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

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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 B-cell acute lymphoblastic leukemia (B-ALL) patients(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 of oncogenesis(2). Of note, the presence of specific gene fusions underpins the latest 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 lesions, with notable efforts focusing on particular events such as Philadelphia chromosome–like (Ph-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 implied 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 regulation mechanism in murine MLL-AF4 leukemia model(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 present 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 (see **Figure**). In part, this discovery could be attributed to m6A-driven RNA stabilization via by IGF2BP3. By comparing decay kinetics of WT and fusion transcripts, they 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. 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 exon 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 present 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 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**). In the case of STK38-PXT1, where β-catenin activation was implicated, mRNA stabilization, protein-interaction rewiring, and pathway activation requires 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 this study, 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 manuscript's therapeutic inference 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 in early preclinical stages(10), which places this observation within a longer-term translational horizon rather than immediate clinical applicability.

REFERENCES

1. Shao X, Xia Z, Cai M, et al. Chromosomal rearrangement-enhanced mRNA stability drives the carcinogenicity of oncofusion in pediatric leukemia. Haematologica. xxx

2. Mertens F, Johansson B, Fioretos T, Mitelman F. The emerging complexity of gene fusions in cancer. Nat Rev Cancer. 2015;15(6):371-381.

3. Steinemann D, Dawidowska M, Russell LJ, Harrison CJ, Gohring G. Genetic alterations in lymphoblastic leukaemia / lymphoma - a practical guide to WHO HAEM5. Med Genet. 2024;36(1):39-45.

4. Roberts KG, Mullighan CG. Genomics in acute lymphoblastic leukaemia: insights and treatment implications. Nat Rev Clin Oncol. 2015;12(6):344-357.

5. Huang H, Weng H, Chen J. m(6)A Modification in Coding and Non-coding RNAs: Roles and Therapeutic Implications in Cancer. Cancer Cell. 2020;37(3):270-288.

6. Sharma G, Tran TM, Bansal I, et al. RNA binding protein IGF2BP1 synergizes with ETV6-RUNX1 to drive oncogenic signaling in B-cell Acute Lymphoblastic Leukemia. J Exp Clin Cancer Res. 2023;42(1):231.

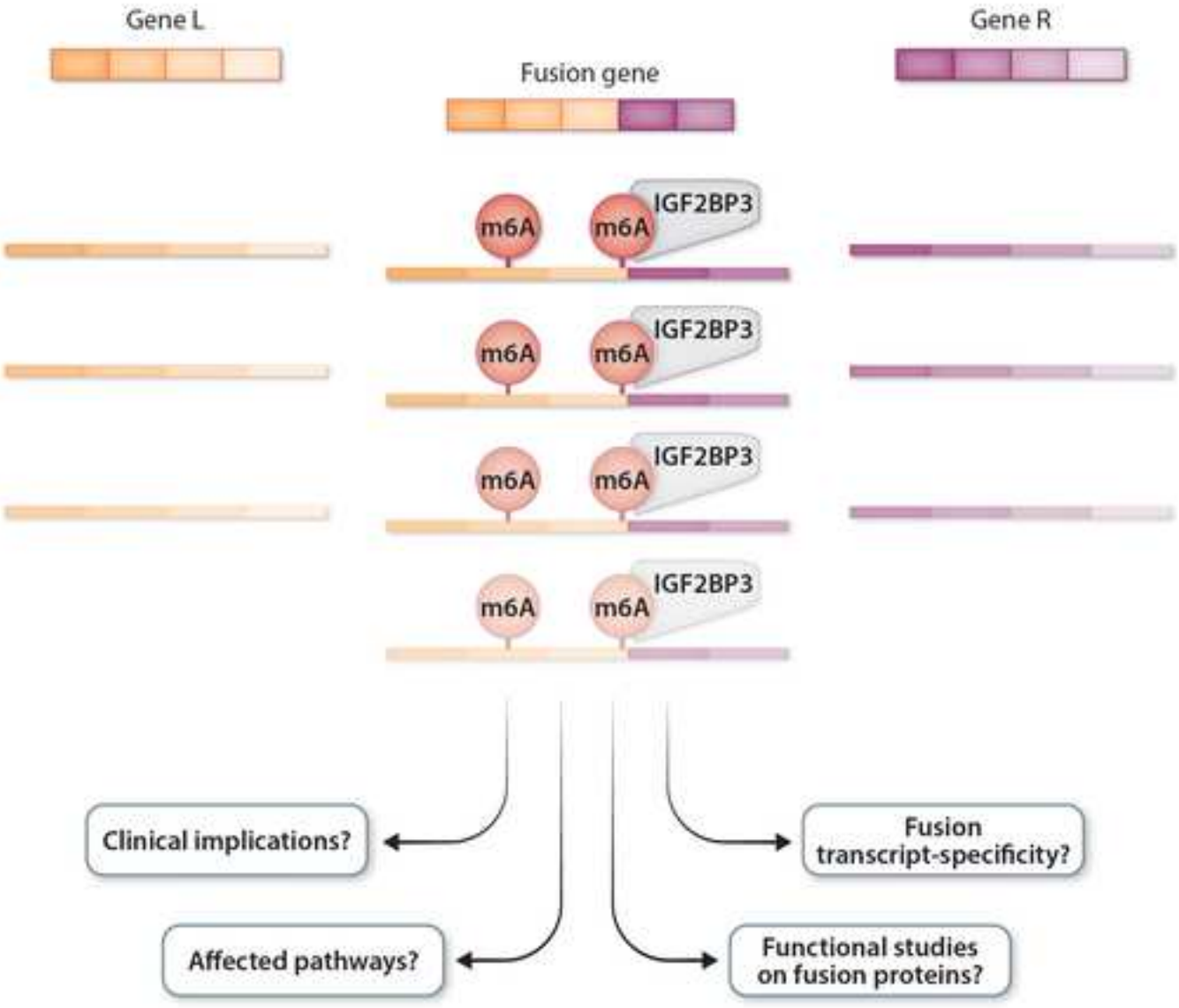
7. Tran TM, Philipp J, Bassi JS, et al. The RNA-binding protein IGF2BP3 is critical for MLL-AF4-mediated leukemogenesis. Leukemia. 2022;36(1):68-79.

8. Bisikirska BC, Adam SJ, Alvarez MJ, et al. STK38 is a critical upstream regulator of MYC's oncogenic activity in human B-cell lymphoma. Oncogene. 2013;32(45):5283-5291.

9. Pawlicka B, Duliban M, Zieba M, et al. Increased DNA strand breaks in spermatozoa of Pxt1 knockout mice. Reprod Fertil Dev. 2023;35(11):589-600.

10. Jaiswal AK, Scherer GM, Thaxton ML, et al. A small molecule inhibitor of RNA-binding protein IGF2BP3 shows anti-leukemic activity. bioRxiv. 2025 Apr 18. doi: 10.1101/2025.04.14.648780 [preprint, not peer-reviewed]

**Figure Legend:** Epitranscriptomic regulation of fusion transcripts by IGF2BP3 and downstream consequences in B-ALL


Gene L
Fusion gene
Gene R
m6A
m6A
IGF2BP3
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IGF2BP3
Clinical implications?
Affected pathways?
Functional studies on fusion proteins?
Fusion transcript-specificity?