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Commentary

miRNA in mechanobiology: The exploration needs to continue

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ABSTRACT

The 2024 Nobel Prize in Physiology or Medicine has once again sparked considerable interest in microRNA (miRNA). Recent advances have unveiled that miRNAs play critical roles in mediating the effects of mechanical stimuli on gene expression, cellular functions, tissue development, and disease progression. This perspective summarized the history of miRNA research and highlighted the promising research directions of miRNAs in the field of mechanobiology.

1. Introduction

The 2024 Nobel Prize in Physiology or Medicine was awarded jointly to American scientists Victor Ambros and Gary Ruvkun for their outstanding work on the discovery of micro ribonucleic acid (microRNA, miRNA, μRNA) and its crucial role in gene regulation. The first miRNA, lin-4, and its post-transcriptional gene regulation of lin-14 was revealed by Victor Ambros and Gary Ruvkun in 1993.[1,2] In 2000, Ruvkun's laboratory identified the highly conserved let-7 as the second miRNA, which facilitated the subsequent identification of homologous miRNAs in a variety of animal species, including humans.[3–7] The first human disease associated with miRNA dysregulation was chronic lymphocytic leukemia, miR-15 and miR-16 were all downregulated in B-cell chronic lymphocytic leukemias.[8] Of note, the first mechanical stretch sensitive miRNA was found in 2005 in *Populus trichocarpa*,[9] a deciduous broadleaf tree species native to western North America. In 2010, mechanosensitive miRNAs were found to be associated with human physiology and pathology.[10,11] Steady laminar shear stress (LSS) regulates cyclin D1 expression via upregulation of miR-19a to inhibit endothelial cells (ECs) proliferation,[10] LSS also elevates miR-21 expression to decrease ECs apoptosis and activate NO pathway[12] while mechanical stretch induced microRNA-26a promotes human airway smooth muscle hypertrophy in severe asthma.[11] So far, the research of miRNA in the field of mechanobiology has made great progress. The brief history of miRNA research progress in mechanobiology was summarized in Fig. 1. Although it has been found that mechanical stress regulates miRNA expression,[11–13] there is still much work needs to be done about the role of miRNA in mechanotransduction.

2. Novel mechanosensitive miRNAs

It is estimated that the human genome encodes more than 1900 miRNAs.[14] However, only approximately 500 human miRNAs have been validated as *bona fide* miRNAs in the manually curated database, MirGeneDB.[15] There is an urgent need for further research to identify additional miRNAs, and the same holds true in the field of mechanobiology. The discovery of new mechanosensitive miRNAs will also facilitate the development of mechanobiology.

3. The dual role of miRNA in mechanobiology

Many miRNAs, including microRNA-181,[16] microRNA-1297,[17] and miR-1298-5p,[18] act as dual-role regulators to suppress or induce human cancers by targeting different genes and signaling pathways. In the cardiovascular system, the inhibition of miR-33 improves atherosclerosis regression by increasing collagen content[19] while miR-33 attenuates arterial mechanical stretch-induced neointimal hyperplasia in the grafted vein via targeting BMP3.[20,21] However, the dual roles of miRNAs in mechanotransduction are poorly studied and require significant attention.

4. Gene transcriptional activation during mechanotransduction

The classic mechanisms of miRNA action involve the negative regulation of gene expression by specifically targeting messenger RNAs, which results in their degradation or translational repression.[2,20] Intriguingly, Xiao et al. elucidated that miRNAs also activate gene transcription epigenetically as an enhancer trigger.[22] There is a need to

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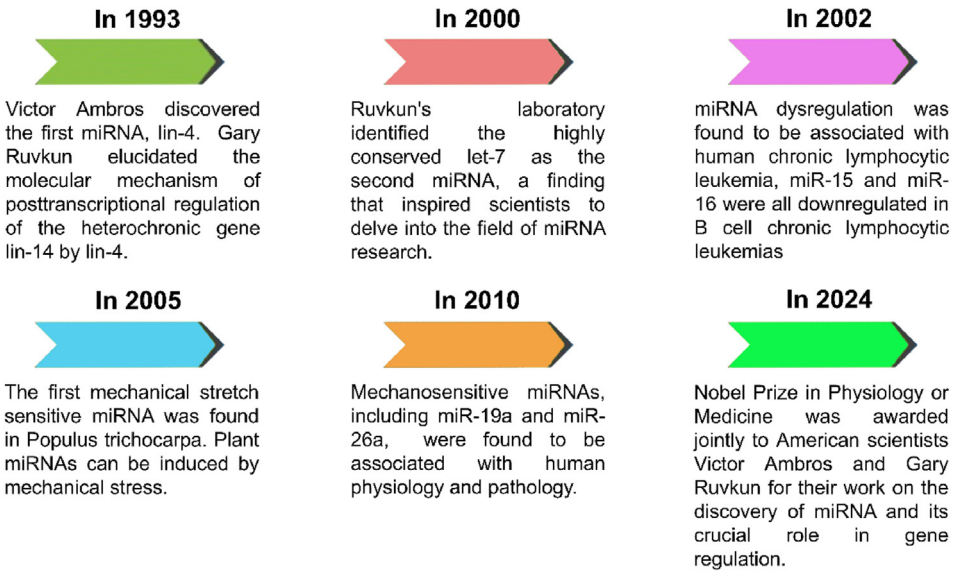

Fig. 1. A brief history of miRNA research progress in mechanobiology. The first miRNA was discovered in 1993 and the first mechanosensitive miRNA was found in plant in 2005.

explore whether miRNAs play a role in gene transcription activation during mechanotransduction.

