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Gene Section
Review

GFI1 (growth factor independent 1 transcription repressor)

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Identity

Other names: FLJ94509; GFI-1; SCN2; ZNF163

HGNC (Hugo): GFI1

Location: 1p22.1

DNA/RNA

Description

The GFI1 locus consists of 7 exons of which 6 are coding. Depending on different reported variants, the position of the first, non-coding, exon 1, can vary.

Pseudogene

None known.

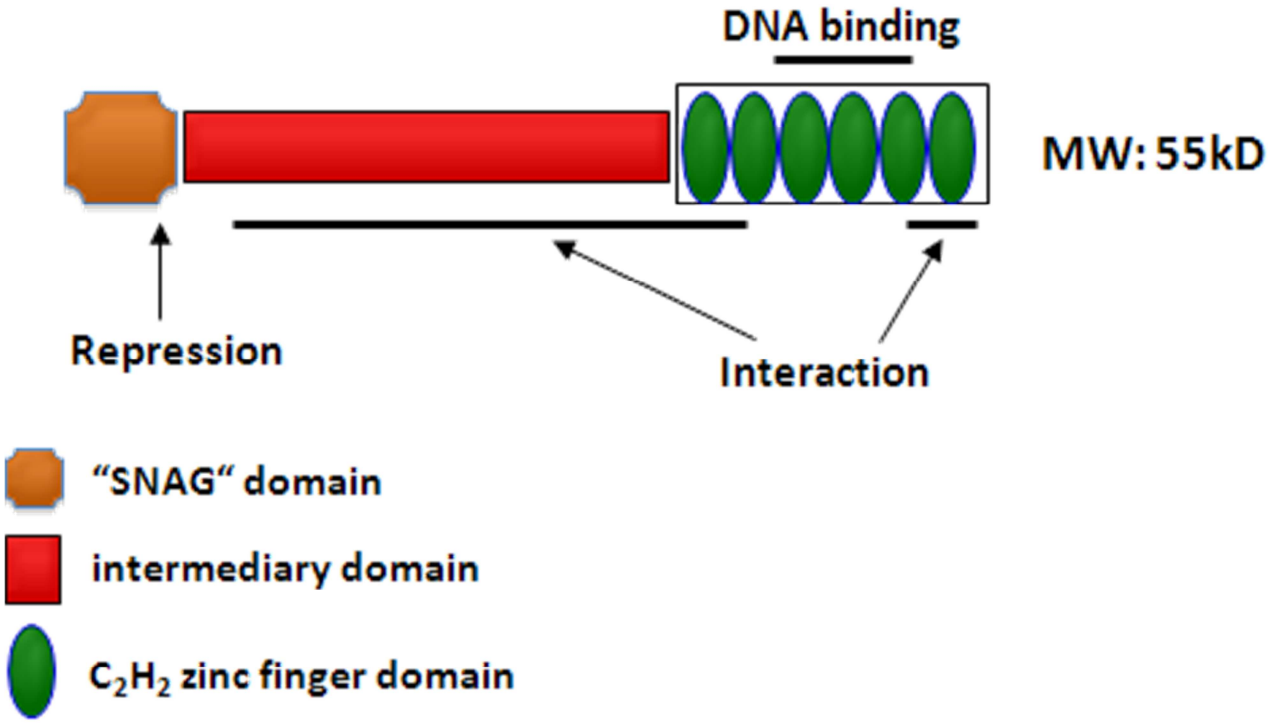

Figure 1. GFI1 protein (from Möröy and Khandanpour).

Protein

Description

Both human and murine Gfi1 proteins consist of 422 amino acids and have a mass of 45297 Da. The isoelectric point is 9.24. Gfi1 contains six c-terminal C_2H_2-type zinc-finger domains and an N-terminal SNAG domain critical for its repressor activity (figure 1). Zinc fingers 3 to 5 of Gfi1 recognize and bind to the DNA sequence taAATCac(t/a)gca. Zinc fingers 1, 2 and 6 are required for the interaction with other proteins (Bell et al., 1995; Duan and Horwitz, 2003; Gilks et al., 1993; Grimes et al., 1996; Hock et al., 2003; Person et al., 2003; Zweidler-Mckay et al., 1996)

Expression

Mice carrying a GFP reporter gene within the Gfi1 locus allowed studying in detail Gfi1 expression during differentiation of the different compartments in vivo (Yücel et al., 2004; Zeng et al., 2004). Gfi1 plays a major role in the stem cell fraction, B-, T- and myeloid compartment, whereas it is relatively low expressed in the megakaryocytic-erythroid compartment. In this cell population, the Gfi1 paralogue Gfi1b exerts important functions. To facilitate the overview we will describe the expression for each compartment separately.

