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Opinion

Small Extracellular Vesicles from Young Plasma May Be a Potential Novel Therapeutic for Treating Erectile Dysfunction

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Approximately 322 million males are predicted to suffer from erectile dysfunction (ED) by 2025, which represents a serious public health threat to the aging population worldwide.[1] Aging has been identified as a crucial risk factor contributing to the onset of ED, independent of the presence of cardiovascular disorders or diabetes mellitus.[2] Notably, the severity of ED significantly increases with aging,[3] which underscores the importance of targeting the biological and physiological processes of aging to reverse the incidence and progression of ED, thereby improving the quality of sexual life in the increasingly healthy aging population. Drug administration remains the mainstay and most common therapeutic approach for treating ED, but its efficacy is still far from satisfactory. Therefore, therapeutics with better efficacy and safety are urgently needed.

We recently reported in *Nature Aging* that young plasma-derived small extracellular vesicles (sEVs) can reverse aging and a range of aging-related tissue functional declines,[4] subsequently extending the lifespan of mouse models. Mechanistically, we demonstrated that this therapeutic effect is dependent on the stimulation of peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) expression by sEV-loaded microRNAs (miRNAs), thereby alleviating mitochondrial defects and reinvigorating mitochondrial vitality and function.

PGC-1α, encoded by the PPARGC1A gene, is a transcriptional cofactor that plays a pivotal role in regulating energy metabolism homeostasis in response to various physiological processes, including adaptive thermogenesis, exercise, and fasting.[5] It is predominantly expressed in tissues with high energy demands, such as the heart, skeletal muscle, brown adipose tissue, liver, kidney, and brain. The expression and activity of PGC-1α are downregulated in aging and age-related diseases, underscoring its importance in human physiology.[5] In the context of aging, PGC-1α is crucial because it modulates mitochondrial biogenesis and dynamics, which are integral to maintaining cellular vitality and function.[5,6] Mitochondrial dysfunction is often associated with aging, and PGC-1α's role in promoting mitochondrial health is therefore particularly significant.[6] In summary, PGC-1α is a master regulator of energy homeostasis with significant implications for aging, muscle and neuronal function, and cellular vitality. Its role in mitochondrial biogenesis, maintenance, and quality control is essential for the health and function of cells, particularly in high-energy-demand tissues.

Our investigation highlights that the young plasma-derived sEVs exhibit potent biological regulatory functions in reversing aging-related deficits and degeneration by enhancing PGC-1α-mediated mitochondrial energy metabolism. However, beyond aging, this study may also provide further insights and directions for aging-related diseases, especially ED.

First, certain miRNAs have been shown to be abnormally elevated in the circulatory system of ED patients, indicating their potential roles in regulating the onset and progression of ED.[7] Moreover, multiple recent studies have reported a range of miRNAs capable of reversing ED symptoms through various mechanisms.[8,9] Nevertheless, the upstream origins of these ED-associated miRNAs remain largely unknown. More importantly, the mechanisms described tend to focus on diabetic ED and do not explore the specific association with aging. Notably, mitochondrial dysfunction has been identified as a key contributor to the onset and progression of ED,[10,11] and the PGC-1α-related signaling pathway has also been implicated in the pathophysiology of ED.[12] These studies suggest that targeting aging-induced mitochondrial dysfunction and PGC-1α could be a valuable approach to reversing the progression of ED. Based on our results presented in *Nature Aging*, we hypothesize that ED patients may exhibit disruptions in the miRNA profile in plasma-derived sEVs, leading to mitochondrial dysfunction and contributing to the onset and progression of ED. Furthermore, the utilization of small extracellular vesicles from young plasma may represent a novel therapeutic strategy for treating ED, based on its positive regulation of mitochondrial function and the subsequent reversal of aging-related tissue degeneration. Additionally, beyond

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Table 1. Potential targets and related mechanisms in the young plasma-derived small extracellular vesicle-based erectile dysfunction therapy

Targets	Mechanisms	References
NO/cGMP pathway	Injury in corpus cavernosum endothelium cells	13
Type I collagen, more flexible Type III collagen, elastin	Tunica albuginea injury	14
Sirtuin 1, Klotho, fibroblast growth factor 21	Arterial vascular impairment	15
nNOS- and GFRa2-positive neurons	Impacts on neuroplasticity of cavernous nerves	16
Testosterone, eNOS	Hormonal imbalances in sexual function	17
Vitamin D	Induction of endothelial dysfunction, diabetes, hypertension, hypercholesterolemia, chronic kidney disease, and gonadal dysfunction	18

cGMP, cyclic Guanosine Monophosphate; eNOS, endothelial Nitric Oxide Synthase; GFRα2, Glial cell line-derived Neurotrophic Factor Receptor Alpha 2; NO, Nitric Oxide; nNOS, neuronal Nitric Oxide Synthase.

