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Review

Stromal interaction molecules as important therapeutic targets in diseases with dysregulated calcium flux☆

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ABSTRACT

Calcium ions have important roles in cellular processes including intracellular signaling, protein folding, enzyme activation and initiation of programmed cell death. Cells maintain low levels of calcium in their cytosol in order to regulate these processes. When activation of calcium-dependent processes is needed, cells can release calcium stored in the endoplasmic reticulum (ER) into the cytosol to initiate the processes. This can also initiate activation of plasma membrane channels that allow entry of additional calcium from the extracellular milieu. The change in calcium levels is referred to as calcium flux. A key protein involved in initiation of calcium flux is Stromal Interaction Molecule 1 (STIM1), which has recently been identified as a sensor of ER calcium levels. STIM1 is an ER transmembrane protein that is activated by a drop in ER calcium levels. Upon activation, STIM1 interacts with a plasma membrane protein, ORAI1, to activate ORAI-containing calcium-selective plasma membrane channels. Dysregulation of calcium flux has been reported in cancers, autoimmune diseases and other diseases. STIM1 is a promising target in drug discovery due to its key role early in calcium flux. Here we review the involvement and importance of STIM1 in diseases and why STIM1 is a viable target for drug discovery. This article is part of a Special Issue entitled: Calcium signaling in health and disease. Guest Editors: Geert Bultynck, Jacques Haiech, Claus W. Heizmann, Joachim Krebs, and Marc Moreau.

1. Introduction

Calcium (Ca^{2+}) and magnesium (Mg^{2+}) ions are useful ubiquitous ions in biology. They both have an oxidation state of +2 which gives them greater strength in interacting with anionic complexes compared to sodium, potassium or other monocations. Therefore, Ca^{2+} and Mg^{2+} fill important roles in processes that require control of larger molecules such as protein folding (Ca^{2+}) and coordinating ATP (Mg^{2+}). Ca^{2+} and Mg^{2+} have evolved into different functions in cells, sometimes countering each other. Mg^{2+} is the eleventh most abundant element in the body and interacts with phosphates in DNA, RNA, ATP and other phosphate-containing molecules, enhancing the mobility and flexibility of the molecules by countering their anionic charges. Therefore, Mg^{2+} is routinely more ubiquitous in the cell. Ca^{2+}, on the other hand, is the fifth most abundant element in the body but 99% of it is sequestered in bone. Among the roles for Ca^{2+}, a major role is acting as a secondary signal to convert signals from the extracellular environment into specific intracellular responses. Also, Ca^{2+} is involved in the rapid depolarization of cells in neurons and muscle cells. These actions need to be tightly controlled. Therefore, Ca^{2+} is kept at low levels in the cell's cytosol until needed. However, in order to rapidly respond when Ca^{2+} is needed, Ca^{2+} is stored in the endoplasmic reticulum (ER) and mitochondria for quick release that initiates Ca^{2+} dependent actions.

2. Calcium flux

2.1. Calcium dependent processes

Calcium ions play vital roles in a variety of important physiological functions of the cell, including control of cell cycle progression, cell differentiation, mitosis, apoptosis, ETosis, cell mobility, macrophage activation, chromatin packaging & modifications, protein folding and control of potassium & calcium channels. Often Ca^{2+} is serving as a secondary messenger, conveying an external signal received through ligand/receptor binding, into specific responses within the cell. Several of these roles of Ca^{2+} can be exemplified by human peptidyl arginine deiminase 4 (PAD4), a calcium-dependent enzyme. PAD4 is inactive until it binds Ca^{2+} (enzyme activation). The structures of inactive PAD4 and active PAD4 have been published (shown in Fig. 1) [1]. Comparison of inactive PAD4 and active PAD4 shows stabilization of residues including around the active site (protein folding) [Fig. 1]. When active, PAD4 can convert arginine residues to citrulline, such as in histones [Fig. 2] [2]. This reduces the histone–DNA interactions and alters chromatin for gene activation or permanently alters chromatin

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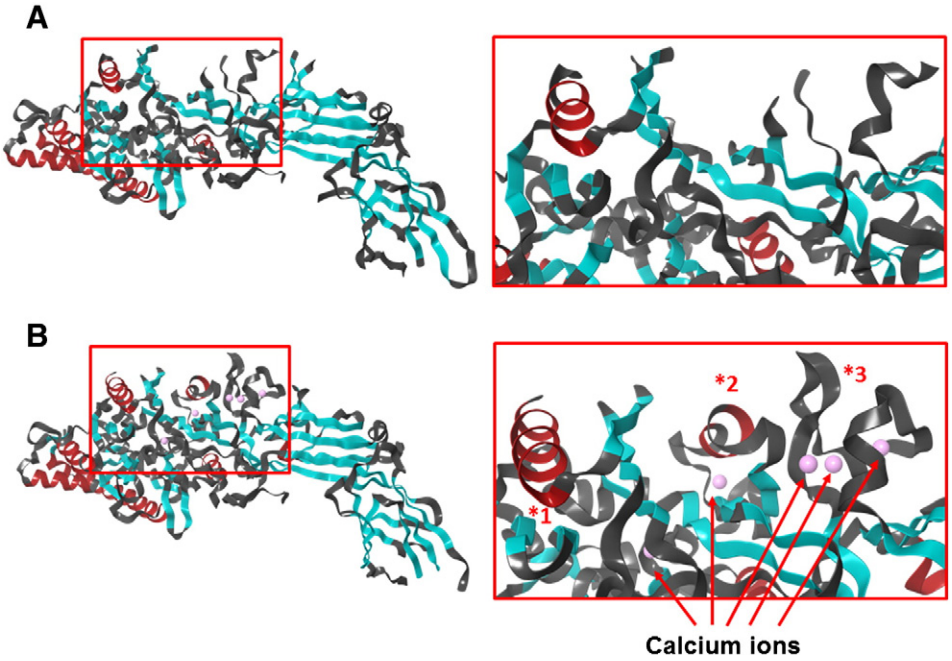

