

Stable, thus in critical condition: m6A-methylated fusion transcripts in B-cell acute lymphoblastic leukemia

Jonas De Kesel¹⁻³ and Panagiotis Ntziachristos¹⁻³

¹Leukemia Therapy Resistance Lab, Department of Biomolecular Medicine, Faculty of Medicine and Health Sciences, Ghent University; ²Cancer Research Institute Ghent (CRIG) and ³Center for Medical Genetics Ghent (CMGG), Ghent, Belgium

Correspondence: P. Ntziachristos
pntziachr@gmail.com
Panagiotis.Ntziachristos@ugent.be

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In this issue of *Haematologica*, Shao and colleagues mined large-scale sequencing efforts to identify a wide range of previously uncovered fusion genes in patients with B-cell acute lymphoblastic leukemia (B-ALL).¹ Via transcriptional deregulation, or aberrant gain- or loss-of-function through acquired or lost protein domains, fusion genes are known to fulfill central roles in oncogenesis.² Of note, the presence of specific gene fusions underpins the latest World Health Organization (WHO) B-ALL subtype classification system (WHO-HAEM5),³ indicating their pathobiological and clinical relevance. In addition, ongoing research continues to refine therapy based on genetic lesions, with notable efforts focusing on particular events such as Philadelphia chromosome-like B-ALL and *KMT2A*-rearranged B-ALL.⁴ The central question tackled by Shao and colleagues was whether, and how, fusion transcripts are more stable compared to the individual partner transcripts, with a particular focus on N6-methyladenosine (m6A) RNA methylation. Indeed, through their protection against transcript degradation, m6A readers such as IGF2BP family members have been implicated in various disease models.⁵ IGF2BP1, for instance, is known to stabilize *ETV6-RUNX1* transcripts, originating from one of the most prevalent translocations in B-ALL.⁶ In addition, IGF2BP3 has been found to orchestrate a complex posttranscriptional mechanism of regulation in a murine model of MLL-AF4 leukemia.⁷ Extending these earlier observations, Shao and colleagues aimed to advance the field by performing a more comprehensive analysis that also incorporated m6A profiling, thereby elucidating the specific contribution of RNA m6A methylation to transcript stability.

The study identified that, for a subset of the fusion transcripts, RNA levels were induced when compared to one, or both, of the fusion partners in genomic wild-type (WT) arrangements. In part, this discovery could be attributed to m6A-driven RNA stabilization via IGF2BP3. By comparing decay kinetics of WT and fusion transcripts, the authors

first showed that classical fusions such as *PAX5-ETV6* and *TCF3-PBX1* exhibit markedly prolonged half-lives, consistent with potential mRNA stabilization and perturbed oncogenic activity (Figure 1). Screening for novel lesions with disproportionate expression when compared to the WT partners, led to the discovery of the previously uncharacterized *STK38-PXT1* fusion. Serine/threonine kinase 38 (STK38; also known as nuclear Dbf2-related kinase 1 [NDR1]) is known to control the cell cycle and is critical for the regulation of MYC in B-cell lymphoma.⁸ Peroxisomal testis enriched protein 1 (*PXT1*), on the other hand, is a largely unstudied gene. In mice, its expression has been found to be limited to spermatogenesis in male germ cells, where it is suggested to control DNA integrity.⁹ The fusion under study is composed of the N-terminal regulatory region of *STK38*, including part of its kinase domain, appended to exons 2 and 3 of *PXT1*. This rearrangement is suggested to alter the resulting protein's interaction landscape and regulatory output. Functional assays demonstrated that *STK38-PXT1* mRNA presents with increased stability, and could induce leukemic transformation *in vitro* and *in vivo*. Transcriptomic profiling further revealed the induction of β -catenin-related pathways in samples harboring this fusion, a finding that could spark more detailed functional follow-up studies.

