Unfriendly protein of GATA1 and mechanisms of bone marrow failure

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Received: March 14, 2024.
Accepted: March 29, 2024.
Early view: April 11, 2024.

https://doi.org/10.3324/haematol.2024.285041

GATA1 is a transcription factor that plays a major role in normal hematopoiesis, but is also associated with bone marrow failure and hematopoietic malignancies. In red blood cells, GATA1 expression is peaked at the stage of early proerythroblast stage,[1] and activates globin genes and hemoglobin synthase, which are critical for red blood cell differentiation.[2] It has also been shown to protect developing erythroid cells by activation of erythropoietin receptor signaling and transcription of anti-apoptotic genes.[3] During thrombopoiesis, GATA1 is up-regulated from the hematopoietic stem cell stage through common myeloid progenitor, megakaryocyte erythroid progenitor, to megakaryocyte.[4] During thrombopoiesis, *GATA1* promotes expression of megakaryocyte-associated genes (e.g. *GPIBA*, *GPIBB*, *PF4*, *MPL*, and *NF-E2*) and endomitosis.[5]

GATA1 belongs to the GATA family of transcription factors. This group of transcription factors is involved in embryogenic development and in various post-embryonic tissue functions. The GATA transcription factors have two highly conserved zinc finger DNA binding domains that recognize and bind specifically to the nucleotide sequence (A/T)GATA(A/G) in regulatory regions of the genes.[6] The *GATA1* gene is on the X chromosome and is composed of 5 coding exons. The mRNA translates two alternative isoforms. One is 413 amino acid long that contains an N-terminal transactivation domain and two downstream zinc finger domains (ZF). The second is a short protein that lacks the N-terminal transactivation domain, and has low functionality and is unable to support erythropoiesis. GATA1 protein regulates transcription of lineage-specific genes in combination with co-factors such as FOG1 and SCL.[1,7]

The first report of an inherited bone marrow failure syndrome caused by a *GATA1* mutation was in 2000.[8] The patients in this study had thrombocytopenia and anemia with a V205M mutation in GATA1, which impedes binding to FOG1. Since then, GATA1 was found to be mutated in patients with inherited bone marrow failure syndromes featuring either isolated anemia, or combined anemia and thrombocytopenia or isolated thrombocytopenia. Mutations in the N-terminal transactivation domain that lead to a short *GATA1* isoform and protein causes an inherited bone marrow failure syndrome with predominantly anemia with partial or complete Diamond-Blackfan anemia (DBA) phenotype.[9] In contrast, mutations in the zinc finger domains were reported in inherited bone marrow failure syndromes with either thrombocytopenia or anemia or both. Many inherited GATA1 missense mutations have been identified in the N-terminal zinc finger domain, which impair the ability of GATA1 to bind FOG1 or chromatin and result in disruption of erythropoiesis and megakaryopoiesis. Insertions, deletions and point mutations that delete exon 2 are seen in abnormal myelopoiesis and myeloid leukemia in Down syndrome and are not related to GATA1-associated anemia/thrombocytopenia.

Diamond-Blackfan anemia is mostly associated with mutations in ribosome proteins or ribosome-related factors. Nevertheless, the association of both ribosome protein mutations and GATA1 mutations with DBA is not completely surprising since mutations in ribosomal protein have been shown to reduce translation of GATA1 mRNA.[10] It is noteworthy that the phenotype of patients with GATA1-associated DBA is slightly different from that with ribosome protein-associated DBA: GATA1-associated DBA more often present with hypocellular bone marrow, dysplastic erythropoietic cells and dysplastic megakaryocytes, and less often with reticulocytopenia and paucity of erythroid cells.[9]

As seen above, much has been learnt about the mechanism of anemia and thrombocytopenia caused by mutations in the N-terminal domain of *GATA1*. However, little is known about the mechanism of hematopoietic defects in patients with mutations in the C-terminal domain of *GATA1*. Using whole exome sequencing, Lu and colleagues found a novel frameshift and truncation mutation (c.1162delGG, p.Leu387Leufs*62) in the C-terminal domain of GATA1 in

