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Review article

New concepts of endoplasmic reticulum function in the heart: Programmed to conserve

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ABSTRACT

Secreted and membrane proteins play critical roles in myocardial health and disease. Studies in non-myocytes have shown that the peri-nuclear ER is the site for synthesis, folding, and quality control of most secreted and membrane proteins, as well as a nexus of a signal transduction system, called the ER stress response, which informs the cell about the status of ER protein folding. Moreover, the dynamic physical and functional association of the ER with mitochondria is a key site responsible for integrating ER function and mitochondrial metabolism, but is only just beginning to be understood in the myocardium. Although a great deal is known about roles played by the sarcoplasmic reticulum (SR) in contractile calcium handling in the heart, little is known about the relative locations and functions of the peri-nuclear ER and the SR in terms of secreted and membrane protein synthesis and folding. In this review we will explore the current state of knowledge of the location of secreted and membrane protein synthesis, folding, and quality control machinery in cardiac myocytes, as well as our understanding of the functional consequences of ER stress and the unfolded protein response in the heart in terms of protein synthesis, cell growth, and metabolic regulation. This article is part of a Special Issue entitled 'Focus on Cardiac Metabolism'.

Contents

1. Introduction: defining the SR and ER in cardiac myocytes

The network of membranes called the endoplasmic reticulum (ER) is a well-studied organelle in various cell types [1]. Since its discovery and visualization by George Palade [2], the rough ER, studded with ribosomes, has been shown to be the major site of secreted and membrane protein synthesis [3]. Proteins synthesized in the ER are routed to the Golgi where they are directed to their final destinations [4]. Although secreted and membrane protein synthesis in the ER has been studied extensively in many cell types [5,6], it remains largely uncharacterized in cardiac myocytes. A network of membranes similar to the ER, called the sarcoplasmic reticulum (SR) (Fig. 1A) has been defined and studied in striated muscle cells, including in cardiac myocytes. The SR surrounds the myofilaments and operates in collaboration with deep invaginations of the sarcolemma, called transverse (t)-tubules (Fig. 1B), to regulate the release of calcium from the SR lumen into the

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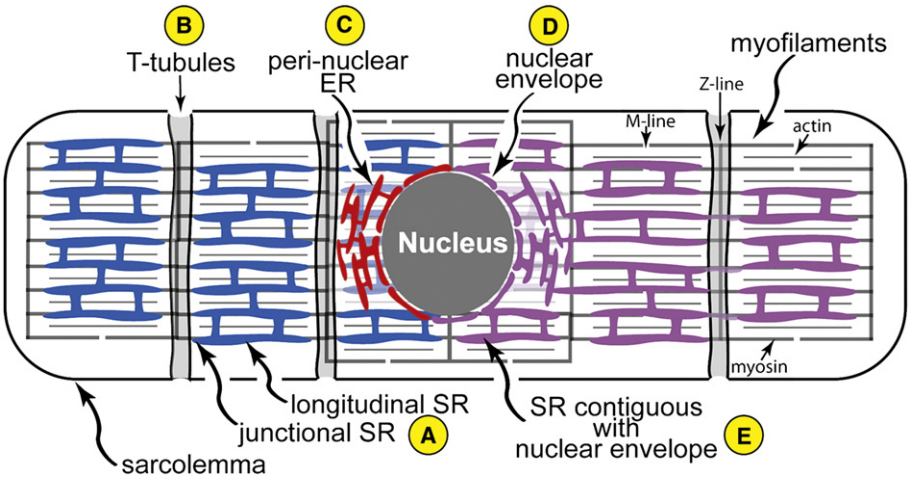

Fig. 1. Sarco/endoplasmic reticulum network in a cardiac myocyte: shown is a diagram of a cardiac myocyte depicting the relationships between the region of the SR near the t-tubule, junctional SR, the longitudinal SR (A), transverse, or t-tubules (B), the peri-nuclear ER (C) and nuclear envelope (D), and a depiction of SR that is contiguous with the nuclear envelope (E) The t-tubules are invaginations of the sarcolemma that reside over the Z-line of the sarcomeres. Also shown are the actin and myosin that comprise major portions of myofilaments, as well as the M- and Z-line regions of the sarcomeres. The nuclear envelope and peri-nuclear ER are contiguous, and constitute a location for secreted and membrane protein synthesis, as well as calcium storage and release. The hypothetical localization of secreted and membrane protein synthesis to only the nuclear envelope and peri-nuclear ER, depicted in red, and not to the SR, depicted in blue, is shown on the left of the diagram. The hypothetical localization of secreted and membrane protein synthesis to the nuclear envelope, peri-nuclear ER and the SR, depicted as a contiguous membranous system, shaded purple, is shown on the right of the diagram.

