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POSTER ABSTRACTS

602.MYELOID ONCOGENESIS: BASIC

Elucidation of the Unique Function of GATA1s in the Development of Transient Abnormal Myeloproliferative Disorders

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Transient abnormal myeloproliferative disorder (TAM) is a pre-leukemic condition that occurs at birth in children with Down syndrome. The responsible gene of TAM, *GATA1*, is a hematopoietic transcription factor integral to hematopoiesis. The *GATA1* gene has two translation start sites, giving rise to two protein variants: GATA1-fl, a full-length protein, and GATA1s, an isoform lacking the N-terminal domain. Notably, TAM blasts express only the GATA1s due to a mutation in the *GATA1* gene, as opposed to normal cells which express both proteins. This implies that the precancerous state is not triggered by the production of an aberrant protein butrather by the absence of the full-length protein and the exclusive expression of the minor isoform protein also present in normal cells. This is in stark contrast with the functions of many other oncogenes. Thus, the prevailing view is that TAM development involves a "loss of function" due to deficiency of GATA1-fl.
However, some studies suggest that GATA1s may have unique functions that actively drive the TAM phenotype. Because of these conflicting findings reported, the precise pathomechanism of TAM development remains elusive, despite the identification of the responsible gene. To address this, we analyzed the function of GATA1s using an induced pluripotent stem cell (iPSC) model of TAM. We previously examined the effect of increasing GATA1s expression levels during early hematopoietic differentiation stage by stage using the TAM-iPSC model. We found that, in the absence of GATA1-fl protein, overexpression of GATA1s in early hematopoietic progenitor cells (HPC) shifted megakaryocytic differentiation toward myeloid lineage, intensifying TAM severity by expanding progenitor cells. These findings suggest that GATA1s has a unique function distinct from that of GATA1-fl.
In this study, we investigated the function of GATA1s proteins as transcription factors using chromatin immunoprecipitation sequencing (ChIP-seq). Our results demonstrated that genes involved in hematopoiesis or cell proliferation belong to the gene cluster to which overexpressed GATA1s (O/E GATA1s) binds solely in the absence of GATA1-fl at the early HPC stage. Gene Ontology (GO) analysis further validated the significant enrichment of terms relevant to the TAM phenotype, including regulation of myeloid cell differentiation and negative regulation of cell differentiation. Intriguingly, the genes to which O/E GATA1s binds when GATA1-fl is present were unrelated to hematopoiesis or cell proliferation. These observations suggest that GATA1s uniquely binds to genes, instigating TAM onset under GATA1-fl deficient conditions, thus confirming TAM as a disorder hallmarked by the absence of GATA1-fl due to the *GATA1* gene mutation.
Our RNA-sequencing data indicate that, at the early HPC stage, O/E GATA1s only induces changes in binding to gene regions involved in TAM pathogenesis, without altering gene expression levels. In contrast, gene expression analyses of other later stage HPC fractions (megakaryocyte-erythroid progenitor-like cells: MEP-like cells), revealed increased STAT3 expression and enrichment of the JAK-STAT pathway and myeloid cell differentiation pathway. These results suggest that TAM development may be influenced by shifts in the gene-binding region of GATA1s in the early HPC, which, in turn, induces TAM in more differentiated MEP-like cells by skewing their differentiation towards the myeloid lineage.
In conclusion, our study provides important insights into the pathological mechanisms of TAM pathogenesis, particularly with respect to the role of GATA1 in driving the TAM phenotype. the unique function of GATA1s and their specific binding to genes involved in TAM pathogenesis shed light on the complex interplay between GATA1s and TAM pathogenesis shed light

on the complex interplay between GATA1s and TAM pathogenesis. Understanding these mechanisms may pave the way for targeted therapies aimed at modulating GATA1s activity and reducing the severity of TAM.

Disclosures No relevant conflicts of interest to declare.

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