Of note, with the limited knowledge regarding *PXT1*'s functionality, and STK38 being believed to be involved in oncogenic programs,⁸ it will be important to further investigate to what extent the here-described molecular pathogenesis of *STK38-PXT1*-driven B-ALL can be distinguished from the intrinsic oncogenic activity of both WT and/or truncated genes. Similarly, as both the fusion transcripts, as well as some of the truncated partner genes, appeared to gain stability upon m6A modification, the possibility exists that the reported m6A-driven stabilization reflects a broader regulatory principle, rather than a phenomenon that is particularly relevant for the fusion constructs under

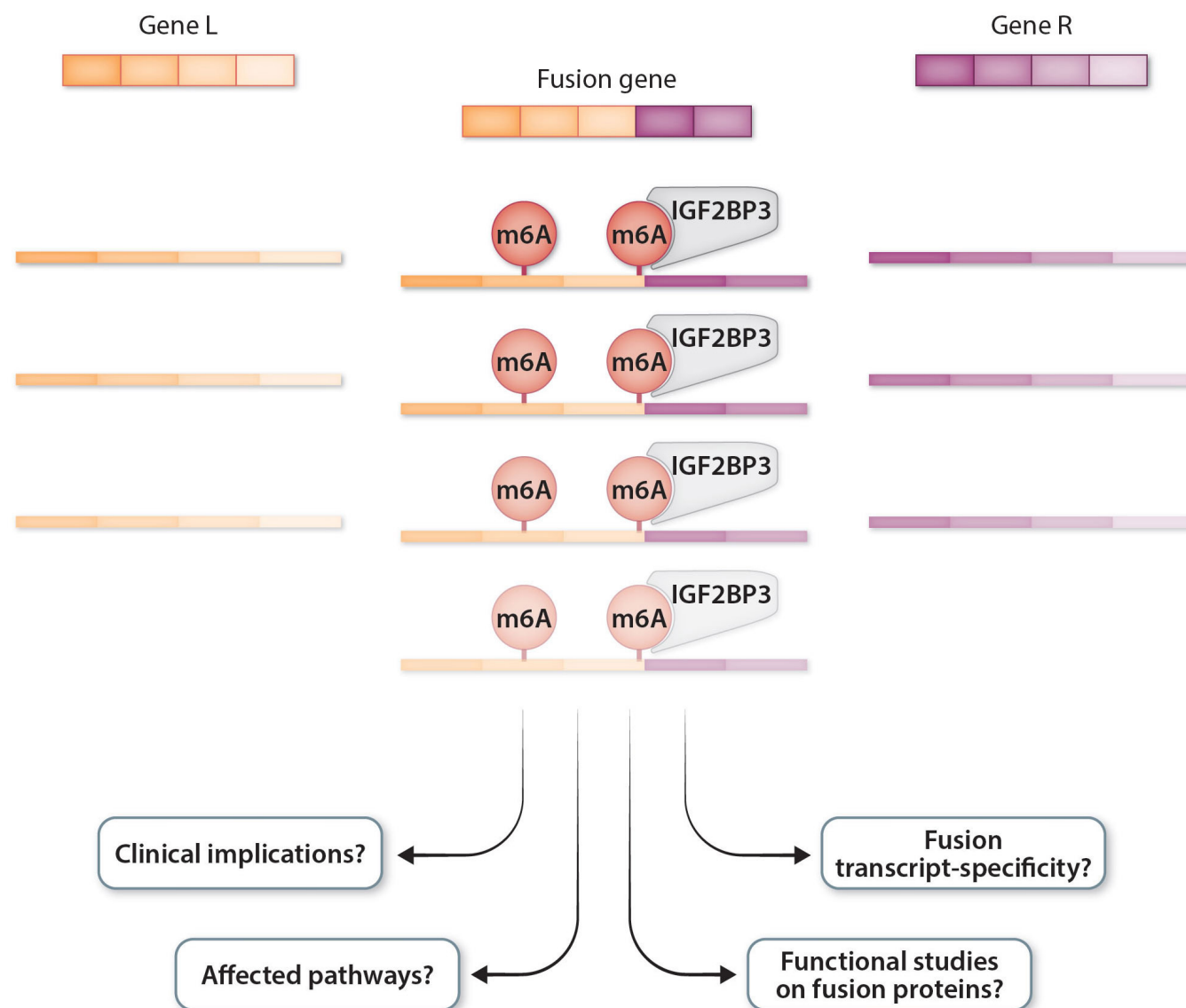


Figure 1. Epitranscriptomic regulation of fusion transcripts by IGF2BP3 and downstream consequences in B-cell acute lymphoblastic leukemia.

