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Letter to the Editor: Comprehensive Prediction of FBN1 Targeting miRNAs: A Systems Biology Approach for Marfan Syndrome

Editöre Mektup: FBN1 Hedefli miRNA'ların Kapsamlı Tahmini: Marfan Sendromu için Sistem Biyolojisi Yaklaşımı

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To the Editor,

In recent years, interest in small and long non-coding RNAs as modulators and potential biomarkers of the aortopathy that defines Marfan syndrome (MFS) has increased. Clinical and translational studies indicate that specific microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) contribute to extracellular matrix (ECM) remodeling, vascular smooth muscle cell (VSMC) phenotypic switching, apoptosis, and dysregulated TGF-β signaling, all of which are central processes in MFS. Synthesizing these findings highlights both opportunities and important gaps before RNA-based approaches can be applied clinically (1,2).

The study by Orhan et al. (1) provides a significant advancement in our understanding of MFS by presenting the first systems-level mapping of the miRNA-FBN1 interactome. By screening the entire human miRNome, they identified 251 potential regulators, thereby shifting the focus from candidate-driven research to a comprehensive regulatory landscape. Importantly, the hsa-miR-181 family, as a high-affinity regulator of FBN1, adds a novel layer to the established paradigm of ECM dysregulation in MFS. miR-181–mediated repression of FBN1 may act upstream of miR-29b–driven ECM remodeling, suggesting complementary but mechanistically distinct pathways that jointly compromise aortic wall integrity. Orhan et al. (1) provide a microfibril-specific mechanism by demonstrating multiple high-affinity binding sites on the FBN1 transcript, while established paradigms highlight the "anti-matrix" activity of miRNAs like miR-29b in general ECM degradation (2).

The miR-29 family, particularly miR-29b, is one of the most consistent players in MFS-associated aneurysm formation. Increased aortic miR-29b has been experimentally linked to increased ECM degradation and VSMC apoptosis, whereas antisense inhibition of miR-29b reduced early aneurysm development in murine MFS, which supports the idea that modulation of this miRNA may influence disease course. These preclinical results are supported by subsequent studies showing long-term benefits of systemic miR-29b suppression in Marfan models, strengthening the rationale for developing miR-29-targeted therapies or biomarker panels.

Similarly, the miR-143/145 cluster maintains the contractile VSMC phenotype. Numerous studies report downregulation of miR-143/145 in thoracic aneurysmal tissues and VSMC phenotypic switching toward a synthetic, matrix-remodeling state — a cellular program highly relevant to MFS aortopathy. The fact that miR-143/145 regulates cytoskeletal and contractile gene networks and interfaces with TGF-β signaling, its dysregulation plausibly

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contributes to the weakened aortic media observed in patients (1,2,3).

Circulating miRNA signatures in patients with MFS have translational potential as noninvasive biomarkers. Case-control studies reveal distinct miRNA profiles in MFS patients, particularly in those with dissecting or rapidly enlarging aneurysms, suggesting that serum/plasma miRNA panels could aid in risk stratification or the early detection of complications. However, heterogeneity between studies in sample processing, cohort size, and inconsistent normalization strategies currently limits clinical application. Larger, prospective cohorts are required (4).

Beyond miRNAs, lncRNAs remain less well characterized in MFS, but increasing evidence indicates altered lncRNA landscapes in affected aortic tissue. Microarray and transcriptomic analyses of MFS aortas have demonstrated differentially expressed lncRNAs that correlate with ECM-related mRNAs and with pathways implicated in aneurysm biology. Reviews synthesizing coding and non-coding transcriptomic data report dysregulation of lncRNAs associated with TGF-β signaling, inflammation, and mitochondrial function — all plausible contributors to the variable penetrance and progression of MFS aortopathy. Nevertheless, functional validation and clinical correlation studies (e.g., linking specific lncRNA levels with rates of aortic dilation or dissection in patients) remain limited (5). The findings of Orhan et al. (1) underscore this gap and highlight the need to move beyond single miRNA–mRNA axes toward an integrated non-coding RNA network analysis, in which miRNAs and lncRNAs are evaluated as coordinated regulators of ECM homeostasis and vascular smooth muscle cell function. The systems-level strategy of Orhan et al. (1) provide a conceptual framework that could be extended to include lncRNAs, enabling reconstruction of higher-order non-coding RNA networks governing ECM integrity in MFS.

Taken together, the evidence supports that miRNAs and lncRNAs are central to molecular circuits that modulate aortic wall integrity in MFS. miR-29b and the miR-143/145 cluster remain strong candidates for translational development: miR-29b for therapeutic antagonism, and miR-143/145 for restoration or as biomarkers of VSMC health. Circulating miRNA panels show promise for noninvasive monitoring, whereas lncRNAs represent an intriguing but still nascent field with a substantial unmet need for mechanistic and longitudinal clinical studies.

To move this field forward, we need (1) standardized protocols for miRNA/lncRNA measurement in blood and tissue, (2) multicenter prospective cohorts linking RNA signatures to imaging-based aortic outcomes, and (3) careful safety assessment of any RNA-modulating therapy, given the systemic roles of these molecules. If these hurdles are addressed, non-coding RNAs could become an important adjunct to genetic testing and imaging in the personalized management of patients with Marfan syndrome.

Sincerely,

Footnotes

Authorship Contributions

Concept: A.A., Design: A.A., Data Collection or Processing: B.B., A.A.,

Analysis or Interpretation: B.B., A.A., Literature Search: B.B., A.A., Writing: B.B., A.A.

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