPGEF5- LOC221838 - IL6 - TOMM7 - DRCTNNB1A - tel.

### DNA/RNA



The gene for IL6 is shown in light blue and comprises 6 exons (with 375 bp, 103 bp, 191 bp, 114 bp, 147 bp and 542 bp in length) and 5 introns (with 920 bp, 162 bp, 1058 bp, 707 bp and 1745 bp in length). The coding part is shown in dark blue.

### Description

6 exons.

### Transcription

1472 bp transcript with a 639 bp of coding sequence.

### Protein



The IL6 protein (shown in light green) shares C-terminal a homologous region (shown in dark green) also found in IL23A and CSF3.

### Description

212 amino acids, 23.7 kd, containing 4 alpha-helices.

### Homology

IL6 shares sequence homology with IL23 (IL23A) and G-CSF (CSF3).

### Mutations

**Note:** G/C polymorphism at nucleotide -174 (promoter region)

Breast cancer prognosis differs between populations. Despite its lower incidence in Blacks when compared to Caucasians, mortality among the former is higher. Genetic factors involved in the molecular pathways regulating tumor development have been adduced to explain these differences, and it has been suggested that the IL-6 gene is a susceptibility factor underlying ethnic differences in breast cancer survival. Reports of a G/C polymorphism at nucleotide -174 within the promoter region of the IL-6 gene support this contention. This polymorphism modulates IL-6 expression and allele/genotype frequencies at the -174 site differ significantly between ethnic groups.

### Implicated in

#### Various cancers

**Note:** Although IL6 necessary to support growth of multiple myeloma cells, and is upregulated in certain tumor types, notably lung (squamous), bladder and prostate carcinomas, no recurrent chromosome rearrangements at 7p21 or IL6 rearrangements have been observed in these neoplasms.

#### Breast cancer

#### Cytogenetics

No rearrangements reported.

#### Oncogenesis

Some cytokines, including IL-6, stimulate breast cancer proliferation or invasion and serve as negative

prognostic indicators. Hitherto IL-2, IFNalpha, IFNbeta, IFNgamma, IL-6, IL-12 have been used for anti tumour treatment of advanced breast cancer either to induce or increase hormone sensitivity and/or to stimulate cellular immunity. Cytokines, such as IL-6 play a key role in regulating estrogen synthesis in normal and malignant breast tissues. The activities of estradiol 17beta-hydroxysteroid dehydrogenase and estrone sulfatase are all increased by IL-6. Prostaglandin E2 may also be an important regulator of estradiol activity in breast tumors while invading macrophages and lymphocytes may also stimulate estrogen synthesis in breast cancers.

### **Multiple myeloma**

#### **Cytogenetics**

No rearrangements reported.

#### **Oncogenesis**

Although interleukin-6 (IL-6) is considered as a key growth factor for myeloma cells, only a few subpopulations of tumor cells, such as CD45(+) immature cells, proliferate in response to IL-6. However, increasing numbers of cytokines, chemokines and cell-to-cell contacts been support growth of MM cells. It has repeatedly shown that oncogenic mutations as well as the bone marrow matrix (BMM) stimulate IL-6-independent signalling pathways that protect MM cells from apoptosis. Hyperdiploid MM tumors contain multiple trisomies involving chromosomes 3, 5, 7, 9, 11, 15, 19, and 21, but rarely have IgH translocations, although CCND-1/CCND-2/CCND-3 dysregulation appears to occur as an early event. This may sensitize these cells to proliferative stimuli, resulting in selective expansion as a result of interaction with BMM that produce IL-6 and other cytokines.

Three types of growth factors have been identified in plasma cells:

- The IL-6 family cytokines, which activate the Janus kinase-signal transducer and activator of transcription (JAK/STAT) and mitogen-activated protein (MAP) kinase pathways;
- Growth factors activating the phosphatidylinositol (PI)-3 kinase/AKT and MAP kinase pathways, and
- B-cell-activating factor (BAFF) or proliferation-inducing ligand (APRIL).

These growth factors may operate synergetically being co-localized together with cytoplasmic transduction elements in membrane caveolae.

Proteasome inhibitors are emerging as a promising class of anti-cancer therapeutic agents in MM, e.g. bortezomib which inhibits NF-kappaB translocation/transcription and critical signalling pathways, notably IL-6-induced proliferation and/or survival.

### **Prostate cancer**

#### **Cytogenetics**

No rearrangements reported.

#### **Oncogenesis**

IL-6 induces divergent proliferative responses in prostate cells. IL-6 is expressed in benign and malignant prostate tissue and levels of both IL-6 and IL-6R increase during prostate carcinogenesis. Serum levels of IL-6 are elevated in patients with treatment-refractory prostate carcinoma. IL-6 has also been shown to promote prostate cell growth, except in LNCaP cells, in which arrest and differentiation are produced. IL-6 induces activation of the androgen receptor (AR) in the absence of androgen. IL-6 also modulates vascular endothelial growth factor expression and neuroendocrine differentiation in prostate cells. Anti-IL-6 antibodies showed an inhibitory effect on PC-3 xenografts. Hence, IL-6 is widely considered a promising potential therapeutic target in prostate cancer.

Androgen receptor (AR), which is generally expressed in prostate cancers, promotes tumor progression in various ways, including ligand-independent activation. IL-6 is among the most important nonsteroidal regulators of AR activity reaching about half the maximum levels achieved by AR alone. At low concentrations of androgen, IL-6 and androgen operate synergistically to activate AR.

In prostate carcinoma cells homeodomain protein GBX2 was identified to contribute directly to IL6 expression by binding within the promoter region containing the consensus sequence for GBX2.

### **Hodgkin lymphoma**

#### **Cytogenetics**

No rearrangements detected.

#### **Oncogenesis**

Hodgkin lymphoma (HL) cells express multiple cytokines, notably IL6, which contributes to the immunoreactive phenotype and of which high levels are associated with bad prognosis. Both transcription factors, NFkB and AP1 are constitutively activated in HL cells driving expression of IL6 and also disturbing the pro/anti-apoptotic balance. Additionally, homeodomain protein HLXB9 contributes to the IL6 expression. HLXB9 is closely related to homeodomain protein GBX2 contributing to IL6 expression in prostate carcinoma cells. So, tumor type specific homeobox genes are involved in high level expression of IL6.

### **Cancer cachexia**

#### **Cytogenetics**

No rearrangements reported.

## Oncogenesis

Unlike acute inflammation which is a defense response, chronic inflammation may promote cancer. Several pro-inflammatory gene products modulate apoptosis, proliferation, angiogenesis, invasion, and metastasis, including IL-6, which is subject to regulation by NF- $\kappa$ B, which is constitutively active in most tumors. About one-in-three cancer deaths are due to cachexia (wasting) following the hypercatabolism of the body's carbon sources. Tumor-inflammatory responses encompass synthesis of cytokines, including IL-6 which induces cachexia by altering lipids and protein metabolism. IL-6-like cytokines inhibit lipid biosynthesis by adipocytes and cause the atrophy and increased catabolism of muscle protein. Reduced serum IL-6 levels induced by medroxyprogesterone acetate has been reported to exert an anti-cachectic effect in advanced breast cancer.

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