Review

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The progress of early growth response factor 1 and leukemia

Jing Tian[1,2], Ziwei Li[1,2], Yang Han[1,2], Tao Jiang[3], Xiaoming Song[4], Guosheng Jiang[1,2,*]

[1] *Key Laboratory for Modern Medicine and Technology of Shandong Province, Institute of Basic Medicine, Shandong Academy of Medical Sciences, Ji'nan, Shandong, China;*
[2] *School of Medicine and Life Sciences, Ji'nan University, Ji'nan, Shandong, China;*
[3] *Graduate School of Xuzhou Medical College, Xuzhou, Jiangsu, China;*
[4] *Graduate School of Bengbu Medical College, Bengbu, Anhui, China.*

Summary **Early growth response gene-1 (*EGR1*) widely exists in the cell nucleus of such as, zebrafish, mice, chimpanzees and humans, and it also can be observed in the cytoplasm of some tumors. *EGR1* was named just after its brief and rapid expression of different stimuli. Accumulating studies have extensively demonstrated that the widespread dysregulation of *EGR1* is involved in hematological malignancies such as human acute myeloid leukemia (AML), chronic myelogenous leukemia, chronic lymphocytic leukemia, multiple myeloma, and B cell lymphoma. With the deep research on *EGR1*, its expression, function and regulatory mechanism has been gradually elucidated, and provides more possibilities for treatment strategies of patients with leukemia. Herein, we summarize the roles of *EGR1* in its biological function and relationship with leukemia.**

Keywords: Early growth response gene-1 (*EGR1*), acute myeloid leukemia, tumor

1. Introduction

Early growth response gene-1 (*EGR1*), also known as *NGFI-A*, *krox-24*, *ZIF268* and *TIS8*, is an immediate early gene which encodes a Cys2-His2-type zinc finger transcription factor widely expressed in eukaryotic cells from yeast to humans (*1-3*). It is one of the largest studies of tumor-specific proteins, which are located in the 5q31 region (*4,5*). It has an important role in controlling synaptic plasticity, wound repair, female reproductive capacity, inflammation, growth control, differentiation, apoptosis and tumor progression (*6*). Experiments have also proved that acute myeloid leukemia and myelodysplastic syndromes are associated with heterozygous loss of *EGR1* (*7*). Here, we focus on the relationship of *EGR1* with acute myeloid leukemia.

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**Address correspondence to:*
Dr. Guosheng Jiang, Key Laboratory for rare & uncommon diseases of Shandong Province, Institute of Basic Medicine, Shandong Academy of Medical Sciences, NO.18877 of Jingshi Road, Ji'nan, Shandong, China.
E-mail: jiangguosh@163.com

2. The summarization of EGR1's discovery and function

EGR1 was first discovered in the mid-1980s (*8*). The EGR family includes *EGR1*, *EGR2*, *EGR3*, *EGR4* four related members, that can quickly and briefly be up-regulated through a variety of external stimuli, including activation, proliferation and differentiation signals, tissue damage and apoptosis signals (*9*). *EGR1*, *EGR2*, *EGR3* and *EGR4* share a highly conserved DNA binding domain, composed of three zinc finger motifs that together bind to a 9-bp G/C-rich consensus sequence (GCGGGGGCG) (*10*). It has been used extensively as a model system for detecting how TFIIIA-like zinc fingers recognize DNA, and how it has served as a basis for engineering some types of artificial DNA-binding proteins (*11*). EGRs are involved in regulating the immune response by means of the induction of differentiation of lymphocyte precursors, and activation of B and T cells (*12*). *EGR1* binds to DNA G/C-rich sequences through 3 zinc-finger motifs in its carboxyl terminal and regulates gene transcription through co-operation with other activating or repressing factors (*13*). It may be divided into three zones. The N-terminal portion (amino acids 1-331) is rich in proline (14.2%) and serine (16%) and has 7.9% alanine and 7.9%, threonine. The C-terminal region (residues 417-533) also contains a very high proportion of proline and serine (15.4% and 26.5%, respectively) as well as 10.3% alanine and 11.1% threonine (*14*).

