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Editorial

Nucleolar Stress: An Emerging Avenue for Cardiovascular Drug Target Identification

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The nucleolus is a highly dynamic, polymorphic membrane-less structure within the eukaryotic nucleus that serves as the primary site for ribosomal RNA synthesis and ribosomal subunit assembly. Although historically regarded as a ribosome biogenesis centre, the nucleolus is now recognised as a central integrator of cellular stress signals with direct relevance to disease pathogenesis. A broad range of pathological stimuli, including oxidative stress, hypoxia, viral infection, and transcriptional inhibition, can perturb nucleolar structure and function, resulting in a condition known as nucleolar stress. This state is characterised by disruption of nucleolar microarchitecture, ribosomal dysfunction and altered nucleolar protein dynamics, which in turn activate downstream pathways governing metabolic adaptation, autophagy, cell cycle regulation and apoptosis.

Mounting clinical and experimental evidence implicates nucleolar stress as an active contributor to cardiovascular disease progression rather than a passive consequence of cellular injury. Across multiple cardiovascular pathologies, nucleolar abnormalities such as nucleolar enlargement, increased ribosomal biogenesis activity and ultrastructural reorganisation, marked by reduced granular components and expansion of fibrillar regions, have been consistently observed. Proteomic analyses further demonstrate stimulus-specific and time-dependent remodelling of the nucleolar proteome, particularly following myocardial infarction, where changes in nucleolar protein composition are linked to cardiomyocyte inflammation, survival and tissue repair. Together, these findings suggest that nucleolar stress responses are dynamically regulated processes that shape disease trajectory and may be amenable to therapeutic intervention.

In this context, Xu et al. presents a comprehensive review entitled 'Nucleolus, Nucleolar Stress and Cardiovascular Diseases,' published in the January 2026 issue of *IJDDP*. This article systematically integrates clinical and experimental evidence linking nucleolar dysfunction to cardiovascular disease progression, highlighting nucleolar stress responses, key nucleolar proteins, and their translational relevance [1].

Mechanistically, nucleolar stress triggers a highly orchestrated signalling response that integrates multiple regulatory layers. The p53 pathway represents the most extensively studied downstream cascade, operating through distinct but interconnected paradigms including nucleolar protein translocation, transcriptional and translational modulation, and direct protein–protein interactions. Beyond p53, emerging evidence indicates that nucleolar stress can also engage p53-independent signalling mechanisms. Stress-induced translocation of nucleolar proteins to extranucleolar compartments, such as the nucleoplasm or cytoplasm, has been shown to modulate key cellular processes, including inhibition of cell cycle progression through CDK4/6 suppression, attenuation of inflammatory signalling via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway modulation, and repression of transcriptional regulators and metabolic mediators. Notably, certain translocated nucleolar proteins are capable of inducing cell cycle arrest or programmed cell death by activating pro-apoptotic factors such as Bax, highlighting the nucleolus as a direct regulator of cell fate decisions under stress.

As our understanding of cellular microarchitecture deepens, the nucleolus has emerged as a critical regulator of cardiovascular disease pathophysiology and an attractive yet underexplored target for translational research. From a mechanistic perspective, further work is required to delineate nucleolar stress signalling networks that specifically drive cardiomyocyte dysfunction and maladaptive remodelling. From a translational standpoint, components of nucleolar stress pathways represent promising candidates for precision therapeutics, offering the possibility of selectively modulating pathological stress responses while preserving essential nucleolar functions. In parallel, nucleolar-associated proteins, together with structural, functional and proteomic alterations of the nucleolus, may serve as sensitive biomarkers for early disease detection, risk stratification and therapeutic response monitoring. Collectively, nucleolus-targeted strategies hold substantial potential to reshape precision

cardiovascular therapeutics by addressing upstream stress integration mechanisms rather than downstream pathological consequences alone.

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Use of AI and AI-Assisted Technologies: No AI tools were utilized for this paper.

References

1. Xu, R.; Jin, X.; Zhang, Y.; et al. Nucleolus, Nucleolar Stress and Cardiovascular Diseases. *Int. J. Drug Discov. Pharmacol.* **2026**, *5*, 100002.