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GATA Transcription Factors in Hematological System

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ABSTRACT

The zinc finger DNA binding GATA transcription factors are evolutionarily conserved among animals, plants and some microorganism. In human, there are 6 GATA members have been described: GATA-1/2/3/4/5/6. Among these GATAs, GATA1/2/3 are expressed in both hematopoietic lineage and non-hematopoietic cells while GATA 4/5/6 are expressed in non-hematotopoietic cells, particularly in the development of heart and gut. In this review, we mainly emphasis on only GATA1/2/3 in human blood system. Understanding the normal biological functions and its crucial roles in leukemogenesis of the GATA transcription factors (GATA-1, GATA-2, GATA-3) in hematological system could have implications for diagnosis and potential therapeutic interventions in the future.

Abbreviations: AMKL: Acute Megakaryoblastic Leukaemia; TAM: Transient Abnormal Myelopoiesis; DS: Down Syndrome; MDS: Myelodysplastic Syndromes; HSCs: Hematopoietic Stem Cells; MMCP: Mouse Mast Cell Protease

Introduction

The GATA transcription factors are evolutionarily conserved among animals, plants flies, worms and fungi (Kudla [1-5]). The GATA family of vertebrate DNA binding regulatory proteins is expressed in diverse tissues and at different times of development. Up to date, six members of the GATA family have been characterized (GATA1-6) which are homologous in mammals, avians and amphibians (Laverriere, et al. [6]). Among these GATAs, GATA1/2/3 are expressed in both hematopoietic lineage and non-hematopoietic cells where their pattern of expression is complicated and may exhibit some minor species variation (Orkin, et al. [7-8]). Several findings reported that GATA2 and GATA3 also exhibited significant functions in the central nervous system, skin, prostate, mammary gland and kidney (Grote, et al. [9-13]). The GATA 4/5/6 are expressed in non-hematotopoietic cells, particularly in the development of heart and gut (Orkin, et al. [6,7,14]).

GATA is a zinc finger protein that contains a set of cysteines and/or histidines within a short region of polypeptide chain and binds to a recognition sequence (A/T) GATA(A/G) via the highly conserved C-terminal zinc finger (Wall et al. [7,15,16]). The Zinc finger domain in transcription factors was first discovered in the Xenopus transcription factor IIIA (TFIIIA) (Brown, et al. [17]). In general, transcription factors in this family contain an antiparallel -sheet and -helix. Two cysteines, which are near the turn in the -sheet region and two histidines which are in the -helix, coordinate a central zinc ion in the form of Zn2+ and hold these secondary structures together to form a compact globular domain. A single zinc finger domain binds DNA via a short -helix in the major groove of the B-DNA and wrap around the double helix of DNA (Pevletich [18]). Each finger has a similar way of binding the DNA and makes base contacts with a three-base-pair subside. All GATA transcription factors have a zinc finger in the form Cys-X2-Cys-X17-Cys-X2-Cys. Among the GATA factors, the N-terminal finger exhibits a variety of functional roles. However, the common role of N-terminal in all GATAs is that it is able to interact with Friend Of GATA (FOG) protein (FOX, et al. [19).

GATA-1

The transcription GATA-1 is a key regulator of erythroid and megakaryocytic commitment during hematopoiesis. In contrast, GATA-1 prevents granulocyte-monocyte and lymphoid development (Orkin, et al. [7,20,21]). GATA-1 also expresses in mast cell, megakaryocytes and multipotential myeloid lines (Crotta, et al. [22-24]). Interaction of GATA-1 to FOG-1 (Friend of GATA) via the N-terminal zinc finger co-

factors is necessary for erythroid or negative development. However, there is down regulation of the cofactors that are necessary for granulocyte-monocyte and lymphoid commitment such as PU. 1, PAX5 and IL-7. GATA1 is also involved directly in the survival of the erythroid precursors. Target genes that are involved in cell cycle regulation or proliferation and differentiation are activated by GATA1 (Chang, et al. [25-27]). Human diseases have been linked to mutations in the GATA1 N-terminal activation domain and the N-zinc finger. Acquired mutations in GATA1 are associated with acute megakaryoblastic leukaemia (AMKL) and transient abnormal myelopoiesis (TAM) in children with Down syndrome (DS). In fact, GATA1 is essential for megakaryocyte and platelet development. Therefore, dysregulation of GATA1 expression may lead to thrombocytopenia or platelet disorders. (Wechsler, et al. [21,28]).

GATA-2

The gene of GATA-2 is located in mouse chromosome 6 (Ciciotte, et al. [29]) and is highly expressed in the ventral region of the embryo by the end of gastrulation and later is expressed in the blood island region and the central nervous system (Kelly, et al. [30]). GATA-2 mRNA is expressed in both hematopoietic cells, e.g. hematopoietic stem cells, mast cells, megakaryocytes, erythroblasts and neutrophils, and other cell types, e.g. embryonic brain cells and endothelial cells (Yamamoto, et al. [12,31-35]). GATA-2 transcription factor also exhibited crucial functions in organogenesis including gonad, placenta, kidney, prostate, ear, tissue, pituitary and thyroid gland (Tremblay, et al. [5]). In the hematopoietic lineage, the transcription factors GATA-1 and GATA-2 show restricted and largely overlapping expression profiles, but GATA-2 is uniquely expressed in early hemopoietic progenitors and mast cells. GATA-2 plays role in early murine hematopoiesis and is consistent with its expression both in early Xenopus embryos and in mammalian hematopoietic progenitors (Zon, et al. 32,36-38]). GATA-2 also has been found to appear as a phosphoprotein in hematopoietic progenitor cells, and stimulation of progenitors with interleukin-3 (IL-3) results in enhanced phosphorylation of GATA-2 which occur within 5 min (Towatari, et al. 39]).