3. Biological function and role in tumors

The *EGR1* gene encodes a zinc finger protein and its expression is modulated in diverse biological systems with kinetics resembling those of c-fos (*14*). *EGR1* together with c-fos is crucial for normal myeloid cell differentiation through transcriptional regulation (*15*). Gene expression analysis revealed that *EGR1* and *c-fos* were down-regulated in hematopoietic primitive cells (*16*). *C-fos* and *EGR1* represent the key transcription factors that are differentially activated by macrophage colony-stimulating factor (M-CSF) and granulocyte colony-stimulating factor (G-CSF) to resolve neutrophil versus monocyte cell fate (*17*). However, *EGR1* has more of an advantage than c-fos because of different structure, which increases its expression and decreases sensitivity to stimulation (*18*). *EGR1* can regulate cell growth, differentiation, growth inhibition, and apoptosis in various kinds of cells (*19*). Many factors can regulate expression of *EGR1*, including *miR-424*, *miR-146a*, *miR-181a*, *E2h2*, wilms tumor suppressor 1 (WT1), and Iron (*9,20-25*). It's also reported in the literature that *EGR1* can be regulated by erythropoietin (EPO) (*26,27*). *MiR675* upregulates long noncoding RNA H19 through activating *EGR1* in human liver cancer (*28*). More importantly, *EGR1* can regulate some signaling such as p53, transforming growth factor beta 1 (TGFβ1), phosphatase and tensin homolog deleted on chromosome ten (PTEN), Fibronectin, and enterovirus 71 (EV71) (*29-32*). The promoter of the human TGFβ1, p53, and the fibronectin gene contains at least two EGR1-binding sites, both of which can bind *EGR1* to activate transcription. The proximal promoter of PTEN is GC rich and contains one functional *EGR1*-binding site (*29*). Moreover, it plays important roles in decidualization, megakaryocyte differentiation, apoptosis, tendon development, lung injury, liver injury, kidney diseases, chronic obstructive pulmonary disease (COPD), angiogenesis, fibrosis, atherosclerosis, cell cycle and other biological functions (*33-52*). *EGR1* has a critical role in promoting autophagy and apoptosis in response to cigarette smoke exposure *in vitro* and *in vivo* (*53*). *EGR1* controls metabolism, especially its suppression of lipolysis and promotes fat accumulation by inhibiting the expression of triglyceride lipase (*54*). Although the expression of *EGR1* is low in most tissues, it is high in islets. *EGR1* regulates insulin gene expression by up-regulating Pdx1 (*55*). *EGR1* gene expression may contribute to the decrease of B-cell proliferation and the consequent cell failure observed in the later stages of type 2 diabetes (*56*). The increase of *EGR1* expression in the brain is associated with formation of emotional memory and schizophrenia (*57*). It has been proved that *EGR1* mutant mice had no changes in short-term memory, but long-term memory was severely damaged (*58*). Ischemia-induced *EGR1* expression may exaggerate brain injury by reducing brain-derived neurotrophic factor (BDNF) expression (*59*). *EGR1* exhibited a biphasic expression behavior. It was previously described to be down-regulated in many breast carcinoma tissues while it was upregulated in highly invasive inflammatory breast carcinoma. It started to be upregulated 4 h after SNAI1 induction, and was repressed after 24 h (*6*). Interestingly, in prostate cancer, kidney cancer and stomach cancer *EGR1* stimulates the growth of tumor cells, and is associated with poor prognosis. In contrast, *EGR1* is a tumor suppressor in fibrosarcoma, glioblastoma, melanoma, esophageal cancer, lung cancer and breast cancer (*60-64*).

4. Pathogenesis mechanism of AML by *EGR1*

In the absence of *EGR1*, a significant increase in cell cycling occurs in hematopoietic stem cells (HSCs), culminating in an increased number of HSCs and an increased frequency of primary reconstitution under limiting dilution conditions. Most interestingly, loss of *EGR1* causes efficient mobilization of HSCs out of their niches (*65*). Abnormalities of chromosome 5 are common aberrations in acute myeloid leukemia (AML), with del(5q) the most frequent (*66,67*). There is also literature, which shows that *EGR-1* was related to recurrent disease following high-dose chemotherapy (*68*). Nevertheless, *EGR1* haploinsufficiency alone *in vivo* does not lead to expansion of HSCs or abnormalities in adult hematopoiesis. It has been proven that loss of a single allele of more than one gene on 5q contributes to the pathogenesis of AML (*69-71*). A number of genes and several microRNAs (miRNAs) located on 5q, including *miRNA-145*, *miRNA-146a*, the ribosomal protein S14 (RPS14), the cell division cycle 25 (CDC25), the adenomatous polyposis coli gene (*APC*) have been implicated in the development of myeloid disorders caused by a gene dosage effect (*72,73*). (Figure 1) *EGR1* may play a functional role in the pathogenesis of AML in patients with del(5q) (*74,75*). The loss of *EGR1* or inactivation increases risk of AML (*76*). Using locus-specific probes, a deletion of the *EGR1* locus 5q31, 7q31 and the *TP53* gene was observed in 103 (82%), in 57 (46%) and in 66 (53%) patients respectively. Thirty patients (24%) showed a deletion of all three loci, and in only 13 cases (10%), 5q31, 7q31, or 17p13 was not deleted. An EGR1 deletion alone was observed in 19 cases (15%) in only five and four AMLs respectively (*77*). In an attempt to define the loss of the 5q31.1 region, fluorescence in situ hybridization analysis was performed in HL-60 cells, which spanned the *EGR1* and *IL9* gene interval, which was previously shown to be a critical region of loss in AML (*78*). Loss of the *EGR1* gene with deletions of 7q31 or TP53 alone played a role in at least two

