

## Gene Section

### Review

# EGR1 (early growth response 1)

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## Identity

**Other names:** AT225, G0S30, KROX-24, NGFI-A, TIS8, ZIF-268, ZNF225

**HGNC (Hugo):** EGR1

**Location:** 5q31.2

## DNA/RNA

### Note

The gene is conserved in chimpanzee, dog, cow, mouse, rat, chicken, and zebrafish.

### Description

Genomic size 3824 bp; 2 exons; + strand of chromosome 5.

### Transcription

mRNA size: 3132, ORF 271-1902 (1632 nt coding sequence).

Rare occurrence of splice variants (2 variants have been described in the brain).

The EGR1 promoter contains five SREs (serum response elements). Increased transcription in

response to growth factors or stress is most commonly mediated by transcription factors of the Elk-1/SAP-1/2 family, which are activated by MAP-Kinase family (mitogen activated protein kinase). Elk-1 associates with CBP (CREB binding protein) and SRF (serum response factor) to form the Ternary Complex Factor, which binds to the SREs.

The promoter also contains several SP1 consensus sequences; a putative AP-1 binding site (not conserved); at least one functional CRE (cAMP regulatory element).

EGR1 regulates its own transcription by binding to functional EBS (EGR1 binding sites). A functional NFkB (p65/RelA) binding site is contained in the EGR1 promoter that allows NF-kB to increase EGR1 transcription in response to UV (ultra-violet) irradiation. EGR1 is a target of ETS transcription factors that are involved in hematopoiesis, angiogenesis and neoplasia. Finally, EGR1 promoter contains two ATF5 (activating transcription factor 5) consensus sequences at a conserved promoter position and is induced by ATF5 in cancer cell lines.

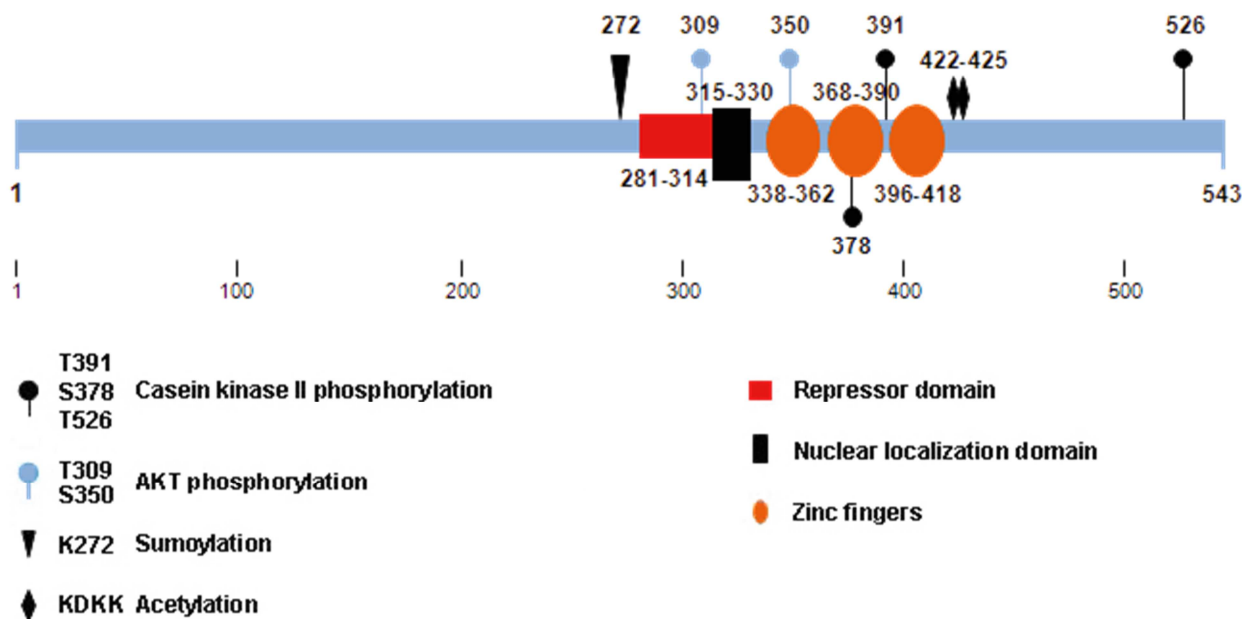


Figure 1.

