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Review

Metabolic regulation of the PMCA: Role in cell death and survival☆

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ABSTRACT

The plasma membrane Ca^{2+}-ATPase (PMCA) is a ubiquitously expressed, ATP-driven Ca^{2+} pump that is critical for maintaining low resting cytosolic Ca^{2+} ($[Ca^{2+}]_i$) in all eukaryotic cells. Since cytotoxic Ca^{2+} overload has such a central role in cell death, the PMCA represents an essential "linchpin" for the delicate balance between cell survival and cell death. In general, impaired PMCA activity and reduced PMCA expression leads to cytotoxic Ca^{2+} overload and Ca^{2+} dependent cell death, both apoptosis and necrosis, whereas maintenance of PMCA activity or PMCA overexpression is generally accepted as being cytoprotective. However, the PMCA has a paradoxical role in cell death depending on the cell type and cellular context. The PMCA can be differentially regulated by Ca^{2+}-dependent proteolysis, can be maintained by a localised glycolytic ATP supply, even in the face of global ATP depletion, and can be profoundly affected by the specific phospholipid environment that it sits within the membrane. The major focus of this review is to highlight some of the controversies surrounding the paradoxical role of the PMCA in cell death and survival, challenging the conventional view of ATP-dependent regulation of the PMCA and how this might influence cell fate.

Contents

1. Introduction

The plasma membrane Ca^{2+}-ATPase (PMCA) is an ATP-driven Ca^{2+} pump ubiquitously expressed in the plasma membrane of all eukaryotic cells. PMCA is encoded by four separate genes (PMCA1-4) and numerous splice variants that give rise to specific tissue distribution, cellular localisation and functional diversity [1,2]. PMCA1 and PMCA4 are ubiquitously expressed whereas PMCA2 and PMCA3 have a more tissue specific expression, mainly in excitable cells [3]. The PMCA is critical for maintaining cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) below 300 nM (~100 nM), due to its high affinity for Ca^{2+} (Kd, ~0.2 μM) [4–6] and is the major Ca^{2+} efflux pathway in non-excitable cells [7]. For many years the PMCA was thought to have a "minor" house-keeping role in maintaining low resting $[Ca^{2+}]_i$ [8]. However, the importance of PMCA in the spatiotemporal shaping of cytosolic Ca^{2+} signalling has steadily increased. PMCA exhibits memory of past $[Ca^{2+}]_i$ increases,

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suggesting an important role in regulating the frequency of Ca^{2+} oscillations [9]. Moreover, the different PMCA isoforms, and numerous splice variants of PMCA, can be differentially expressed in specific regions of cells and can also be differentially regulated by a sophisticated repertoire of additional signalling pathways [10–13].

Despite the emerging role of the PMCA in dynamic Ca^{2+} signalling, the importance of the house-keeping role of the PMCA should not be under-estimated, especially when one considers how important maintaining low resting $[Ca^{2+}]_i$ is for cell survival and the prevention of Ca^{2+}-dependent cell death. In this regard the PMCA can be regarded as the "last gatekeeper" for the maintenance of low resting $[Ca^{2+}]_i$; an essential "linchpin" for the delicate balance between cell survival and cell death [14–17]. Moreover, the PMCA is inextricably linked to the specific nature of cell death. Not only does PMCA prevent Ca^{2+} overload associated apoptosis, but the PMCA is an ATP-driven pump and since ATP depletion induces necrosis, a decline in PMCA activity will accompany and exacerbate necrosis [17–20]. Therefore, PMCA activity may act as an important switch between apoptosis and necrotic cell death, a key determinant of numerous disease processes. Thus the maintenance of PMCA activity is critical for cell survival, particularly in the face of modest-to-severe global ATP depletion, whereas inhibition of PMCA even when global ATP is maintained will facilitate Ca^{2+}-dependent apoptosis.

2. Physiological regulation and key structural features of the PMCA

In order to understand the role of the PMCA in cell death and survival it is necessary to highlight some of the key structural features and regulatory mechanisms. Structurally, PMCA consists of ten transmembrane domains, two cytosolic loops with both N- and C-terminal cytosolic tails (Fig. 1) [1,2]. Arguably the most functionally important structural domain is the C-terminal tail which contains the autoinhibitory calmodulin (CaM)-binding motif [21]. At low resting $[Ca^{2+}]_i$, the autoinhibitory CaM-binding motif interacts with the catalytic site (first and second cytosolic loops) thereby inhibiting the PMCA (Fig. 1A). When $[Ca^{2+}]_i$ is elevated, binding of Ca^{2+}/CaM to this autoinhibitory motif induces a conformational change which reduces its affinity for the catalytic site thereby increasing the Ca^{2+} transporting activity of the PMCA (Fig. 1B) [5]. The C-terminus also contains additional high affinity allosteric Ca^{2+} binding sites [22] and an acidic phospholipid binding site [23,24]. Binding of acidic phospholipids such as phosphatidylinositol (PI) and phosphatidylserine (PS) increases the Ca^{2+} and ATP affinity of the PMCA. Phosphoinositide 4,5-bisphosphate (PIP_2) is also a major activator of PMCA and is thought to account for ~50% of the activity of PMCA at rest [4,5]. The last few amino acid residues of the C-terminus of the PMCA contain PDZ-binding motif, which facilitate PMCA dimerization [25] which increases PMCA activity [26]. In addition, the PDZ-binding motif also facilitates the recruitment of the actin cytoskeleton [27], numerous scaffolding proteins and signalling complexes [28–33]. Such targeting only occurs for the full-length b-variants, suggesting specialised signalling roles for different PMCA isoforms. Specifically, PMCA4b functionally interacts with neuronal nitric oxide synthase (nNOS) [34,35], calcineurin [36] and the pro-apoptotic tumour suppressor Ras-associated factor 1 (RASSF1) [37], thereby regulating their downstream signalling.