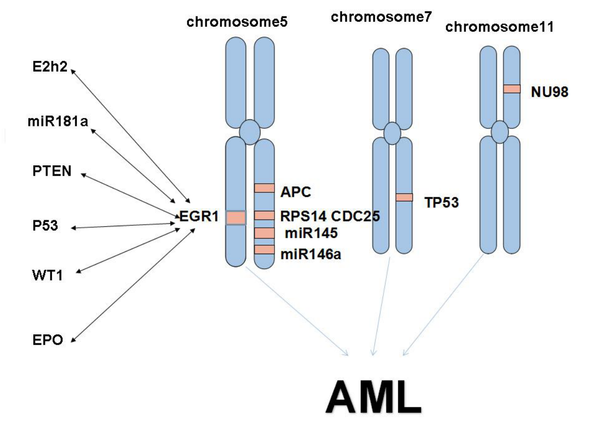

Figure 1. E2h2, miR181a, PTEN, P53, WT1, EPO and EGR1 can regulate each other. The cooperation of EGR1, APC, RPS14, CDC25, miR145, miR146a, TP53 and NU98 may lead to the formation of AML.

aspects. First, *EGR1* directly controls the expression of fibronectin (FN1) through pathways that involve GFB1 and plasminogen activator-1 (PAI1). Thus, FN1 and PAI1 act together to inhibit the growth of cancer cells. Second, *EGR1* is required for p53-dependent apoptosis through the mediation of retinoblastoma (*79*). To examine the role of *EGR1* in hematopoiesis, $EGR1^{+/-}$ and $EGR1^{-/-}$ mice was characterized, and found that $EGR1^{+/-}$ and $EGR1^{-/-}$ mice develop T-cell lymphoma or a myeloproliferative disorder (MPD) at an increased rate and a reduced latency over that observed in wild-type littermates. $EGR1^{+/-}$ and $EGR1^{-/-}$ mice develop T-cell lymphoma or MPD at the same rate and latency, suggesting that loss of a single allele of EGR1 is sufficient for disease predisposition. This is consistent with observations in patients with AML characterized by abnormalities of chromosome 5, in that only 1 EGR1 allele is affected (*80*). Interestingly, *EGR1* is regulated by multiple factors in AML. The cyclin-dependent kinases (CDK) CDK6 and Src family kinases (SFKs) inhibit expression of *EGR1* (*81,82*). On the contrary, Llgl1 (lethal giant larvae homolog 1) and PMA (Phorbol 12-myristate 13-acetate) contribute to the differentiation of hematopoietic stem cells (*83,84*). Andra Schaefer *et al*. found that the expression of EGR-1 had a regulatory role in Epo signal transduction in leukemia cells (*85*).

5. The possibility of *EGR1* as therapy target of patients with AML

The primary structure of the EGR1 protein suggests that it is a DNA-binding protein with transcriptional regulatory activity, and it may function as a tumor suppressor locus whose absence or loss of function could lead to deregulated cell growth (*86*). This gives us an inclination that *EGR1* or *EGR1* target gene is useful for treatment of blood malignant tumors (*87*). One study mentioned that *EGR1* and p21 are key signaling molecules of genipin-induced apoptosis in gastric cancer cells (*88*). Another article revealed that the down-regulation of EGR1-p21 expression provides a mechanism for improved hematopoiesis (*89*). Histone deacetylase (HDAC) inhibitors can reactivate EGR1 in various cell types, leading to decreased cell proliferation and increased cell apoptosis (*90*). HDAC recruitment may participate in the repressive mechanism that EGR1 directly represses myocyte enhancer factor 2 (MEF2) activity for treatment of cardiac disease (*91*). Experimental evidence has demonstrated that EGR1 diminished the aggressiveness of M1myc leukemia and abrogated the leukemic potential of IL-6-treated M1myc cells. Altered EGR1 expression can work together with deregulated c-Myc in exacerbating the leukemic phenotype (*92*). It is also reported that *EGR*-1 plays an indispensable role in the regulation of platycodon D-induced cell death and the 1, 25D3-induced cessation of cell proliferation, which is characteristic of the terminal stage of differentiation of these cells (*93,94*). *EGR1* and WT1 are structurally related transcription factors and bound to quite similar DNA sequences (*95*). This gives us a revelation that down-regulating the expression of WT1 can up-regulate the expression of *EGR1*. In this way, inhibition of proliferation and differentiation of leukemia cells is no longer a problem. *EGR1* is also important for development of the macrophage lineage (*96*). It is interesting to note that *EGR-1* abrogates the block in M1 terminal differentiation imparted by oncogenic c-Myc or E2F-1, suppressing their leukemia promoting function in nude mice (*97*). A novel mechanism of thalidomide in the treatment of leukemia is that thalidomide could suppress leukemia cell invasion and migration by upregulation of *EGR*-1 (*98*). Also that paeoniflorin (PF) playing a role in human leukemia U937 cells is based on the regulation of *EGR1* (*99*). LY294002 (LY29) is a commonly used pharmacologic inhibitor of phosphatidylinositol 3-kinase (PI3 K) and has shown an antitumorigenic effect. It could suppress leukemia cell invasion and migration at least in part through up-regulation of *EGR-1*, independent of its PI3 K-Akt inhibitory activity (*100*). In summary, we believe that *EGR* is likely to be a target for treatment of AML.

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