## Protein

### Description

The protein contains 543 amino acids. Its predicted molecular weight is 57.5 kDa, however the protein migrates at an apparent molecular weight of 75-85 kDa in SDS-PAGE. It has a very short half-life of ~30 minutes to 1 hour.

EGR1 contains a highly conserved DNA-binding domain composed of three Cys2-His2 type zinc-fingers that bind to the prototype target sequence GCG(G/T)GGGCG; a nuclear localization signal that requires amino acids 361-419 (zinc fingers 2 and 3) and amino acids 315-330; two activator domains; a repressor domain between amino acids 281-314. EGR1 binds to regulatory proteins called NAB-1 (NGFA-I binding protein) and NAB2 through its repressor domain.

Post-translational modifications include phosphorylation, acetylation, ubiquitination and sumoylation (figure 1).

### Expression

Ubiquitous. Exhibits a distinct expression pattern in the brain. Constitutive protein expression is low in many tissues. EGR1 expression is very rapidly and strongly induced by growth factors and mitogens, cytokines, environmental and mechanical stresses, as well as DNA damage (hpr).

### Localisation

Nuclear. Occasional cytoplasmic localization observed in cancer cells.

### Function

EGR1 is an early response transcription factor with DNA binding activity that activates the transcription of several hundred genes. Depending on the cell type and the stimulus, EGR1 induces the expression of growth factors, growth factor receptors, extracellular matrix proteins, proteins involved in the regulation of cell growth or differentiation, and proteins involved in apoptosis, growth arrest, and stress responses.

EGR1 can compete with transcription factor SP1, which is involved in the constitutive expression of housekeeping genes and other regulatory genes. Because the consensus sequence for SP1 and EGR1 binding overlaps, EGR1 often displaces SP1 from gene promoters.

EGR1 transcriptional activity is inhibited by direct interaction with the proteins NAB1 and NAB2. Their expression is also inducible, albeit delayed compared to EGR1 induction. NAB1 and NAB2 impose an early negative feedback and thus ensure that EGR1 activity is transient, before the protein is degraded. It should be noted that deregulated expression of NAB proteins in disease may contribute to alteration of EGR1 function. For example, elevated expression of NAB2 in endothelial cells reduces angiogenesis, whereas loss of NAB2 in prostate cancer contributes to increased EGR1 activity.

EGR1 has various neurocognitive functions. It is involved in the regulation of neuronal activity and may control neuronal plasticity. EGR1 controls tissue repair, wound healing, liver regeneration, atherosclerosis, fibrosis, and other inflammation or stress-related

responses. It is considered a key master regulator in cardiovascular pathology by promoting atherosclerosis, intimal thickening following vascular injury, ischemia, allograft rejection and cardiac hypertrophy. Finally, EGR1 regulates cell response to hypoxia, promotes the formation of new blood vessels from the pre-existing vasculature, and triggers tumor angiogenesis.

In cancer, EGR1 is traditionally considered a tumor suppressor. However, accumulating evidence now indicates that it can act both as a tumor suppressor and as a tumor promoter, depending on the context.

EGR1 protects normal cells from transformation by inducing apoptosis or growth arrest upon DNA damage. A strong evidence for EGR1 pro-apoptotic function is that EGR1<sup>-/-</sup> mouse embryo fibroblasts are resistant to apoptosis induced by ionizing radiation. Although EGR1-deficient mice do not spontaneously develop tumors, they display accelerated tumor growth in a two-step carcinogenesis model of skin cancer. As an example, UV-B radiation of keratinocytes induces EGR1 expression through activation of NFκB (p65/RelA), which mediates apoptosis and acts as a protection mechanism against the tumorigenic effect of UV. These observations support the notion that EGR1 participates in the suppression of DNA damage-induced tumors.

