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Calcium signaling in membrane repair

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ABSTRACT

Resealing allows cells to mend damaged membranes rapidly when plasma membrane (PM) disruptions occur. Models of PM repair mechanisms include the "lipid-patch", "endocytic removal", and "macrovesicle shedding" models, all of which postulate a dependence on local increases in intracellular Ca^{2+} at injury sites. Multiple calcium sensors, including synaptotagmin (Syt) VII, dysferlin, and apoptosis-linked gene-2 (ALG-2), are involved in PM resealing, suggesting that Ca^{2+} may regulate multiple steps of the repair process. Although earlier studies focused exclusively on external Ca^{2+}, recent studies suggest that Ca^{2+} release from intracellular stores may also be important for PM resealing. Hence, depending on injury size and the type of injury, multiple sources of Ca^{2+} may be recruited to trigger and orchestrate repair processes. In this review, we discuss the mechanisms by which the resealing process is promoted by vesicular Ca^{2+} channels and Ca^{2+} sensors that accumulate at damage sites.

Contents

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1. Introduction

Plasma membrane (PM) disruptions occur in most cells, especially in those residing in mechanically-active environments, such as skeletal and cardiac muscle [1,2]. Resealing is a repair process that allows cells to mend damaged membranes, preventing the loss of terminally-differentiated cells [1,2]. Recent studies have suggested that damaged cells are able to restore the lipid bilayer barrier by adding membrane components from intracellular vesicles to the cell surface [3].

Three distinct mechanisms of PM lesion repair have been described (see Fig. 1). The first is the so-called "lipid-patch" model in which intracellular vesicles fuse with one another to form membrane patches, after which the patches fuse with the PM, thereby mending lesions [4,5]. Among the intracellular vesicles, lysosomes are the primary candidate [4,6]. The second mechanism is the so-called "endocytic removal" model, in which membrane lesions are removed through endocytosis [2,7,8]. Upon injury, acid sphingomyelinase (aSMase) is secreted to the extracellular space through lysosome exocytosis [2,7,9], and then aSMase-mediated hydrolysis of sphingomyelins (SMs) triggers ceramide-driven membrane invagination, mediating lesion removal [2,7,9]. The third mechanism is the recently-reported "macro-vesicle shedding" model, in which the damaged membranes undergo "outward" shedding upon injury [10–12]. This process involves the assembly of endosomal sorting complex required for transport (ESCRT) machinery [10,13] to generate an outward curvature [14]. Depending on cell type, injury size, and type of injury, one or more of the aforementioned repair mechanisms may be recruited.

All three of the aforementioned repair process models entail a strict dependence on Ca^{2+} [1,2,7,8,10–12]. Membrane damage causes a significant increase in intracellular calcium concentration ($[Ca^{2+}]_{injury}$) at PM injury sites [15–17]; and preventing the $[Ca^{2+}]_{injury}$ response with calcium chelators has been shown to block PM repair [15–17]. Furthermore, multiple calcium sensors, including synaptotagmin (Syt) VII and dysferlin, have been shown to promote lysosomal exocytosis in repair models 1 and 2 [4,6]. In support of repair model 3, the Ca^{2+}-binding protein apoptosis-linked gene-2 (ALG-2) was shown to be essential for recruitment of ESCRT to damage sites [10,13]. Cytosolic calcium ion concentration $[Ca^{2+}]$ is kept low at rest (~100 nM) in most cells. Conversely, the $[Ca^{2+}]$ in the extracellular space and in intracellular stores [*e.g.*, in endoplasmic reticulum (ER) and endolysosomes] are maintained at 2 mM and 0.5–1 mM, respectively [18,19]. Both the extracellular space and intracellular stores could contribute to $[Ca^{2+}]_{injury}$ fluxes. However, almost all previous studies have focused on extracellular Ca^{2+}. Very recently, Ca^{2+} release from intracellular stores was also shown to be important [20]. Hence, depending on injury size and the type of injury, one or both sources of Ca^{2+} may be used to trigger repair processes. In this review, we discuss the mechanisms by which PM resealing processes are promoted by intracellular Ca^{2+} channels and Ca^{2+} sensors.