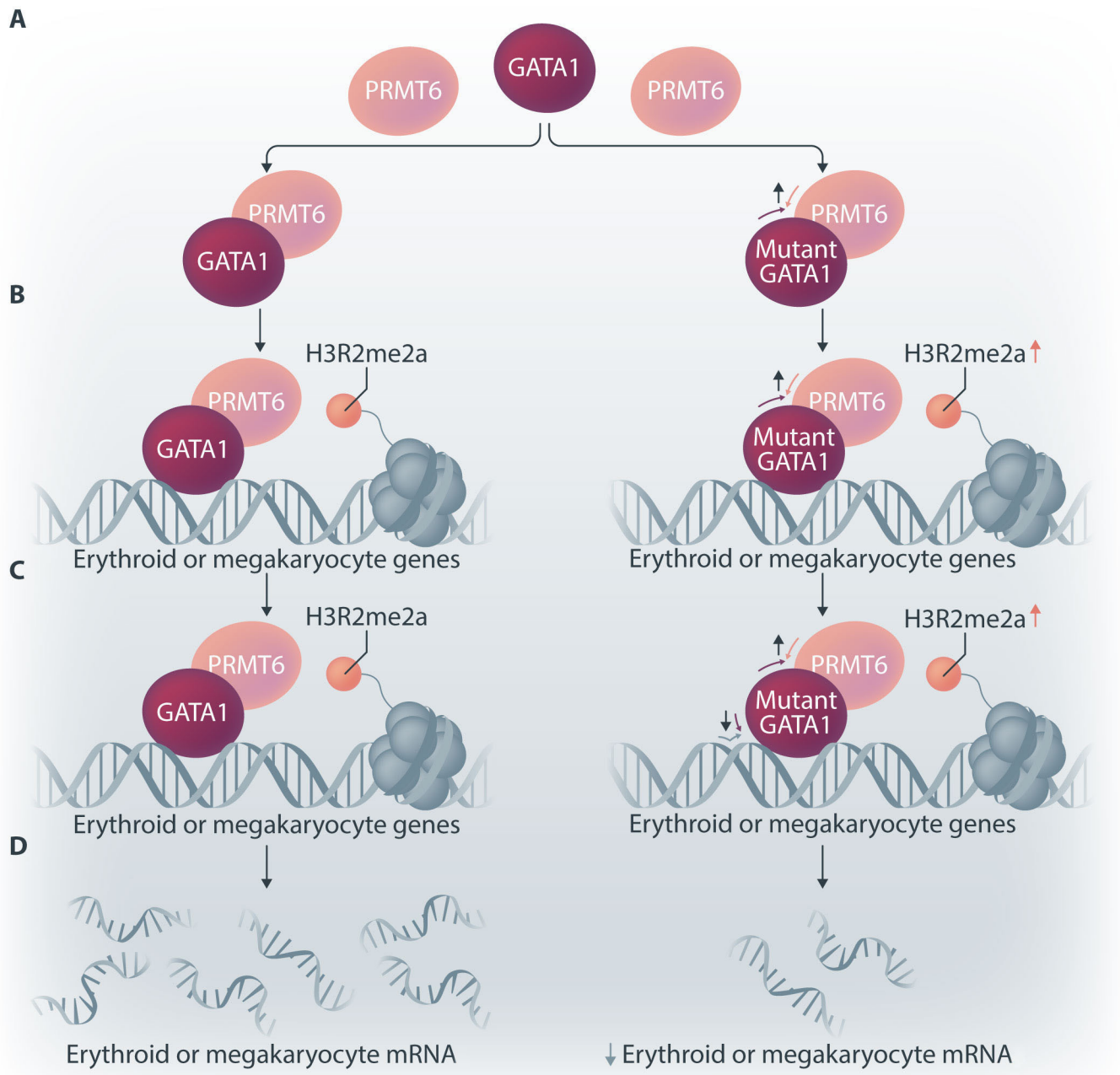

Figure 1. Consequences of the *GATA1* Leu387fs mutation on transcription. (A) Increased binding of PRMT6 to the mutant GATA1 compared to the wild-type GATA1. (B) Increased repressive histone modification H3R2me2a, caused by PRMT6. (C) Reduced GATA1 binding to erythroid and megakaryocytic differentiation genes in cells with mutant GATA1. (D) Reduced transcription of erythroid and megakaryocyte mRNA in cells with mutant GATA1.

a patient with severe congenital anemia and intermittent thrombocytopenia.[11] To interrogate the mutation effect on hematopoiesis, the authors removed the wild-type *GATA1* in cell lines and introduced the novel mutation by CRISPR/Cas9, or knocked down GATA1 by shRNA. Introduction of the mutation decreased transcription of GATA1-associated erythroid genes and led to defective differentiation and increased apoptosis of erythroid cells. In addition, the mutation caused a block in megakaryocyte differentiation and reduced expression of platelet function genes. Interestingly, the authors found that PRMT6, a histone modification factor that normally suppresses transcription activity, can bind to N-terminal zinc finger domain as well as the c-terminal domain of the wild-type and mutant GATA1, though the binding to the mutant *GATA1* Leu387fs was stronger. In the GATA1 mutant cells, the association of PRMT6 with GATA1 enhanced the binding of PRMT6 to transcriptional regulatory elements of GATA1-target genes, and increased the repressive modification H3R2me2a by PRMT6 in these regulatory elements, resulting in reduced transcription of erythroid and megakaryocytic genes. Importantly, treatment of GATA1 mutant cells with a PRMT6 inhibitor partially rescued transcription and erythroid differentiation.

The work of Lu and colleagues provides novel information about the function of the C-terminal domain of GATA1, and the mechanism of disease caused by disruption of this region. This work also sheds light on the function of PRMT6 in normal and failed erythropoiesis and megakaryopoiesis.

Disclosures

No conflicts of interest to disclose.

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