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Review article

An integrated mechanism of cardiomyocyte nuclear Ca^{2+} signaling

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ABSTRACT

In cardiomyocytes, Ca^{2+} plays a central role in governing both contraction and signaling events that regulate gene expression. Current evidence indicates that discrimination between these two critical functions is achieved by segregating Ca^{2+} within subcellular microdomains: transcription is regulated by Ca^{2+} release within nuclear microdomains, and excitation–contraction coupling is regulated by cytosolic Ca^{2+}. Accordingly, a variety of agonists that control cardiomyocyte gene expression, such as endothelin-1, angiotensin-II or insulin-like growth factor-1, share the feature of triggering nuclear Ca^{2+} signals. However, signaling pathways coupling surface receptor activation to nuclear Ca^{2+} release, and the phenotypic responses to such signals, differ between agonists. According to earlier hypotheses, the selective control of nuclear Ca^{2+} signals by activation of plasma membrane receptors relies on the strategic localization of inositol trisphosphate receptors at the nuclear envelope. There, they mediate Ca^{2+} release from perinuclear Ca^{2+} stores upon binding of inositol trisphosphate generated in the cytosol, which diffuses into the nucleus. More recently, identification of such receptors at nuclear membranes or perinuclear sarcolemmal invaginations has uncovered novel mechanisms whereby agonists control nuclear Ca^{2+} release. In this review, we discuss mechanisms for the selective control of nuclear Ca^{2+} signals with special focus on emerging models of agonist receptor activation.

Contents

Abbreviations: Ang II, angiotensin II; E–C, excitation–contraction; ER, endoplasmic reticulum; ET-1, endothelin-1; IGF-1, insulin-like growth factor-1; INM, inner nuclear membrane; $InsP_3$, inositol 1,4,5-trisphosphate; $InsP_3R$, $InsP_3$ receptor; NE, nuclear envelope; ONM, outer nuclear membrane; PI4P, phosphatidylinositol-4-phosphate; PIP_2, phosphatidylinositol bisphosphate; PLC, phospholipase C; PS, perinuclear space; RyR, ryanodine receptor; SR, sarcoplasmic reticulum.

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1. Introduction

Calcium homeostasis is regulated by the combined action of a variety of channels, transporters, and binding proteins which allow cells to increase or decrease intracellular Ca^{2+} concentration on demand [1]. Ca^{2+}-releasing events, or Ca^{2+} transients, occur when Ca^{2+} channels embedded within either the plasma membrane or in select internal membranes open, allowing Ca^{2+} to move down its electrochemical gradient from either external sources or intracellular Ca^{2+} stores, flooding the cytosolic compartment. Cytosolic Ca^{2+} increases a remarkable 50-fold this way with each heart beat (0.1μM in diastole to ≈5μM in systole). Then, Ca^{2+} is rapidly removed from the cytosol by Na^{+}–Ca^{2+} exchangers and ATP-dependent transporters that pump Ca^{2+} out of the cell or back into intracellular stores [2]. This Ca^{2+} cycle defines the Ca^{2+} transient, whereas repeated Ca^{2+} cycles comprise a Ca^{2+} oscillation [3,4].

Ca^{2+} oscillations can be tuned in frequency, amplitude, and duration, providing a biological signal with limitless possible combinations for encoding information [5]. Cardiac contraction provides an excellent example of the importance of Ca^{2+} oscillations, and the need to maintain them under fine control [6]. Under normal conditions, the human heart beats once every second, therefore, each cardiomyocyte undergoes a full, coordinated Ca^{2+} cycle nearly 60 times per minute [2]. Many biological inputs ultimately exert control over heart rate by impacting various components governing Ca^{2+} oscillation.