2. Calcium acts locally

Virtually all aspects of cellular life are affected by Ca^{2+}, which is appreciated for being an evolutionarily conserved cellular signaling molecule with key functions in synaptic transmission, muscle contraction, granule secretion, gene expression, and membrane repair [21]. Ca^{2+} adds charge to Ca^{2+}-binding proteins, thereby initiating conformational changes and switching Ca^{2+} sensor protein functions "on" and "off" [19,21]. There exist hundreds of Ca^{2+} sensor proteins with binding affinities in the nM to mM range that are known to trigger a wide variety of Ca^{2+}-sensitive cellular processes [19,21]. There are 5,000- to 20,000-fold Ca^{2+} concentration gradients between the cytosol (~100 nM) and extracellular

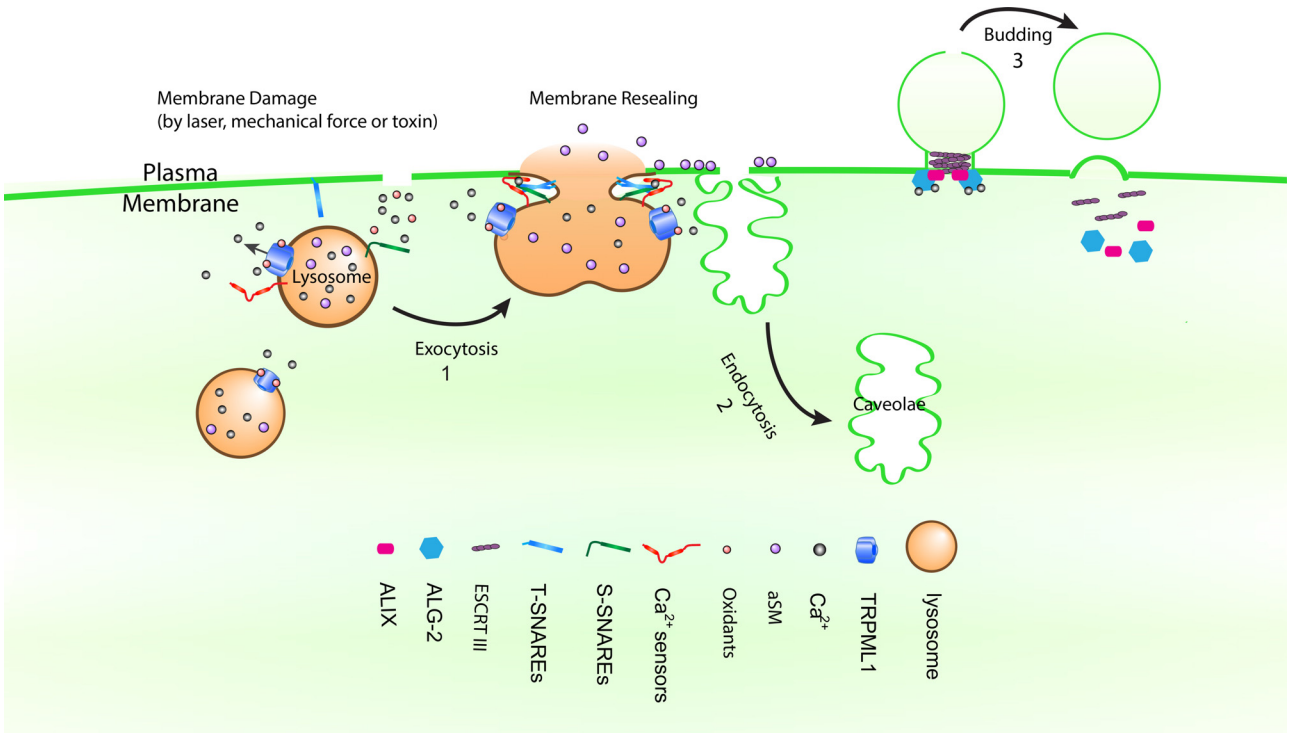

Fig. 1. *Three working models for membrane repair.* In the "lipid-patch" model (1), TRPML1, Syt-VII, dysferlin, and SNAREs participate in membrane repair. Upon the incursion of membrane damage, an influx of oxidants and Ca^{2+} promotes TRPML1 conducted lysosomal Ca^{2+} release, activating Syt-VII and other Ca^{2+} sensors. Subsequently, lysosomal exocytosis is triggered to reseal the disrupted membranes. In the "endocytic removal" model (2), lysosomal exocytosis mediates the release of aSMase to catalyze ceramide-dependent rapid lesion removal by caveolar endocytosis. In the "macro vesicle shedding" model (3), an injury-triggered Ca^{2+} surge recruits ALG-2 to the injury site. Accumulation of ALG-2 facilitates the assembly of ALIX and ESCRT III at the injury site, resulting in the cleavage and shedding of the damaged span of membrane.