study. Further efforts will therefore be valuable to delineate whether the observed m6A-dependent stabilization reflects a fusion-specific mechanism, or whether it is a more general epitranscriptomic status that is of particular advantage for leukemic cells.

The integration of two large genomic datasets, TARGET and CNpALL, provides a clinically representative landscape to study fusion diversity in pediatric B-ALL. Consequently, this foundation creates a clear opportunity for future work to extend functional interrogation into models that more closely recapitulate human B-cell precursor biology, thereby clarifying how stabilized fusion transcripts operate within their native developmental context. Although the use of MeRIP in the current study offered an important initial demonstration of m6A involvement, technologies such as m6A-eCLIP, DART-seq or long-read sequencing that can map methylation events at a higher resolution will enable precise attribution of specific m6A residues to fusion transcript biology. Additionally, the potential m6A players that recognize these fusions, their activity and functions in different cancer contexts need to be further characterized. In this sense, the present work lays a platform on which increasingly granular mechanistic and translational insights can be built.

Although m6A-dependent mRNA stabilization is likely to be an important regulatory tier, the downstream consequences of fusion genes that confer leukemic fitness, such as lineage blockade, altered survival signaling, or metabolic rewiring, remain to be delineated (Figure 1). In the case of STK38-PXT1, in which β -catenin activation was implicated, mRNA stabilization, protein-interaction rewiring, and pathway activation require further mechanistic refinement. In addition, the presented evidence does not exclude that m6A-mediated transcript protection is just one contributor, rather than a unifying mechanism. Indeed, across B-ALL cohorts, the majority of fusion events has remained functionally uncharacterized to date, and only a portion of the novel fusions unveiled in the study by Shao and colleagues exhibited clear transcriptional induction when compared to the individual WT gene partners. This gap underscores once again the need for frameworks capable of distinguishing pathogenic fusions from passenger events, particularly as large-scale sequencing efforts continue to expand the catalog of rearrangements.² In this light, transcript stabilization could serve as a practical tool for prioritizing previously unclassified fusions. This approach could provide a measurable functional readout that can be integrated with recurrence, mutual exclusivity,

pathway activation signatures, or clinical correlates. Such an approach could help focus mechanistic and preclinical resources on a subset of events most likely to contribute to leukemogenesis.

The therapeutic inference of the paper by Shao and colleagues is centered on heightened venetoclax sensitivity and would benefit from contextual nuance. The enhanced venetoclax response is derived from overexpression systems, where gene dosage and clonal adaptation may influence drug sensitivity. Although reduced oxidative phosphorylation offers a compelling explanatory hypothesis, its relationship to the fusion event itself is hitherto rather correlative. Further research is warranted to identify whether venetoclax sensitivity is truly fusion-specific or reflects a more general B-ALL vulnerability arising from metabolic stress. In parallel, the identification of IGF2BP3 as a stabilizing

reader for fusion transcripts highlights an emerging theme in RNA-binding protein biology. IGF2BP family members have been implicated in post-transcriptional control across multiple leukemic contexts, and their upregulation here suggests a convergent dependency. Still, the therapeutic tractability of IGF2BP3 remains limited at present, and existing inhibitors are only in early preclinical stages,¹⁰ which places this observation within a longer-term translational horizon rather than immediate clinical applicability.

Disclosures

No conflicts of interest to disclose.

Contributions

JDK and PN co-wrote the manuscript.

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