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Review

Growth factor independence 1 (Gfi1) as a regulator of lymphocyte development and activation

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ABSTRACT

T- and B-lymphocytes are important elements in the immune defense repertoire of higher organisms. The development and function of lymphoid cells is regulated at many levels one being the control of gene expression by transcription factors. The zinc finger transcriptional repressor Gfi1 has emerged as a factor that is critically implicated in the commitment of precursor cells for the lymphoid lineage. In addition, Gfi1 controls distinct stages of early T- or B-lymphoid development and is also critical for their maturation, activation and effector function. From many years of work, a picture emerges in which Gfi1 is part of a complicated, but well orchestrated network of interdependent regulators, most of which impinge on lymphoid development and activation by transcriptional regulation. Biochemical studies show that Gfi1 is part of a large DNA binding multi-protein complex that enables histone modifications, but may also control alternative pre mRNA splicing. Many insights into the biological role of Gfi1 have been gained through the study of gene deficient mice that have defects in B- and T-cell differentiation, in T-cell selection and polarization processes and in the response of mature B- and T-cells towards antigen. Most importantly, the defects seen in Gfi1 deficient mice also point to roles of Gfi1 in diseases of the immune system that involve auto-immune responses and acute lymphoid leukemia and lymphoma.

1. General introduction

Lymphoid cells play several important roles in the immune defense and are indispensable for a healthy organism [1]. In addition to the large spectrum of myeloid cells and macrophages of the innate immune system, lymphocytes represent the second pillar of the immune system and are responsible for the adaptive or acquired immune system [2]. All lymphoid cells develop from precursor cells that reside and develop in the bone marrow or in the thymus and are produced as all other cells of the immune system by hematopoietic stem cells (HSCs) [3,4]. Two types of lymphocytes can be distinguished: T- and B-cells. T-cells originate in the thymus from precursors that travel from the bone marrow through the bloodstream and settle in the thymus [3]. The early thymic T-cells give rise to effector cells that mainly reside in the spleen and lymph nodes but are also found dispersed in tissues. In contrast, B-cells develop in the bone marrow and exert their function in various peripheral lymphoid organs. Both B- and T-cell circulate in the blood with low frequencies. B- and T-cells express cell surface receptors that enable the recognition of foreign antigens, however B-cells are able to produce antibodies, which are soluble forms of their receptor, whereas T-cells maintain their receptor on the cell surface [5]. The ability of these cells to produce an extremely large repertoire of antigen receptors, which they realize by rearranging and altering their genome, is a particular feature of lymphocytes that sets them apart from all other mammalian cells. To generate the antibody and T-cell receptor repertoire B- and T-cell undergo V(D)J recombination that ensures that all foreign antigen structures are met with a cognate receptor [6]. B-cells are able to further refine the affinity of their receptor and the properties of their antibodies by somatic hypermutation and class switch recombination [7].

Lymphocytes also play a crucial role in the onset and development of autoimmune diseases and are crucial for immune surveillance of malignancies and a disrupted lymphoid development and an altered function of lymphoid cells is causative for the above-described diseases [8,9]. It is therefore important to gain complete insight into the mechanisms underlying the normal development and function of lymphocytes to better understand malfunction of these cells in diseases. The knowledge gained on lymphoid development and function will form the basis to develop new strategies to treat a large spectrum of diseases. In this review we will focus on the role of the transcriptional repressor

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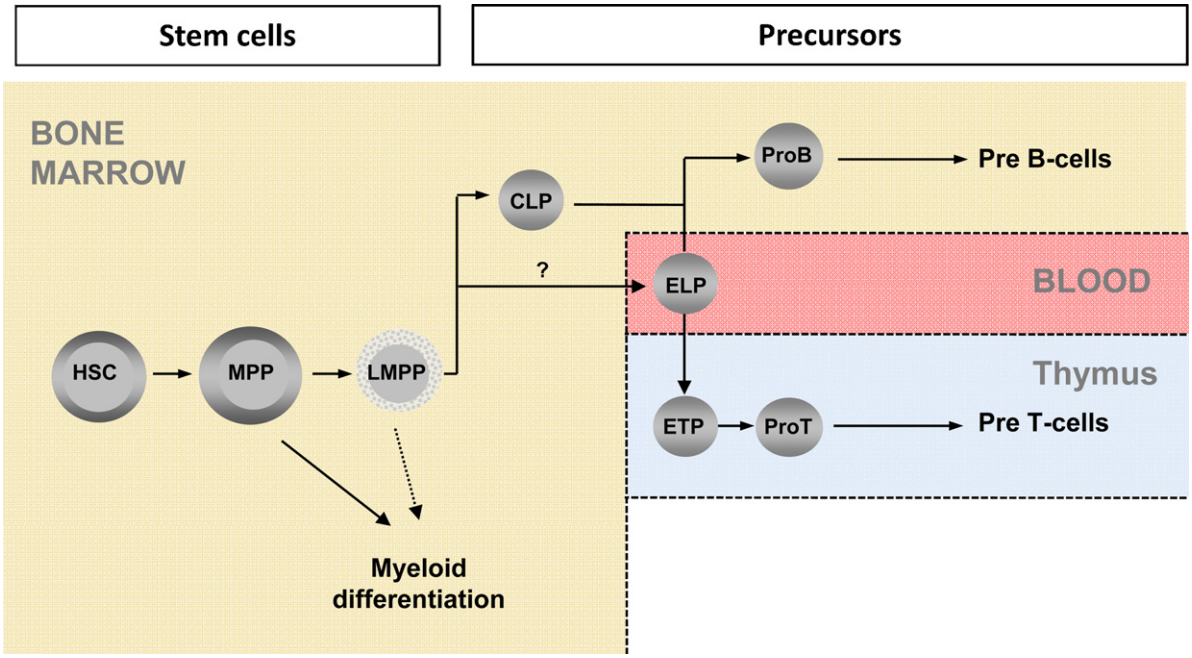

