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Gene Section
Review

IRF1 (interferon regulatory factor 1)

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Identity

Hugo: IRF1
Other names: IRF-1; MAR
Location: 5q23.3
Note: Interferon regulatory factor 1 belongs to a family of transcription factors described for their role in regulating type I and type II interferons. Specifically, IRF1 has been identified as an activator of interferon alpha and beta transcription. Furthermore, it has been shown to play a role in the regulation of tumour suppression. IRF1 lies between interleukin (IL)-5 and CDC25C and is centromeric to IL-3 and GM-CSF. A number of mechanisms have been identified through which IRF1 is inactivated in various cancers. These, mechanisms include, deletion of the IRF1 region of chromosome 5q31; expression of IRF2; exon-skipping; binding of nucleophosmin; inactivation of tumour suppression by human papilloma viral oncogene, E7; and alternative splice variants lacking exons 7, 8, 9.

DNA/RNA

Description

7.72 kb with 10 exons and 9 introns.

Transcription

2.035kb mRNA. Coding sequence: CDS 198-1175. IRF1 mRNA is expressed in low levels in a variety of tissues including, heart, lung, thymus, kidney and activated spleen.

Protein

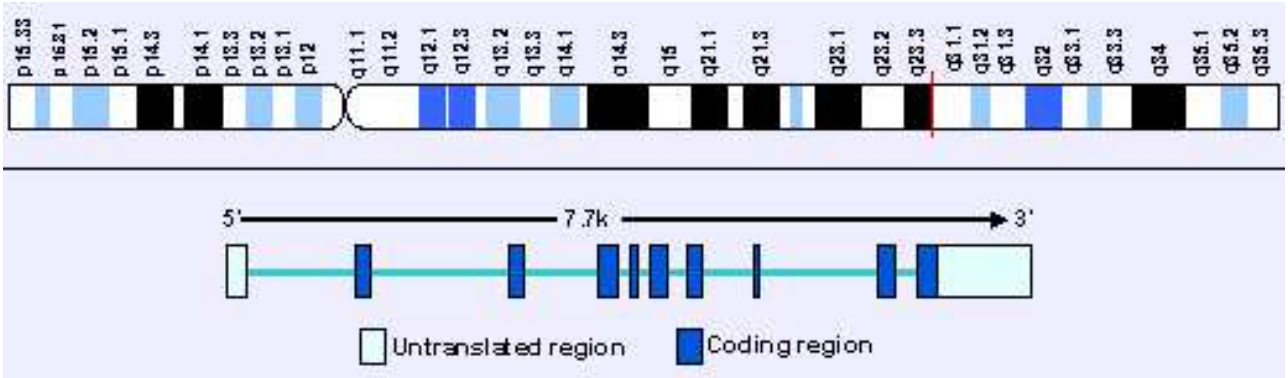
Note: IRF1 protein consists of 325 aa (36 kDa).

Description

IRF1 protein has an half-life of approximately 30 min.

Localisation

Nucleus.



Function

Transcriptional activator of type I interferons.

Mutations

Note: Deletion in 5q rearrangement of IRF1 are associated with preleukemic myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML). The most commonly reported cytogenetic abnormalities in leukaemia and preleukaemic myelodysplastic syndromes are found within 5q or loss of the entire choromosome 5. The most commonly deleted region was found to be 5q31. Willman et al. reported the tumour suppressor gene, IRF1 is situated within this 5q31 region. A common translocation found in AML is between chromosome 8q22 and chromosome 21q22. This translocation is found in approximately 40% of FAB-M2 AML and 8-20% of all AML.

Implicated in

Acute myeloid leukaemia (AML)

Disease

AML is an heterogenous disease representating clonal haematopoietic stem cell disorders. Initially classified under a French-American-British (FAB) co-operative group describing eight categories dependent on cell morphology on May-Grunwald-Giemsa (MGG) staining of peripheral blood and bone marrow smears. More recently, the World Health Organisation (WHO) proposed a new classification dependent on morphological, cytochemical, immunophenotypic, cytogenetic and molecular determinants that incorporates more recent developments in this disease and thereby reduce the limitations experienced under the FAB classification. Activation of the mutant N-ras gene in some myeloid cell lines induced growth suppression through IRF1.

Prognosis

Prognosis is poor for most AML patients, depending on age and other unfavorable biological features.

Cytogenetics

Translocations: t(8;21)(q22;q22), inv(16)(p13q22), t(15;17)(q22;q21), t(11;17)(q23;q21), or 11q23 rearrangements.

Preleukaemic myelodysplastic syndromes (MDS)

Note: 30% of patients exhibit a deletion in chromosome 5q.