EGR1 is involved in the chemopreventive or antiproliferative effect of natural compounds such as curcumin, genistein, isoflavone, green tea extracts, and others. It also mediates the anti-proliferative effects of NSAIDs (non-steroid anti-inflammatory drug) and of other chemotherapeutic agents such as cisplatin.

In many cancer cells, EGR1 is induced by radiation, chemotherapeutic drugs, steroids and anti-inflammatory drugs, and is required for the growth arrest or apoptotic effect of these treatments. Lack of EGR1 response confers chemoresistance. This may be exploited by restoring EGR1 expression through gene therapy to increase the efficacy of radiotherapy of chemotherapy.

At later stages of cancer EGR1 tumor suppressor function is impaired by the frequent inactivation, in

human tumors, of two major tumor suppressor targets of EGR1 (namely PTEN and TP53). In addition, EGR1 induction by growth factors or stress is blocked in some types of cancer cells ("resistance" to induction). This has been described in fibrosarcoma, prostate cancer, colon cancer, and RAS-transformed cells. Several mechanisms are involved.

For example, RAS-induced transformation of fibroblasts results in the aberrant constitutive activation of PI3-kinase (phosphatidylinositol 3-kinase), which causes degradation of SRF and prevents Elk-1-mediated induction of EGR1. In colon cancer cells, it is the mutational activation of Wnt-1 that prevents the SRF-mediated induction of EGR1 and other early genes in response to mitogens. Alternatively, overexpression of phospholipase D in glioma cells attenuates mitogen-induced EGR1 expression through activation of PI3-kinase.

On the other hand, EGR1 overexpression in some cancer types directly promotes cancer progression and tumor growth by increasing the expression and secretion of growth factors and cytokines, extracellular matrix proteins and proteases. Mechanisms that can cause EGR1 overexpression in tumor cells include p53 mutations (observed in gliomas and prostate cancer). Mutant p53 upregulates EGR1 in prostate cancer cells by activating ERK (extracellular regulated kinase) through undefined mechanism. Constitutive activation of the ERK pathway in tumor cells appears to be a consistent cause of EGR1 expression and is often due to genetic defects affecting upstream regulators of the ERK pathway. For example, a mutation of EGFR (epidermal growth factor receptor) commonly found in lung cancer cells causes EGR1 overexpression and activation through activation of the ERK pathway. Similarly, a mutation of B-RAF present in a high percentage of melanoma results in constitutive activation of ERK and up-regulation of EGR1.

### **Homology**

Three other family members: EGR2, EGR3 and EGR4 (see figure 2).