Fig. 1. Expression of Gfi1 during lymphopoiesis. Hematopoietic stem cells (HSC), which reside in the bone marrow give rise to multipotent progenitor cells (MPP) that gradually loose self-renewal capacity and at the same time gain lineage commitment (LMPP). Depicted is the part of hematopoiesis that leads to the development of lymphoid cells in thymus, and peripheral lymphoid organs such as spleen and lymph nodes. Gfi1 is expressed at various levels in all depicted cells.

Growth factor independence 1 (Gfi1), which is expressed during lymphopoiesis (Fig. 1) and not only controls the development of lymphoid cells from the early stages to mature lymphoid cells, but also exerts a role in the process following antigen-mediated activation.

2. Biochemical function of Gfi1

Gfi1 is a DNA binding transcriptional repressor protein with an important role in several hematopoietic lineages. It is expressed in HSCs and in early lymphoid and myeloid precursors. At later stages in hematopoiesis Gfi1's expression is differentially regulated [10–23] and any interference with this regulation affects the correct development and function of both B- and T-lymphocytes [24–29]. Gfi1 is a small nuclear protein of about 55 kDa that contains six c-terminal C_2H_2-type zinc-finger domains and an N-terminal SNAG domain critical for its repressor activity (Fig. 2). Zinc fingers 3–5 of Gfi1 are necessary for binding to its cognate consensus DNA recognition sequence taAATCac(t/a)gca, zinc fingers 1, 2 and 6 very likely have a role in the interaction with other proteins [11,19,30–34].

Gfi1 exerts its role as transcriptional repressor by interacting with a number of histone modifying enzymes [33,35,36]. These enzymes and Gfi1 are part of a larger protein complex, which binds to a specific promoter area defined by the Gfi1 binding site. The recruitment of this complex by Gfi1 to specific target gene promoters leads to transcriptional silencing at this locus. The main components that Gfi1 can recruit to target genes are the histone demethylase complex LSD-1/CoRest, which removes methyl groups from the N-terminal Lysine 4 of histone H3 (H3K4) and the histone deacetlyases HDAC-1, -2 and -3, which remove acetyl groups from various histone H3 residues (Fig. 3). Both demethylation and deacetylation of histones by these enzymes lead to a transcriptional repression, which may be reversible once the complex is dissolved or degraded [33,35,36]. In addition to these well-known histone modifiers other proteins may be contained in the Gfi1 repressor complex, the newly identified Gfi1 binding protein Ajuba may be one of them, although more work is necessary to precisely define the role of Ajuba in connection with LSD-1/Corest and HDACs [37].

In addition to this, Gfi1 can interact the methyl transferase G9a that dimethylates Histone H3 at lysine 9 (H3K9), which in turn can recruit the chromatin protein HP-1 and may lead to a heterochromatinization of the locus [35,36]. This may represent a way to irreversibly silence the locus in contrary to the reversible silencing by the LSD-1/CoRest/HDAC complex [35,36]. A working model has been proposed in which these complexes form in a stepwise manner at Gfi1 target gene promoters (Fig. 3). How the Gfi1 complex is directed to histones and in particular how it is reorganized after DNA replication is an open question, but it can be speculated that other chromatin regulatory elements may be involved. One future question of particular interest is how exactly the repressive action of Gfi1 can be terminated, once this may be needed. Proteasomal degradation may be one mechanism [38], but a role of regulatory RNAs may also have to be considered.

Many examples have been reported where Gfi1 acts as a transcriptional repressor, however two groups have found evidence that Gfi1 can also function as an co-activator in concert with CEBPe or induces expression of the RAS-GRP1 gene [39,40]. However, it remains to be shown how this can be achieved mechanistically and whether it is a direct or indirect effect of Gfi1. In the case of CEBPe and Gfi1, binding of the two proteins to closely spaced binding sites was postulated, but a direct interaction was not shown. Thus, if and how Gfi1 can be implicated in transcriptional activation is also ground for future studies. Other interactions between Gfi1 and regulatory proteins have been reported. The negative regulator of the STAT-signaling pathway, PIAS3, has been shown to bind to Gfi1 and to modulate the response to IL-6, which signals though STAT3 [41]. It remains open, whether the activity of PIAS proteins as E3 ligases for SUMO residues plays a role in this interaction [42,43], but it is attractive to speculate that Gfi1, which has so far not been shown to be sumoylated, may serve as a docking site for other proteins that