Hematopoietic stem cells and early progenitors

All blood cells originate from hematopoietic stem cells (HSCs). These cells have a high self-renewal capacity and upon cell division, either one HSC gives rise to two HSC daughter cells or to one HSC and one so-called Multipotential Progenitors (MPPs). These MPPs differentiate via MPP1, MPP2 and MPP3 to the different progenitors of the myeloid, erythroid, megakaryocytic and lymphoid compartments. Gfi1 is present in HSCs, albeit at low levels compared to HSC progeny such as MPP1 and MPP2 (measured in Gfi1: GFP knockin reporter mice (Khandanpour et al., 2010b).

Myeloid compartment

MPPs can differentiate to so called common myeloid progenitor cells (CMPs), which in turn give rise to either megakaryocyte-erythrocyte progenitors (MEPs) or granulocytic monocytic progenitors (GMPs). GMPs develop either into cells of the monocytic or granulocytic lineage. Gfi1 expression increases upon differentiation of CMPs towards GMPs and finally to granulocytes (Zeng et al., 2004). Yet, commitment of CMP towards MEPs and the mature erythroid and megakaryocytic compartment is accompanied by increasingly lower level of Gfi1. In this fraction, the paralogue Gfi1b plays a more important role (Vassen et al., 2007).

B-cells

The common lymphoid progenitors (CLPs) are thought to be one of the earliest B-cell precursors. During early B-cells differentiation, Gfi1 is expressed highest in CLPs and upon differentiation of CLPs into the different more mature B-cell progenitor fractions, Gfi1 expression is gradually down regulated and it is hardly detectable in immature IgM positive B-cells (Yücel et al., 2004; Zeng et al., 2004). However, upon antigen stimulation, mature B-cells induce expression of Gfi1 (Igwe et al., 2008; Rathinam and Klein, 2007; Rathinam et al., 2008).

T-cells

T cells originate in the thymus, where they develop from early lymphoid progenitors (ELPs) that migrate from the bone marrow to the thymus where they become early thymic progenitors (ETPs). ETPs differentiate via various CD4, CD8 double negative (so called "DN") stages to double positive (DP, CD4+, CD8+) cells to single positive (CD4+, CD8+) cells (Awong et al., 2010; Dervovic and Zúñiga-Pflücker, 2010; Holmes and Zúñiga-Pflücker, 2009; Michie et al., 2007; Wang et al., 2010; Zúñiga-Pflücker, 2009; Zúñiga-Pflücker and van den Brink, 2007). During these developmental stages, Gfi1 expression is differentially regulated. A peak of expression is observed in DN3 cells at the time of beta selection (Yücel et al., 2004), suggesting that Gfi1 plays a role in this first receptor mediated selection process during pre T-cell development. In peripheral T-cells, Gfi1 expression is lower than in thymocytes, but is still detectable and can be induced upon stimulation of the T cell receptor by antigen.

Outside the hematopoietic system

Gfi1 is also expressed in sensory epithelia such as inner ear hair cells, in specific cells of the retina, the intestinal and lung epithelia and in the central nervous system in Purkinje cells (see below).

Localisation

Gfi1 is localized in the cell nucleus and immune fluorescence staining demonstrates a typical dot-like pattern of distribution. Occasionally Gfi1 can be found at the nuclear membrane. These patterns vary whether endogenous or over-expressed Gfi1 is detected.