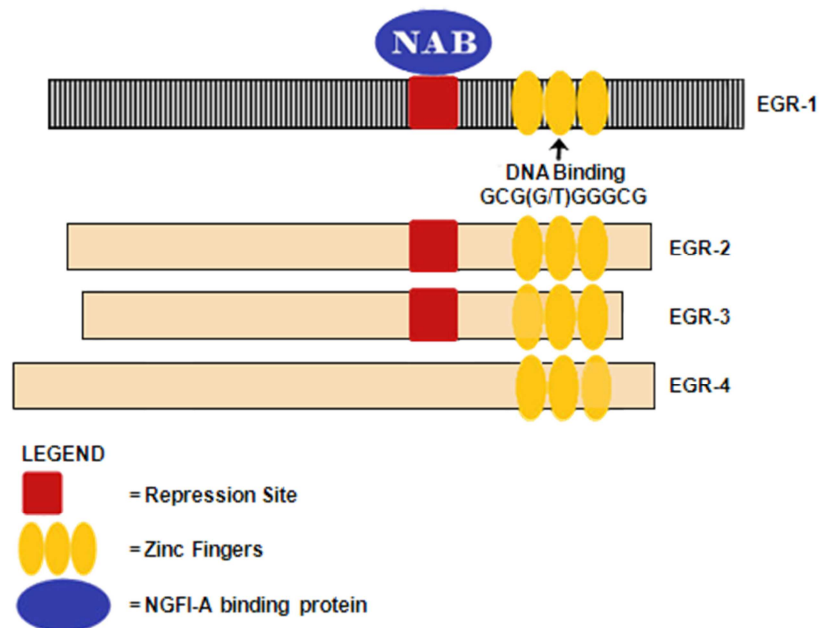


Figure 2. Image designed by Melody W Lin.

## Mutations

### Note

Mutations in the EGR1 gene have not been found; altered expression level is the most common contributor to tumorigenesis.

Chromosome loss/deletions:

- The long arm of chromosome 5 in which EGR1 is located is consistently deleted in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Loss of chromosome 5 or deletion in 5q is the most common karyotypic abnormality in MDS, occurring in 10% of new MDS/AML patients and in 40% of patients with therapy-related MDS or AML. Mice lacking at least one allele of EGR1 develop symptoms similar to that of MDS after they are exposed to a carcinogen (i.e. mono- or bi-allelic loss of EGR1 accelerates the development of pre-leukemic disorders).

- Loss of 5q is consistently associated with estrogen receptor-negative (ER<sup>-</sup>) breast carcinoma and is seen in 86% of breast carcinomas carriers of BRCA1 (breast cancer 1) and BRCA2 mutations. Fluorescence in situ hybridization confirmed the association of EGR1 loss with ER<sup>-</sup> breast carcinoma; loss of EGR1 correlated with high grade.

## Implicated in

### Various cancers

#### Note

EGR1 (protein and/or mRNA) is downregulated in colon cancer, lung cancer, esophageal carcinoma, astrocytomas, glioblastomas, breast cancer, compared to non-cancer tissue. EGR1 expression is sharply decreased in leiomyoma compared to normal

myometrium (reduction in 100% of tumors). Transfection of EGR1 into myometrial cells decreases cell proliferation.

In some types of cancers EGR1 expression is high in the adjacent tissue of the tumors, but low in the tumor cells. In esophageal carcinoma, EGR1 expression is higher in the dysplastic tissue, whereas no expression is detected in the tumor tissue. This may reflect the existence of a reactive stroma, and possibly inflammation.

Early observations indicated that in v-sis-transformed NIH-3T3 cells, transfection of EGR1 inhibits colony formation and growth in soft agar. It also delays tumorigenicity in nude mice. Conversely, EGR1 antisense accelerates cell growth and colony formation. EGR1 expression is upregulated in human diffuse large B cell lymphoma because of constitutively active ERK and JNK (Jun N-terminal kinase) pathways and promotes cancer cells survival. Overexpression of EGR1 (both mRNA and protein) is observed in gastric cancer and in prostate cancer. It is also seen in the "normal" tissue adjacent to the tumors, but it is not expressed in the normal tissues from healthy patients. The mRNA expression is higher in metastatic cases of gastric cancer. EGR1 is much higher expressed in cervical cancer tissues than in the normal cervix.

### Leukemia

#### Note

In myeloblastic leukemia, upregulation of oncogene E2F-1 blocks the myeloid terminal differentiation program, resulting in proliferation of immature cells in the presence of interleukin-6. EGR1 abrogates the E2F-1-driven block in myeloid terminal differentiation, decreases the tumorigenic potential of leukemia cells in

vivo and their aggressiveness. EGR1 also abrogates the block in terminal myeloid differentiation imparted by oncogenic c-myc.

### **Fibrosarcoma**

#### **Note**

Human fibrosarcoma cells express almost no EGR1 and are "resistant" to EGR1 induction in response to growth factors or stress. Forced expression of EGR1 inhibits cell growth and suppresses xenograft tumor growth in athymic mice. Conversely, silencing EGR1 using antisense increases the transformed character of these cells.