GATA2 is critical for the maintenance and function of hematopoietic stem cells. Mutations in GATA2 have been linked to familial predisposition to myelodysplastic syndromes (MDS) and AML. These mutations often affect the self-renewal capacity and differentiation potential of hematopoietic stem cells (HSCs) (Wlodarski, et al. [21,40]). Up to date, GATA2 mutation have been involved in some complex clinical syndromes overlapping features which include familial myelodysplastic syndrome (MDS), AML, Mono MAC syndrome characterized by peripheral monocytopenia, Emberger syndrome (primary lymphedema with MDS), and B- and NIC-cell lymphocytopenia, increased susceptibility to mycobacterium infection and a predisposition to acute myeloid leukaemia and myelodysplastic syndrome. Patients with familial AML-MDS associated with GATA2 mutation have increased risks for severe infections, particular intracellular organisms. (Abunimye, et al. [21]).

GATA-2 and Mast Cells

Mast cells are derived from hematopoietic stem cells and need GATA-2 for maintenance of their early progenitors (Tsai, et al. [41]). GATA-2 appears at high levels in hematopoietic stem cells and mast cells, especially proliferating mast cells (Martin, et al. [42-45]). In general, the C-terminal zinc finger protein is required for binding while the N-terminal finger assists with it to provide full stability and specificity of binding (Leonard, et al. [46]). In mast cells, there are several GATA-binding sites in cis regulatory elements in promoters and in enhancers of expressed genes including the IgE receptor chain enhancer and chain promoter, the mast cell chymase promoter, mouse mast cell protease (MMCP) promoters, the mast cell specific IL-4 enhancer and carboxypeptidase A promoter (Weiss, et al. [32,47,48]).

Although GATA-1 and GATA-2 have been reported to co-express in mature mast cells (Zon, et al. [32-33]), GATA-1 cells derived from yolk sac or fetal liver of GATA-1+/- chimeric mice can differentiate into mast cells at normal frequency and with a similar phenotype as the wild type mast cells suggesting that GATA-1 is largely dispensable for mast cell development (Pevny, et al. [49]). Introduction of GATA-2 antisense in ES cells abrogated erythromyeloid colony-forming ability and this hematopoiesis-deficient phenotype could be rescued by ectopic expression of full-length GATA-2. In addition, GATA-2 knock out embryonic stem cells show a profound deficiency of mast cell colonies, and GATA-2 knock out embryos die with severe anemia. These studies suggest the important role of GATA-2 in early hematopoiesis and mast cell development (Tsai, et al. [41,50,51]). Recently, GATA2 promotes robust gene transcription to maintain mast cell identity and respond to antigenic stimulation by binding to super-enhancer regions with dense GATA2 binding sites available at key mast cell genes (Li, at al. [52]).

GATA-3

GATA-3 is found exclusively in the commitment to early T cell durring T cell lineage development of hematopoietic lineage and immune regulation. GATA-3 also plays a role in the long-term self-renewal of HSCs through the control of cell cycle entry (Frelin, et al. [53,54]). In addition, the development of CD4+ Th2 cells can be promoted by GATA3. Increased expression of GATA3 identifies a biologically distinct subgroup in peripheral T cell lymphoma associated with overall poor prognosis (Abunimye, et al. [21]). The gene expression profile of the GATA3 subset of peripheral T cell lymphoma also identifies increase expression of Th2 associated transcripts. This observation provides insight in understanding the pathogenesis and potential oncogenic pathways for the peripheral T cell lymphoma. Interestingly, aberrant expression of the T cell transcription factor GATA3 is observed in B cell-derived Hodgkin Reed-Sternberg tumor cells. The dysregulated GATA3 expression is likely due to constitutive binding of NFkB and Notch-1 pathways to GATA3 promoter elements (Abunimye, et al. [21]).

Aberrant expression or dysregulation of GATA3 has been implicated in T-ALL. In some cases of T-ALL, GATA3 expression levels may be altered or mutations affecting GATA3 function can contribute to leukemogenesis. These alterations could disrupt normal T-cell development and differentiation, leading to the uncontrolled proliferation of leukemic T cells. GATA3 is crucial for directing T-cell differentiation towards the T-helper 2 (Th2) cell lineage. Its dysregulation might influence the balance of T-cell subsets, potentially impacting immune responses and contributing to leukemic transformations (Hosoya, et al. [21,55]).

Conclusion

GATA1/2/3 exhibit many biological roles in both functions in hematological system and leukemogenesis which affect human health and diseases. Understanding the normal biological functions and its crucial roles in leukemogenesis of the GATA transcription factors (GATA-1, GATA-2, GATA-3) in blood system could have implications for diagnosis and potential future therapeutic interventions.

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