Function

The molecular function of Gfi1 is that of a DNA-binding transcriptional repressor. A target gene sequence has been defined (Gilks et al., 1993; Zweidler-Mckay et al., 1996) and a number of target genes have been validated by different groups (see below under "Biolocigal role"). By binding to target gene promoters Gfi1 can recruit a number of cofactors that modify histone H3 N-terminal ends to the effect of transcriptional repression. The best characterized co-factors are histone deacetylases (HDAC1; HDAC2; HDAC3), histone methyl transferases (G9a) and histone de-methylases (LSD1 and the LSD1-CoRest complex). It has been proposed that Gfi1 can initiate transient transcriptional silencing via histone deacetylation and de-methylation in particular at H3K4, but can also induce more permanent repression by

recruiting G9a, which mediates the di-methylation of H3K9. It is possible that other methyl transferases are recruited such as SUV39H1 that induce H3K9 trimethylation and heterochromatin formation, which leads to permanent gene silencing (Saleque et al., 2007; Duan et al., 2005).

- Biological role

The generation of constitutive and conditional Gfi1 deficient mouse strains has helped to elucidate the biological role that Gfi1 plays in the hematopoietic system. Similar to the approach in the passage describe above, we will describe the role of Gfi1 in the different hematopoietic compartments.

Hematopoietic stem cells

$Gfi1^{-/-}$ HSCs are characterized by their severely disturbed self-renewal and their inability to reconstitute hematopoietic lineages in a transplanted host (Hock et al., 2004; Möröy, 2005; Zeng et al., 2004). Two physiological functions of Gfi1 may explain these observations. Gfi1 restricts HSC proliferation by controlling the expression of the negative cell cycle regulator waf/cip1 ID: 139>. The mechanisms underlying this regulation are unclear, but two independent studies confirmed that Gfi1 deficient HSCs undergo more cell cycling and express reduced levels of $p21^{waf/cip1}$ compared to HSCs from wt mice. It is postulated that this increased proliferation impairs the function of $Gfi1^{-/-}$HSCs (Hock et al., 2004; Zeng et al., 2004). In addition, Gfi1 was found to be critical to protect HSCs against stress-induced apoptosis (e.g. induced by transplantation). In support of this, expression of a Bcl-2 transgene that counteracts apoptotic signals rescued partially the defects of Gfi1 deficient HSCs (Khandanpour et al., 2010a).

Myeloid cells

Gfi1 plays an important role in myeloid differentiation. $Gfi1^{-/-}$ mice have increased numbers of myeloid precursors (CMPs, GMPs) (Horman et al., 2009; Zeng et al., 2004) with an increased expression of Hoxa9, Pbx or Meis1. Gfi1 seems to be required to down regulate Hoxa9, Pbx1, Meis 1 expression to ensure a proper differentiation from CMPs to GMPs and finally to neutrophil granulocytes. Moreover, Gfi1 represses the expression of PU.1, CSF1R, miR-21, miR-196b, Egr-Nab and Id2, mostly by directly binding to their promoters. All of these genes are implicated in myeloid development (Li et al., 2010; Spooner et al., 2009; Velu et al., 2009). Loss of Gfi1 leads to de-repression of these genes favoring a development towards the monocytic lineage and inhibiting the development of granulocytes. Consequently, $Gfi1^{-/-}$ mice are neutropenic, lack granulocytes and display a strong expansion of atypical $Mac\text{-}1^{+}$, $Gr1^{lo}$monocytes (Karsunky et al., 2002). The requirement of Gfi1 for the formation of neutrophil granulocytes is corroborated by a report that human patients with neutropenia carry germline mutations in the coding region of Gfi1 affecting the zinc finger regions (Person et al., 2003).

B-cells

Gfi1 plays a role in the early stages of B-cell differentiation. Evidence for this comes mainly from the study of Gfi1 deficient mice that show reduced numbers of CLPs (an early yet not fully committed B-cell lineage progenitor) and a defective maturation of early B-lineage precursors, which leads to a reduced number of B-220+ cells in bone marrow and spleen (Rathinam et al., 2008). One important factor in the early steps of B-cell development is the cytokine Interleukin 7 (IL-7) and its receptor IL-7R. Gfi1 interferes with IL-7/IL-7R signaling by regulating the activity of Janus kinases (Jak) and subsequently the phosphorylation of STAT5, which is an important downstream signaling molecule in the IL-7R pathway. While the details of this regulatory function remain to be elucidated, Gfi1 seems to be involved in the control of the expression level of the Jak inhibitor SOCS3 (Rathinam and Klein, 2007; Yasukawa et al., 2000).

