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Review

Stressing on the nucleolus in cardiovascular disease ☆

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ABSTRACT

The nucleolus is a multifunctional organelle with multiple roles involving cell proliferation, growth, survival, ribosome biogenesis and stress response signaling. Alteration of nucleolar morphology and architecture signifies an early response to increased cellular stress. This review briefly summarizes nucleolar response to cardiac stress signals and details the role played by nucleolar proteins in cardiovascular pathophysiology. This article is part of a Special Issue entitled: Role of the Nucleolus in Human Disease.

1. Introduction

The nucleolus is a suborganelle within the nucleus and was one of the first intracellular structures identified by simple light microscopy back in the mid-1800s [1]. Nucleoli are disassembled during cell division and re-formed at the end of mitosis around chromosomal regions termed nucleolar organizing regions consisting of tandem repeats of ribosomal DNA (rDNA) [2,3]. With the identification of ribosomal RNA (rRNA) and proteins within the nucleolus, the organelle was determined as the site for nascent ribosomal biogenesis and assembly, nearly a century after its initial discovery [1,2]. Over the past few decades however, the nucleolus has been associated with many diverse cellular functions. Of 4500 nucleolar proteins discovered, approximately 30% are linked to ribosomal assembly and processing [3,4] and a predominant population of nucleolar proteins play vital roles in cell cycle control, signal recognition particle assembly, cell growth, microRNA biogenesis, viral replication, cell death, nuclear transport, stem cell fate and commitment, cellular senescence, and stress response signaling in eukaryotic cells [1,2,5–10]. This review discusses the role of the nucleolus and nucleolar proteins in regulating cardiovascular pathophysiology.

2. Nucleolus as a stress sensor in cardiac disease

The mammalian nucleolus is normally tripartite having three morphologically distinct subcompartments, the fibrillar center, the dense fibrillar component and the granular component (Fig. 1) [1,2,11]. The nucleolus functions as a sensor of cellular stress and responds by undergoing morphological and molecular reorganizations of its architecture (Fig. 2) [3,12]. Nucleolar enlargement is indicative of increased protein synthesis and growth and is one of the early changes observed in hypertrophied human hearts [13,14]. Neonatal rat cardiac myocytes treated with phenylephrine, an α1-adrenergic receptor agonist and stressed cardiac myocytes in the border zone of a myocardial infarction (MI) also display enlarged, irregularly shaped nucleoli [15]. An increase in nucleolar size concomitantly associated with alterations in the ultrastructure is observed during ischemic and dilated cardiomyopathies in humans, wherein nucleoli become less granular and more fibrillar, suggestive of increased ribosomal activity [16]. Nucleolar hypertrophy also results from polyploidy and endoreduplication of chromosomes [13]. Disruption of the nucleolus is common in response to DNA damage, genotoxic stress, change in temperature, hypoxia, and treatment with chemotherapeutic drugs that inhibit transcription and ribosomal subunit processing [3,12,17,18]. The nucleolus shrinks, segregates (separation of granular component and fibrillar center upon compaction of the nucleolus) [19] or fragments (decondensation and unraveling of rDNA) [12] upon receiving cues for increased cellular stress. Treatment with chemotherapeutic drugs Actinomycin D and doxorubicin in cardiac myocytes causes decondensation and shrinkage of the nucleolus with delocalization of nucleolar stress sensor proteins [15]. Nucleolar and ribosomal stress have been demonstrated to elicit p53 dependent and independent signaling pathways to activate stress response signaling, which in turn leads to increased apoptosis, cell cycle arrest or senescence in a cell type and stimulus dependent manner [3,17,20,21].

3. Nucleolar organizing region as a determinant of cardiac pathology

Nucleolar organizing regions (NORs) are tightly aggregated chromosomal DNA involved in transcription of rRNA and present in the nucleoli of cells in interphase [22–24]. Since NORs contain acidic,

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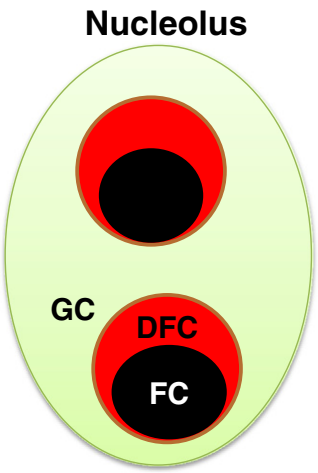

Fig. 1. The nucleolus is tripartite and has 3 subcompartments — Fibrillar center (FC, black), dense fibrillar component (DFC, red) and granular compartment (GC, green).

non-histone proteins which have increased affinity for silver ions, staining with silver (Ag) acetate enables easy visualization of NORs (termed Ag-NOR) [24]. Ag-NORs which are identified as black dots under the light microscope correspond to the proteins in the fibrillar center and dense fibrillar component and correlate with cellular proliferation rate in cancer cells [24,25]. Activity of cardiac NORs correlates positively with myocardial weight, left ventricular wall thickness and maximal diastolic pressure in hypertensive hearts [26], suggestive of increased NOR and nucleolar activity during hypertrophy [13]. Ag-NORs are decreased in cardiomyocytes of hearts with severe ischemia and heart failure, owing to decreased metabolic activity and diminished rRNA synthesis [26,27]. Cardioplegia or temporary cardiac arrest also decreases Ag-NORs, while reperfusion increases them [27,28]. Doxorubicin induced cardiotoxicity increases number of Ag-NORs, but also causes them to be morphologically altered (enlarged and rod shaped compared to small round dots) [22]. Collectively, these observations imply that NORs function as highly sensitive indicators of cardiac function and disease.