Fig. 1. Peptidyl arginine deiminase 4. A) Structure of PAD4 without calcium ions (based on X-ray data in 1WD8.pdb [1]). B) Structure of PAD4 with calcium ions, shown as 5 pink spheres (based on X-ray data in 1WD9.pdb [1]). Comparing the close-up views (at right) of A & B, note how calcium ions associate with stabilization of: (*1) residues near the active site; (*2) a short stretch of alpha helix; (*3), and a loop of residues. When calcium ions are not present (A), the residues at these sites are too randomly distributed to determine specific 3D coordinates and, therefore, they do not appear in the final pdb file.

as part of calcium-dependent programmed cell death (apoptosis and ETosis) [3,4].

2.2. Calcium storage and release

PAD4 involvement in apoptosis demonstrates a critical need for control of intracellular Ca^{2+} in order to prevent inappropriate activation of calcium-dependent processes. To prevent such aberrant events, the available Ca^{2+} is kept at approximately 100 nM in the cytosol, whereas in the extracellular environment, Ca^{2+} is typically at 1 mM or greater. Regulation of intracellular Ca^{2+} involves: 1) Ca^{2+} release from intracellular organelles, such as the ER and mitochondria, 2) Ca^{2+} entry from the extracellular environment, and 3) reestablishment of stored Ca^{2+} levels and lower cytosolic Ca^{2+}. These processes are referred to as

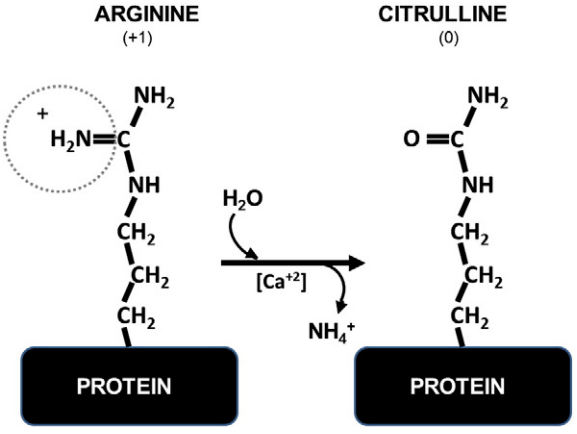

Fig. 2. Deimination reaction of PAD4. PAD4 can convert peptidyl arginine residues to citrulline in proteins, such as histones. Deimination, also referred to as citrullination, reduces the positive charge of arginine to a neutral citrulline. In the case of histones, this can loosen their interactions with DNA. PAD4 can also convert methylated arginine residues and PAD4 can undergo self-deimination, potentially inactivating itself [2].

calcium flux. One process that can connect stored Ca^{2+} release and extracellular Ca^{2+} entry is called store-operated calcium entry (SOCE) [5]. In SOCE an initial event, such as a ligand binding to a receptor, triggers release of stored Ca^{2+} from the ER. One example is when a G protein-coupled receptor (GPCR) binds its ligand which activates phospholipase C (PLC) to convert phosphatidyl inositol 4,5-bisphosphate (PIP_2) to inositol 1,4,5-trisphosphate (IP_3). IP_3 then traverses through the cytosol to the ER membrane surface where it activates the IP_3 receptor (IP_3R). The IP_3R receptor is a family of ER transmembrane proteins (IP_3R types I, II and III) that, upon activation, can open as a channel to release Ca^{2+} into the cytosol [6,7]. Another family of ER transmembrane proteins, the ryanodine receptor (RyR-1, RyR-2), is also a Ca^{2+} channel for release of ER stored Ca^{2+} [8,9]. Both IP_3R and RyR are strongly biased towards Ca^{2+} release as opposed to monocations. IP_3R is the dominant responder when ER Ca^{2+} release is needed. The PLC activation that results in IP_3 which activates IP_3R can begin from a number of different plasma membrane receptors but GPCRs, with their great variety of sequences and ligands, are very frequently the initiators. RyRs, on the other hand, respond to Ca^{2+}, such as inflow of extracellular Ca^{2+}, which activates RyR opening to release ER stored Ca^{2+}. The actual activation of the IP_3R and RyR channels is dependent on spatial and temporal differences in the Ca^{2+} flow and concentrations. For example, within the ER lumen, Ca^{2+} aids in the folding of nascent proteins that are destined for extracellular exposure and, therefore, there is a focus of Ca^{2+} in the ER lumen at those sites where signal recognition particle (SRP) receptors are docked with actively translating ribosomes. The spatial and temporal differences in Ca^{2+} are often referred to as waves or oscillations and the intensity and persistence of the wave can impact the strength and duration of the activity of ER Ca^{2+} channels which then impact the cytosolic and nuclear Ca^{2+}-dependent activities. Cytosolic Ca^{2+} can affect the ER Ca^{2+} release channels but, as research continues, we are learning that some proteins can also influence the channels, giving further complexity to the secondary messenger activity of Ca^{2+} [10]. Another purported ER Ca^{2+} release channel is presenilin (PS). This is a family (PS-1, PS-2) of multi-pass ER transmembrane proteins that is purported to coordinate the expression, induction and activity of IP_3R and RyR channels in order to control Ca^{2+} homeostasis [11]. PS