Besides the IL-7R pathway, Gfi1 also regulated the expression of PU.1, which is another transcription factor with an important role in both myeloid and lymphoid development. PU.1 enables precursors to differentiate into certain lineages and high levels favor myeloid over lymphoid development. Gfi1 regulates the function of PU.1 by two mechanisms: Gfi1 can form a complex with PU.1 and inhibits binding of PU.1 to its target genes. In addition, Gfi1 also binds independently of PU.1 to PU.1 target genes and represses their transcriptional activation (Dahl et al., 2007; Spooner et al., 2009; Wilson et al., 2010). In the absence of Gfi1, PU.1 is thus hyperactive and drives precursors into the myeloid lineage while impeding the formation of lymphoid cells, in particular B-cells. By reducing PU.1 protein quantity (e.g. heterozygosity of PU.1) in Gfi1 deficient mice, B-cell differentiation defects can be overcome (Spooner et al., 2009). Based on these and other findings, interactive regulatory networks have been proposed, in which Gfi1 favors B-cell development whereas PU.1 and Egr1 inhibit B-cell development and favor monocytic differentiation (Spooner et al., 2009).

PU.1 and EGR1/Nab also induce the expression of different Id (Inhibitor of DNA binding) proteins. Gfi1 on the other hand represses Id2 expression. Thus Gfi1-deficiency correlates with increased Id1 and Id2 levels in particular thymocyte subsets (Yücel et al., 2003). Ids mainly function by restricting access of the transcription factor E2A to DNA. E2A, in conjunction with EBF, is required to induce B-cell specific factors such as Pax5 or Rag1/Rag2. Hence, high expression of Id proteins contributes to the Gfi1 deficiency phenotype (Spooner et al., 2009), as they impede up-regulation of these important B-lineage regulators. Consequently knock-down or heterozygosity of Id2 in Gfi1 deficient mice rescues partially the disturbed differentiation of B-cells. To fulfill all these regulatory tasks, Gfi1 itself has to be induced upon initiation of B-

cell lineage commitment. Ikaros, another transcription factor important for early B-cell differentiation, acts upstream of Gfi1 and ensures its up-regulation after commitment of the progenitors to the lymphoid lineage (Spooner et al., 2009).
Gfi1 is also required for the maturation and activity of B-cells. Gfi1 restricts an overshooting of antibody production after antigenic stimulation. When challenged with different antigens in-vivo, Gfi1 deficient mice exhibited a higher number of PNA/CD19+ germinal center B-cells in the spleen and accentuated production of antigen specific IgG2a and IgG2b antibodies (Igwe et al., 2008). On the molecular level, increased level of TGF beta might explain this, as TGF beta promotes expression levels of different IgG subtypes. In accordance with disturbed regulation of the immune response, Gfi1 deficient mice are characterized by an increased predisposition to develop autoimmune diseases (Park et al., 2005; Snapper et al., 1993).

T-cell development

Gfi1 deficient mice have a reduced number of thymocytes compared to littermate controls (Karsunky et al., 2002; Yücel et al., 2003; Yücel et al., 2004). This is the result of a disturbed pre T-cell differentiation at different stages. Gfi1 is required for the proper transition from the DN1 to DN2 stage, to control beta selection in DN3 cells and to promote formation of DP cells (Yücel et al., 2003; Yücel et al., 2004). As in the case of B-cell development, one explanation for these deficiencies is a function of Gfi1 in the regulation of IL-7R signaling. One hypothesis would be that unrestricted SOCS3 signaling in the absence of Gfi1 would disturb IL-7 receptor signaling in thymocytes, but this remains to be shown. Also similar to the B-cell fraction, an unbalanced expression of PU.1, Egr and Id proteins may affect the differentiation of the ETPs to the different DN stages (Li et al., 2010; Spooner et al., 2009). Other pathways that are important in pre T-cell development such as those initiated by Notch, Wnt or the pre-TCR itself remain to be analyzed in Gfi1 deficient mice to gain more insight into the full spectrum of Gfi1's regulatory role in this compartment.
Gfi1 is also implicated in the differentiation and activation of the mature peripheral T-cell subpopulations. Generally, Gfi1 is important for the proper function and development of CD4 T-cells (Pargmann et al., 2007). And more specifically, within the CD4 T-cell fraction, Gfi1 plays a major role in Th2 cells. Loss of Gfi1 is associated with decreased number of Th2 cells and increased number of Treg-cells (Ichiyama et al., 2009; Shinnakasu et al., 2008; Zhu et al., 2006).