The effect of EGR1 in HT-1080 fibrosarcoma cells is mediated by increased secretion of active TGFbeta-1 (transforming growth factor-beta1), a direct target of EGR1. TGFbeta-1 strongly inhibits cell growth in an autocrine mechanism. Further, EGR1 regulates cell adhesion and migration through increased secretion of fibronectin and plasminogen activator inhibitor-1 (PAI-1). Although fibronectin is a direct target of EGR1, PAI-1 increase is mediated by EGR1-induced TGFbeta-1.

### **Lung cancer**

#### **Note**

EGR1 (RNA and protein) is expressed at higher levels in human normal lung tissue adjacent to non-small cell lung cancer (NSCLC), and is downregulated in the tumor tissue compared with normal lung. Also downregulated in human lung adenocarcinomas and lung squamous cell carcinomas.

High expression of EGR1 in NSCLC patients correlates with high PTEN expression. Low levels of EGR1 after surgical resection are associated with poor outcome.

### **Brain cancer (astrocytoma/glioblastoma/neuroblastoma)**

#### **Note**

EGR1 mRNA and protein are strongly suppressed in astrocytomas and glioblastomas compared to normal brain. Downregulation correlates with grade in human tissue, or with the presence of wild-type p53 in cell cultures. Tumors or primary cell lines that exhibit higher EGR1 expression contain p53 mutations. EGR1 induces growth arrest of glioma cells mediated by increased secretion of TGF-beta1, PAI-1 and fibronectin. EGR1 expression is induced by hypoxia in glioblastoma multiforme and up-regulates tissue factor that promotes plasma clotting.

Two EGR1 mRNA variants are detected in astrocytomas, one that contains N-methyl-D-aspartate-receptor (NMDA-R)-responsive element. An increase in the expression of this EGR1 variant is seen in astrocytoma cells following NMDA stimulation. EGR1 expression is restricted to tumor cells expressing NMDA-R, is up-regulated in astrocytomas compared

with normal brain, and is associated with enhanced patient survival.

In neuroblastoma cells, re-expression of EGR1 induces apoptosis, whereas EGR1 antisense increase cell viability. The apoptotic activity of the EGR1 is mediated by activation of p73 (a member of the p53 family).

### **Breast cancer**

#### **Note**

Breast cancer cell lines and clinical cancer tissues exhibit reduced EGR1 expression while normal mammary tissues express high levels. EGR1 is also downregulated in experimentally induced rat mammary tumors. Downregulation of gelsolin, which is an indicator of breast cancer, is correlated with suppression of EGR1.

Some studies have shown that re-expression of EGR1 inhibits human tumor cell growth and suppresses tumorigenicity in mice. However, two other studies found that EGR1 silencing decreases breast cancer cell proliferation, migration, and growth of xenograft tumors in nude mice.

In estrogen receptor-positive breast cancer cell lines, EGR1 expression is induced by estrogen through activation of RAF-1 kinase, the MAP-kinase pathway, and Elk-1/SRF.

### **Hepatocellular carcinoma (liver cancer)**

#### **Note**

While one study reports EGR1 overexpression, another one describes the downregulation of EGR1 expression in hepatocellular carcinoma. In the latter study, re-expression of EGR1 decreased cell growth and tumorigenicity in nude mice.

There are arguments in favor of a pro-tumorigenic function: HGF (hepatocyte growth factor), a cytokine involved in the progression of hepatocarcinoma, up-regulates EGR1 and increases cell scattering and migration through EGR1-mediated up-regulation of snail. HGF also increases angiogenesis through up-regulation of EGR1-mediated VEGF (vascular endothelial growth factor) and interleukin 8.

Of note, EGR1 is crucial for the proliferation of hepatocytes and plays an important role in liver regeneration: liver regeneration following partial hepatectomy is impaired in EGR1-null mice.