The following section will detail the role played by evolutionarily conserved nucleolar proteins in regulation of cardiovascular diseases. Although a myriad of proteins translocate into the nucleolus in response to stress signaling and either activate or attenuate different signal transduction pathways, for purposes of this review, we will focus only on four proteins which are predominantly localized to and function mainly within the nucleolus.

4. Nucleolar proteins associated with cardiac pathophysiology

4.1. Nucleolin

Nucleolin (Ncl or C23) is a multifunctional, nucleolar phosphoprotein with important roles in ribosomal biogenesis, cell cycle regulation, growth, cell death and signal transduction [29–31]. Ncl is mainly associated with cell growth and pro-survival responses in the heart, consistent with loss of proliferation and increased apoptosis observed upon Ncl downregulation in C2C12 skeletal myoblasts [32]. Transcriptional regulation of Ncl occurs in rat cardiac myocytes during development and early postnatal growth, when cardiomyocytes retain their limited proliferative potential. However, translation but not transcription is increased in cardiac myocytes during hypertrophic growth indicating differential regulation of Ncl in response to hyperplastic and hypertrophic stimuli [33]. Ncl is required for cell survival and mediates the antiapoptotic effects downstream of heat shock protein 70 upon oxidative stress in cardiac myocytes [34]. Transgenic mice with cardiac specific overexpression of Ncl are resistant to ischemia–reperfusion injury and have reduced infarction size and cell death [35]. The important role played by Ncl in regulating cell proliferation and survival also has implications in heart diseases in humans. Patients receiving heart transplant show 9 fold higher levels of antibodies against Ncl, suggesting that Ncl inhibition is associated with coronary artery disease and allograft failure in heart transplant patients owing to increased apoptosis and decreased endothelial cell proliferation [36]. Although predominantly nucleolar, Ncl translocates to the nucleoplasm, cytoplasm and cell surface in proliferating endothelial cells [37,38]. Antibodies against cell surface Ncl inhibit angiogenesis *in vitro* and *in vivo* [38,39]. Increases in Ncl protein expression and nucleolar localization are observed during ischemic and dilated cardiomyopathies, which also correlate with altered left ventricular dimensions and cardiac function [16]. Therefore as a pro-survival and pro-growth molecule, Ncl is involved in regulating the structure and function of the heart.

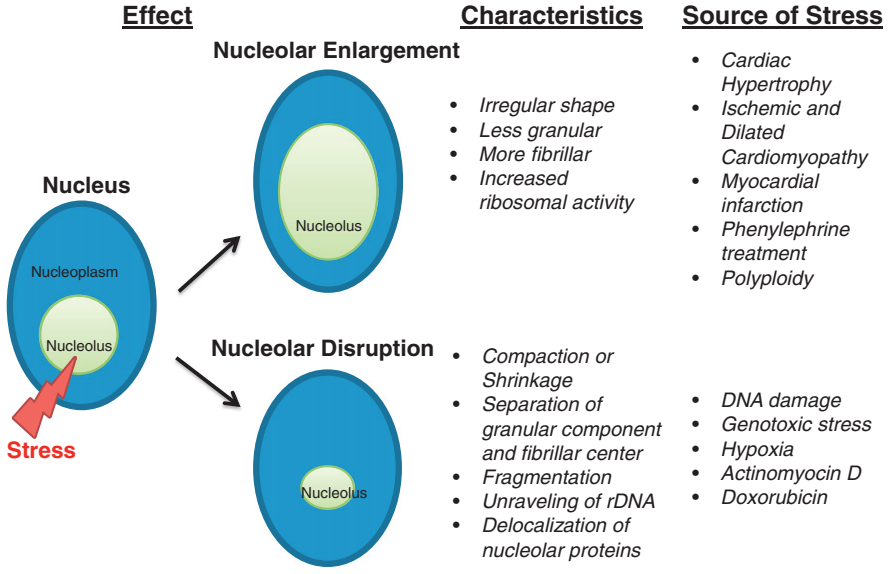

Fig. 2. The nucleolus functions as a stress sensor and responds by undergoing enlargement or disruption leading to further ultra structural modifications. The characteristics and sources of nucleolar stress are listed based on the effect seen (see text for details). Nucleolar subcompartments are not shown.