- Functions of GFI1 outside the hematopoietic system

Outside the hematopoietic system, Gfi1 is required for the integrity and function of inner ear hair cells and in the central nervous system for Purkinje cells. In addition Gfi1 plays a role in the lineage decision process during intestinal cell differentiation (Bjerknes and Cheng, 2010; Hertzano et al., 2004; Shroyer et al., 2005; Tsuda et al., 2005; Wallis et al., 2003). Gfi1 deficient mice show defects in all these cell lineages, but the degeneration of inner ear hair cells is most dramatic since it leads to deafness of the animals (Hertzano et al., 2004; Wallis et al., 2003).

Mutations

Germinal

In patients suffering from neutropenia, two types of mutations have been discovered to occur in the region of the Gfi1 gene coding for its zinc finger domains. This leads to amino acid replacements at two positions; N382S and K403R, respectively. Similar to the neutropenic Gfi1 deficient mice, these patients also display an increased number of aberrant monocytes (Person et al., 2003).
In addition to these mutations, a variant form of Gfi1 (GFI36N) was found that differs from the more common GFI136S form at amino acid position 36, where a serine is replaced by an asparagine. The 36N variant predisposes to the development of acute myeloid leukemia (AML) with an 1.6 times elevated risk for the carriers to develop the disease. On the molecular level, GFI136N features a different nuclear localization than the more common form of GFI (GFI136S). Probably as a result of this aberrant localization, GFI136N is no longer able to interact in-vivo with specific binding partners or co-factors such as AML1/ETO (Khandanpour et al., 2010c).

Implicated in

Lung cancer

Note

Gfi1 might also be linked to lung cancer, as abundant Gfi1 expression was reported in a certain subtype of lung cancer (small cell lung cancer). In line with this observation, constitutive over expression of Gfi1 enhances the malignancy of lung cancer cells (Kazanjian et al., 2004).

Prostate cancer

Note

A role of Gfi1 in the pathogenesis of prostate cancer has been proposed. It was reported that 25-Dihydroxyvitamin D (1,25D) inhibits growth of prostate cancer cells. The cellular synthesis of 25-Dihydroxyvitamin D (1,25D) depends on the presence of 25-hydroxyvitamin D 1alpha-hydroxylase (CYP27B1). However the expression of this enzyme is repressed in prostate cancer cells. One possible explanation for this repression is that Gfi1, which binds to the promoter of this enzyme, is over expressed and thus represses its expression thereby contributing to prostate cancer development (Dwivedi et al., 2005; Dwivedi et al., 2007).

Human leukemia

Note

Gfi1 might be involved in the pathogenesis of chronic myeloid leukemia (CML). CML has a tri-phasic course and upon transformation from the least aggressive stage (chronic phase) to the most aggressive stage (blast crisis) an upregulation of Gfi1 expression was reported (Huang et al., 2010).

Murine leukemia

Note

Infection of mice with the non-acute transforming Moloney-type retrovirus (MoMuLV) leads to development of clonal T-cell lymphomas (Mikkers and Berns, 2003). Common proviral insertions that are selected for during tumorigenesis typically include genomic areas close to neighbouring oncogenes. The Gfi1 gene is one of the most frequent common insertion sites in MoMuLV induced tumors, comparable to sites close to the c-Myc and Pim-1 oncogenes (Scheijen et al., 1997; Schmidt et al., 1998; Zörnig et al., 1996). This suggested a causal role of Gfi1 in T-cell tumorigenesis. Constitutive over expression of Gfi1 accelerated the onset of T-cell leukemia in conjunction with the expression of other oncogenes such as Pim1 or L-Myc (Schmidt et al., 1998; Zörnig et al., 1996). These early experiments established the role of Gfi1 as a dominant oncogene in T-cell tumorigenesis.

Autoimmune diseases

Note

Loss of Gfi1 induces a number of autoimmune diseases in mice, which can be explained by the loss of function of Gfi1 deficient B- and T-cells. So far, a role for Gfi1 in human autoimmune diseases has yet to be found (Rathinam et al., 2008).

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