Disease

MDS is an heterogenous group of diseases representing clonal bone marrow disorders. They are characterised by cytopenias with ineffective haematopoisis often progressing despite bone marrow transplants and may result in acute myeloid leukaemia. Chromosomal abnormalities are commonly found in this disease.

Breast cancer

Disease

The transcriptional regulation of human caspase-8 gene expression in the breast tumour cell line, MCF-7 was studied and found to be induced by IFN-gamma inducible transcription factor IRF1. Further studies have shown that IRF1 behaves as a tumour suppressor gene in breast cancer through caspase activation and induction of apoptosis. This suppression of apoptosis was observed independently of p53. Pizzoferrato et al., showed that ectopic expression of IRF1 using an adenovirus delivery system led to a decrease in survivin expression and an increase in cell death in breast cancer cell lines. This study also showed that p21 was up-regulated in IRF1-infected breast cancer cells independent of p53 modulation. Microarray analysis of clinically defined invasive breast carcinoma identified a negative correlation with IRF1 expression and tumour grade. High-grade breast carcinomas were found not to maintain IRF1 expression. IRF1 has also been shown to induce ligand-independent fas-associated death domain/caspase-8 mediated apoptosis in breast cancer cells.

Cytogenetics

A single nucleotide polymorphism, A4396G in IRF1 was found to occur more frequently in breast cancer cell lines than in the general population. In addition, this polymorphism was more frequently expressed in the African American population than the European population.

Cervical cancer

Note: Alternative splicing of exons 7, 8 and 9 is implicated in cervical cancer.

Disease

Lee et al., demonstrated that $p27^{Kip1}$ inhibits hTERT mRNA expression and telomerase activity through post-transcriptional up-regulation by IFN-gamma/IRF-1 signalling.

Gastric cancer

Note: A point mutation in the second exon of the IRF1 gene with a methionine substituted with leucine at codon 8 was identified.

Disease

Loss of heterozygosity at the IRF1 locus was found in 9 cases of histologically differentiated gastric adenocarcinomas. A mis-sense mutation in the residual allele was found in one case. This mutation in IRF1 was reported by Nozawa et al. to lead to reduced transcriptional activity but no change in its DNA-binding activity was observed. The loss of functional IRF1 is a key factor in development human gastric cancer.

Oesophageal cancer

Disease

Oesophageal cancer is an aggressive tumour with two subtypes described, including: oesophageal squamous cell carcinoma (ESCC) and oesophageal adenocarcinoma. Following IFNgamma stimulation of three oesophageal cancer cell lines IRF1 was produced but did not lead to cell death. In contrast, adenoviral-IRF1 (Ad-IRF1) infection of these cell lines induced high IRF1 production resulting in apoptosis. Furthermore, a murine model of oesophageal cancer injected with Ad-IRF1 moderately inhibited tumour growth but did not induce tumour regression. Analysis of primary samples of oesophageal squamous cell carcinoma revealed decreased IRF1 expression and increased IRF2 expression compared to adjacent normal oesophageal tissue. In addition, overexpression of IRF1 inhibited tumorigenicity of ESCC cells when injected in vivo in nude mice.

Prognosis

Ranked eighth most common malignancy and sixth most frequent cause of cancer worldwide.

Cytogenetics

The most frequent occurance is loss of heterozygosity either single or multiple loci on chromosome 5q. The smallest deletion is found at 5q31.1 the same position for the IRF1 gene.

Ovarian cancer

Disease

Interferon gamma has been shown to inhibit proliferation of a number of ovarian cancer cell lines in vitro. This growth inhibition and apoptotic effect in ovarian cancer cells was associated with a sustained increase in both IRF1 and p21. Kim et al., proposed a role for IRF1 in mediating IFNgamma-induced apoptosis through activation of caspase-1 gene expression in IFNgamma-sensitive ovarian cancer cells. IFNgamma was shown to induce IRF1 through the IFNgamma signalling pathway which in turn activated caspase-1. This was shown to lead to apoptosis of ovarian cancer cells, 2774 and PA-1, both sensitive to IFNgamma.

Prognosis

Early stage diagnosis of epithelial ovarian cancer one can anticipate 90% survival. However, only 20-30% of patients with stage III epithelial ovarian carcinoma survive after 5 years.

Melanoma

Disease

Lowney et al., described evidence showing IRF1 protein expression correlated to morphologic characteristics associated with less advanced disease in human melanoma.

Bladder cancer

Disease

Bladder cancer is ranked 9th in worldwide cancer incidence. A recent study determined that tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) expression and downstream TRAIL-regulated apoptotic mechanisms are involved in IFNalpha-induced cell death in human bladder cancer cell line through a STAT1 /IRF1-dependent pathway.

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