cytoplasm, where it regulates myocyte contraction [7,8]. However, the relative locations, protein synthetic functions, and protein expression profiles of the ER and the SR in cardiac myocytes are unclear [9,10]. Some evidence suggests that the ER and, thus, the site for secreted and membrane protein synthesis in cardiac myocytes is in a peri-nuclear network that is contiguous with the nuclear envelop (Figs. 1C and D), while other evidence suggests that protein synthesis may also take place in the SR [11–14]. This latter concept is supported by findings that at least part of the SR is physically contiguous with the peri-nuclear ER (Fig. 1E), as shown by studies demonstrating that calcium can diffuse freely between the two membrane systems [15].

Secreted and membrane proteins made in the heart have important functions in the heart, as well as in other locations [4]. Since the folding and synthesis of secreted and membrane proteins can be impaired during some cardiac pathologies, there is heightened interest among cardiovascular researchers in the unfolded protein response (UPR), sometimes called the ER stress response [16]. This interest has driven studies aimed at delineating the location of the ER in cardiac myocytes [16]. Electron microscopy has been used extensively to examine the ultrastructure of cardiac myocytes. While this technique may be useful for assessing some aspects of myocyte structure, the location and extent of the ER in cardiac myocytes have been difficult to determine by electron microscopy due to technical limitations [17]. Moreover, while confocal immunocytofluorescent microscopy has thus far played a major role in localizing many SR proteins that are associated with excitation–contraction coupling, it has been used in only a few studies to localize proteins associated with ER protein synthesis, folding, and quality control in myocytes. Such studies have shown that proteins involved in ER protein synthesis, folding, and quality control can be found in peri-nuclear regions of cardiac myocytes, as well as in peripheral areas, where they adopt an SR-like pattern [11–14,18,19]. However, additional studies are required to settle fundamental questions about whether the SR serves as a site of protein synthesis, and if not, whether the separate network of membranes around the nucleus in cardiac myocytes is sufficient to fulfill the needs of cardiac myocytes to synthesize secreted and membrane proteins. But since it is clear that most secreted and membrane proteins must be synthesized within a network of cellular membranes, the definition of which, in cardiac myocytes, is a topic of ongoing investigation, for the purposes of this review, we will refer to the network in which protein synthesis and folding take place as the ER, and to the unfolded protein response emanating from the ER, as the ER stress response.

2. The ER stress response

Nearly all proteins must be folded into functional configurations [20]. The folding of proteins synthesized in the ER takes place co- and post-translationally, and involves a complex cast of characters that reside in the ER, which constitute the ER protein synthesis, folding, and quality control machinery [21,22]. An important function of this machinery is sensing the status of ER protein folding by detecting slight changes in the levels of unfolded proteins, and then communicating a status report proactively to the other parts of the cell that respond by adjusting the capacity of the system, thus homeostatically balancing the protein folding demand with the capacity of the protein folding machinery [23]. Drastic changes in the status of protein folding that threaten this homeostatic mechanism initiate a more reactive version of this response, which is sometimes called the ER stress response [10,24–27].

The ER stress response can be activated by conditions that alter the ER environment in ways that impair nascent ER protein glycosylation, disulfide bond formation, or calcium levels; such conditions are often observed in the ischemic, hypertrophic, and failing heart [13,28,29] (Fig. 2A). Three ER-transmembrane signaling proteins are major proximal sensors of unfolded proteins in the ER: PERK (protein kinase RNA-like ER kinase) [30,31], IRE-1 (inositol-requiring protein-1) [32–35], and ATF6 (activating transcription factor 6) [36–38] (Figs. 2B–D). When activated by misfolded proteins in the ER, these sensors facilitate the activation of the transcription factors, ATF4, XBP1, and ATF6 (Figs. 2E–G), which mediate the induction of ER stress response genes that encode ER-targeted chaperones, calcium-binding proteins, and disulfide isomerases, as well as many proteins targeted to other cellular locations. Together, these proteins enhance nascent ER protein folding. ER stress also suppresses most protein synthesis, while selectively increasing translation of selected mRNAs, most of which encode ER stress response genes (Fig. 2H) [39]. This selective translational repression is thought to conserve energy and reduce demands on the ER protein folding machinery [22]. ER stress also augments the ER-associated protein degradation system (ERAD), leading to proteasome-mediated degradation of terminally misfolded ER proteins, which helps relieve ER stress

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