### **Skin cancer/melanoma**

#### **Note**

EGR1 expression is decreased in basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) but is elevated in psoriasis. EGR1 inhibits the growth of benign and malignant epidermal cells in vitro.

A single topical treatment with the tumor promoter TPA in a multistage carcinogenesis model induces EGR1 mRNA expression both epidermis and dermis of the mice. Primary papillomas and carcinomas generated in these animals contain high EGR1 mRNA

compared with normal epidermis. EGR1-null mice reveal an accelerated development of skin tumors in the multistage carcinogenesis model compared to EGR1+ mice.

On the other hand, EGR1 may contribute to cancer progression in melanoma. The HGF receptor c-Met induces EGR1 activation via the Ras/ERK1/2 pathway in melanoma cells, which in turn induces fibronectin expression and its extracellular assembly. Fibronectin promotes migration and invasiveness of melanomas and is associated with metastatic potential.

About 60% of melanoma contain an activating mutation in the B-RAF gene. In these cells, constitutive up-regulation of EGR1 caused by activation of RAF/ERK signaling results in high fibronectin levels and increases invasiveness.

### Prostate cancer

#### Note

EGR1 mRNA is expressed at higher levels in prostate tumors compared with normal tissues and correlates with Gleason score (a measure of prostate cancer stage). EGR1 expression in the primary tumor correlates with complete control of the local tumor by radiation, whereas in post-irradiated tissue EGR1 expression correlates with treatment failure. NAB2 is down-regulated in clinical primary carcinoma. Thus, upregulation of EGR1 and loss of NAB2 both determine the high level of EGR1 activity in human prostate tumors.

EGR1 knock-out mice crossed with transgenic mouse models of prostate cancer show significantly impaired tumor growth compared to Egr<sup>+/+</sup> mice and increased survival. Although it does not prevent tumor initiation, EGR1 deficiency delays the progression of prostate carcinoma. EGR1 is also overexpressed in the tumors of the transgenic mice, whereas NAB2 expression is decreased.

Silencing of EGR1 in prostate cancer cells decreases cell proliferation in vitro, and injection of EGR1 antisense in vivo delays the occurrence of prostate cancer. Alternatively, forced expression of EGR1 in non-cancer cells increases proliferation in vitro.

EGR1 up-regulation in prostate cell lines is due to mutation of the TP53 gene. EGR1 is also up-regulated by SV40-T antigen, a viral oncogene that is used very often to immortalize non-transformed cells. In human prostate cancer cells EGR1 stimulates the production of many growth factors and cytokines that are involved in the progression of prostate cancer and of proteins involved in metastasis.

A crosstalk between EGR1 and the androgen receptor (AR) may explain the particular role of EGR1 in prostate cancer. EGR1 physically interacts with AR in hormone-sensitive prostate cancer cells and the complex binds to the promoter of endogenous targets of AR. Forcing EGR1 activity in hormone-sensitive cancer cells increases proliferation in vitro. It enhances tumor growth in mice upon castration (which mimics

hormone therapy in human patients): EGR1 may be involved in the acquisition of resistance to hormone therapy.

### Esophageal carcinoma

#### Note

According to some reports, the expression of EGR1 (mRNA and protein) is high in pre-cancerous human lesions of the esophagus and in dysplastic tissue adjacent to esophageal carcinoma, but is very low in cancer tissue. The number of apoptotic cells in EGR1-positive tumors is higher than in EGR1 negative tumors, suggesting that EGR1 promotes apoptosis. In addition, EGR1 is up-regulated in the tumors of patients treated by irradiation compared to the tumor tissue of non-irradiated patients, and EGR1 expression level seems to correlate with better prognosis.

Another study, however, shows overexpression of EGR1 in esophageal tumor tissues and constitutive expression in esophageal cancer cell lines.

EGR1 silencing inhibits cell proliferation through G2/M cell cycle block. On the other hand, forced stable expression of EGR1 into esophageal carcinoma cells also decreases cell proliferation in vitro and tumor growth in vivo.

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