PGC-1α, a range of crucial functional molecules and adaptors may also serve as potential therapeutic targets in the young plasma-derived sEV-based ED therapy, as summarized in Table 1.[13–18]

However, several points need to be highlighted before translating this hypothesis into clinical practice. Firstly, the plasma-derived sEVs-contained miRNAs from young individuals need to be sequenced and filtered to identify the crucial functional miRNAs. This will involve advanced bioinformatics analysis to uncover patterns and differences that could be pivotal in understanding the therapeutic potential of sEVs. Furthermore, both *in vivo* and *in vitro* experiments are required to verify the therapeutic effect of young sEVs on ED. These experiments should be designed with rigorous scientific methodology to ensure the reproducibility and validity of the findings. In addition, the internal mechanisms need to be fully explored. This includes understanding how sEVs interact with the cellular environment and the specific pathways they may influence in ED pathology. Advanced imaging techniques and molecular biology assays could be employed to elucidate these mechanisms. Looking ahead, the integration of nanotechnology and precision medicine could offer novel approaches for delivering sEVs more effectively and targeting specific cells or tissues within the body. This could lead to personalized treatment strategies for ED, tailored to an individual's unique genetic and physiological profile.

We hope our study and this opinion article serve as inspiration for further investigations into the therapeutic potential of young plasma-derived sEVs for treating ED. We anticipate that future research will not only validate our findings but also expand upon them, leading to the development of innovative therapeutics. We expect this research direction will provide new ideas and hope for overcoming the clinical challenge of ED, potentially revolutionizing the way we approach and treat this condition. The graphical abstract is summarized in Figure 1, which illustrates the mechanism

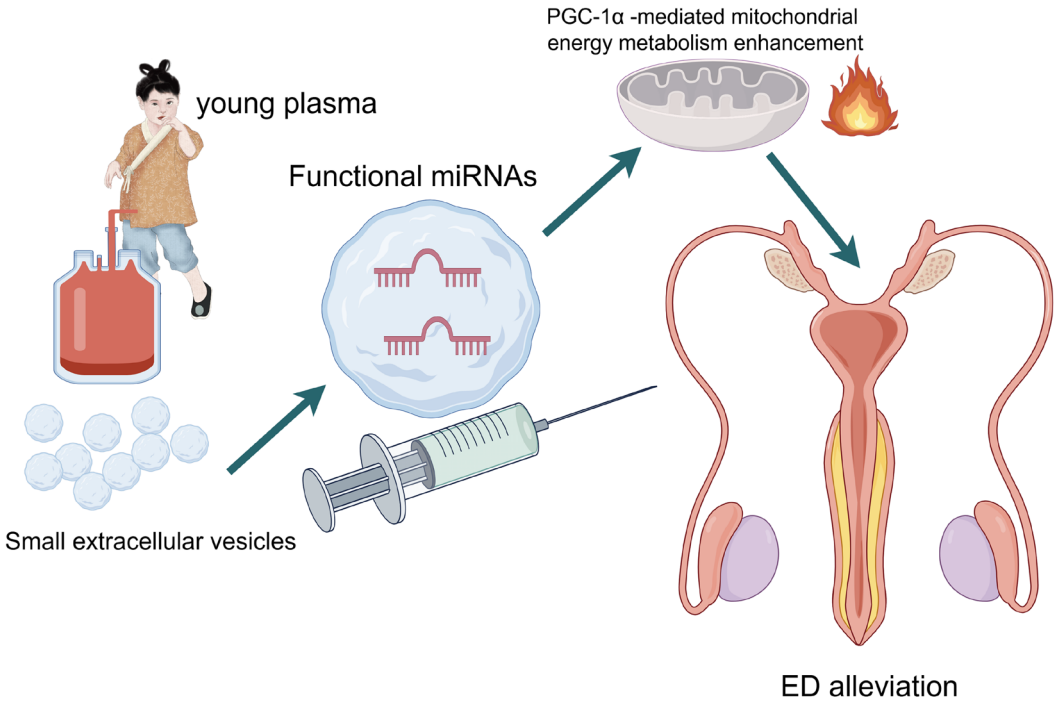

Fig. 1. The mechanism of the potential novel therapeutic for treating ED by utilizing small extracellular vesicles from young plasma. ED, erectile dysfunction; PGC-1α, Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1 Alpha.

of the potential novel therapeutic for treating erectile dysfunction using small extracellular vesicles from young plasma.

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Conflict of interest

The authors declare that no conflict of interest exists in this study.

Author contributions

Conception (TL, XC, MC), discussion of the core scientific idea (TL, XC, MC), drafting, and revision (TL, XC, MC). All authors agreed on the final version of this manuscript.

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