Although Ca^{2+} oscillations are central to driving cardiomyocyte contraction, non-contractile Ca^{2+}-dependent signaling has emerged as an important regulatory mechanism of both transcriptional control and structural remodeling in the heart. In a wonderfully intricate manner, Ca^{2+} manages to regulate these processes independent of the whole-cell Ca^{2+} oscillations that drive contraction. Ca^{2+}-mediated changes in gene expression often occur in response to agonist binding to receptors at the plasma membrane, or sarcolemma [7,8]. This mechanism allows cells to reprogram their gene expression profiles to meet ever-changing cardiac demand. Ca^{2+}-mediated signaling can also influence transcriptional control of cardiomyocyte development [9], differentiation [10], survival [11], hypertrophic growth [12,13], metabolism [14] and cell death [11]. At present, we are only beginning to understand how a cardiomyocyte decodes a Ca^{2+} signal to alter gene expression without interfering with, or being controlled by, the essential and ongoing process of contraction [15]. A growing body of evidence indicates that such discrimination is accomplished by triggering local Ca^{2+} release in segregated subcellular compartments (cytosol versus nucleus) or specific sub-regions of these compartments, generating microdomains of localized Ca^{2+}-signaling events. In this review, we focus on mechanisms currently proposed to explain such selective control of nuclear Ca^{2+} signals.

2. Cytosolic source of nuclear Ca^{2+} signals

Although it is currently controversial whether the initiation of nuclear Ca^{2+} signals derives from cytosolic Ca^{2+} entry into the nucleus, or generated by the nuclear release of Ca^{2+}, there is evidence that both mechanisms exist in cardiomyocytes (as summarized in Fig. 1). Indeed, several studies in cardiomyocytes and other cell types suggest that elevations nuclear Ca^{2+} are the direct consequence of changes in cytosolic Ca^{2+} [16–18]. On the other hand, it has also been shown in different cardiac muscle cells that changes in nuclear Ca^{2+} can be regulated independent of cytosolic Ca^{2+} and derive from Ca^{2+} released inside, or in close proximity to, the nucleus [18–20].

2.1. Ca^{2+} diffusion through the nuclear pore complex

It was initially held that primary access for Ca^{2+} to the nuclear compartment occurred through passive diffusion of cytosolic Ca^{2+} through nuclear pores connecting the nucleus and the cytoplasm. This is a reasonable hypothesis given that the nuclear pore complex, a multiprotein structure integral to the nuclear envelope (NE), has an approximate diameter of 8nm although this was estimated in isolated Xenopus oocyte nuclei [21]. Although Ca^{2+} has an ionic radius of only 0.99°Å, its hydrophobicity in solution gives it an effective diameter of 12Å per hydrated ion (or 1.2nm). This would allow unlimited traffic of Ca^{2+} ions between the cytoplasm and nucleus as postulated by pioneer studies in amphibian and insect cells [22,23].

The concept of passive diffusion of Ca^{2+} into the nucleus from a cytoplasmic source is supported in cardiomyocytes by several lines of evidence, such as the observations of synchronous elevations in nuclear and cytoplasmic Ca^{2+} [16]. Indeed, the cytosolic Ca^{2+} wave propagated during cardiomyocyte contraction can invade the nucleoplasm via diffusion [16], favored by the lower Ca^{2+} buffer capacity of the nucleus [24]. In this model, the NE functions as a barrier and the nuclear pores provide the entryway for regulated diffusion of high cytosolic Ca^{2+}, and this has also been observed in mouse neuroblastoma cells [25].

Like any gate, the nuclear pore is subject to regulation. Diffusion through nuclear pores is complex and regulated by several mechanisms, including passive diffusion of small molecules (up to 10kDa), Ca^{2+}-regulated transport of intermediate molecules (10–70kDa) and also involves active transport for larger molecules [26]. Ca^{2+} itself can influence diffusion through nuclear pores, and Ca^{2+} store depletion decreases diffusion of intermediate but not small size molecules or ions [26–28]. Consistent with this, atomic force microscopy demonstrates that the nuclear pore complex is a dynamic structure capable of responding to changes in intracellular Ca^{2+} [29]. Indeed, some hormones that increase cytosolic Ca^{2+} levels also increase permeability of the nuclear pore complex [30]. Thus, regulation of nuclear pore