5. miRNA-assisted diagnosis of challenging disease

The assessment of the severity of some diseases can be challenging. For instance, a size greater than 5.5 cm is currently the only parameter that abdominal aortic aneurysm (AAA) requires open repair and endovascular aneurysm repair.[23–26] However, the rupture rate of AAAs exceeding the 5.5 cm threshold in the contemporary era is significantly lower than previously reported and numerous large AAAs do not rupture at all.[24] Consequently, it is acknowledged that factors beyond the size of the aorta play a crucial role in predicting outcomes in AAA disease. Others and we have proved that miRNAs are dysregulated in human AAAs.[23,27] Besides, miRNAs are stable and measurable with high sensitivity in human blood. Therefore, miRNAs have great potential in diagnosing the severity of AAA and guiding clinical treatment strategies.

6. Mitochondrial function/dysfunction under mechanical stress

Mounting evidence revealed that mechanical stress plays a vital role in regulating mitochondrial function/dysfunction.[28] However, the role of miRNAs in these processes has not been explored before and requires further investigation.

7. Nuclear morphology, structure, and function under mechanical stress

Numerous studies have demonstrated that mechanical stress modulates nuclear morphology, structure, and function across various cell types.[29,30] Nevertheless, it remains unclear whether miRNAs are involved in these processes, as well as the underlying mechanobiological mechanisms.

8. Conclusion

Since the discovery of the first miRNA in 1993, miRNA research has developed rapidly. As of November 2, 2024, the number of search results for miRNA in PubMed has reached 177,447. However, the research on miRNA in the interdisciplinary field of mechanobiology is still relatively lagging. In addition to the six research areas (Fig. 2) listed above that need to be strengthened, there is also a need to explore "the interactions between miRNA and long non-coding RNA (lncRNA)", "the role of miRNA in helping environmental adaptability", "the role of miRNA in

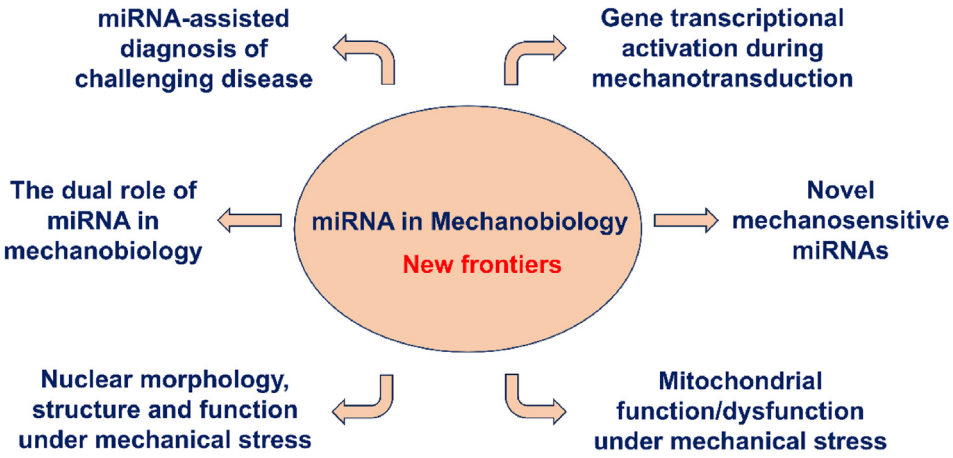

Fig. 2. The promising research directions of miRNAs in the field of mechanobiology. Novel mechanosensitive miRNAs, the dual role of miRNA in mechanobiology, gene transcriptional activation during mechanotransduction, miRNA-assisted diagnosis of challenging disease, mitochondrial function/dysfunction under mechanical stress and nuclear morphology, structure and function under mechanical stress may become key focuses and hotspots in the study of miRNA in mechanobiology.

modulating metabolism" and "the crosstalk between miRNA and extracellular matrix". We believe that research in these fields can effectively promote the development of mechanobiology.

CRediT authorship contribution statement

Kai Huang: Conceptualization, Funding acquisition, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Yingxin Qi:** Funding acquisition, Supervision, Writing – review & editing.

Ethical approval

This study does not contain any studies with human or animal subjects performed by any of the authors.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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