The N-terminal tail exhibits the greatest diversity between the different isoforms [38] and contains an inhibitory 14-3-3-binding motif [39,40]. In addition to part of the binding site for the autoinhibitory calmodulin (CaM)-binding motif [41] (see Fig. 1B), the first cytosolic loop of the PMCA, which spans between the second and third transmembrane domains, contains a stimulatory acidic phospholipid-binding site [42,43] and splice site A important for the apical membrane targeting in epithelial cells [44–46]. The second cytosolic loop between the fourth and fifth transmembrane domains contains the major catalytic site (including the critical aspartate residue that becomes phosphorylated during the reaction cycle and ATP binding) and the second part of the binding site for the autoinhibitory CaM-binding motif within the C-terminal tail [47].

3. The controversial role of PMCA in cell death

3.1. Intrinsic Ca^{2+}-dependent cell death

Since the PMCA is critical for the regulation of low resting $[Ca^{2+}]_i$ and the prevention of cytotoxic Ca^{2+} overload, in order to under-

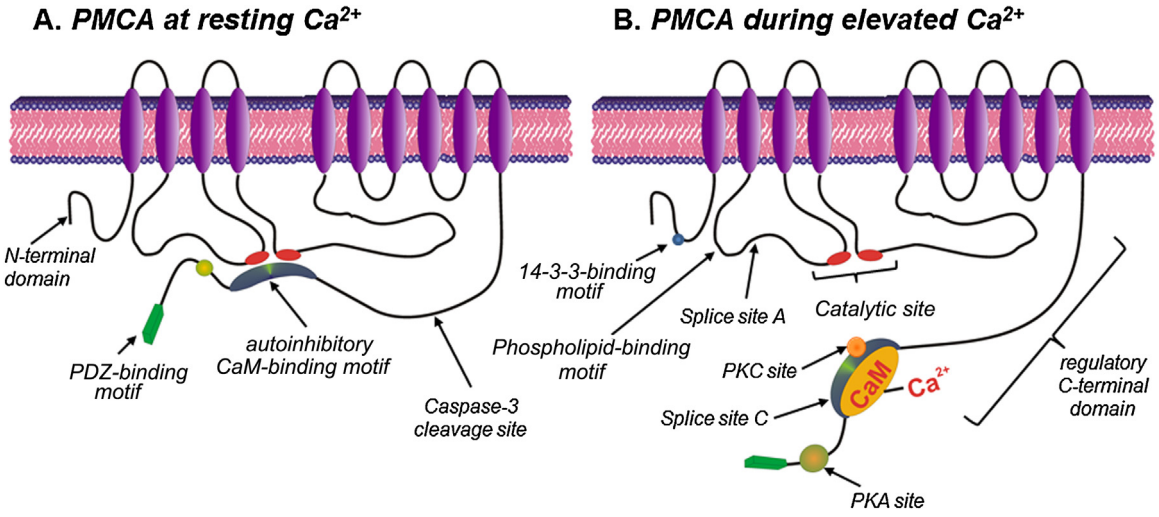

Fig. 1. Two-dimensional topological model of the structure of the PMCA at low resting $[Ca^{2+}]_i$ and following activation at elevated $[Ca^{2+}]_i$. ***A***., at low resting $[Ca^{2+}]_i$ the autoinhibitory CaM binding motif within the C-terminal tail of the PMCA associates with the catalytic motif, thereby preventing Ca^{2+} binding and thus Ca^{2+} transport. ***B***., when $[Ca^{2+}]_i$ is elevated, Ca^{2+}/CaM binds to the autoinhibitory CaM binding motif inducing a conformational change that causes dissociation from the catalytic motif, thereby allowing access to Ca^{2+} and thus the transport of Ca^{2+}. Additional regulatory motifs include an inhibitory 14-3-3-binding site in the N-terminal region, a stimulatory phospholipid-binding motif in the first cytosolic loop and PKA/PKC phosphorylation consensus sites and a PDZ binding motif in the C-terminal tail. Splice sites A and C can generate splice variants with specific tissue-specific distribution, cellular localization and differential regulation.

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