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Plasma membrane repair: the adaptable cell life-insurance

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The plasma membrane is the most basic element necessary for the cell to exist and be distinguishable from its environment. Regulated mechanisms allow tightly controlled communication between intacellular and extracellular medium allowing the maintenance of a specific biochemical environment, optimized for cellular functions. The anarchic and uncontrolled opening of a hole in the PM induces a change in the concentration of ions and oxidizing agents perturbing homeostasis. Fortunately, the cell possesses mechanisms that are capable of reacting to sudden extracellular medium entry and to block the leakage locally. Here we summarize the known mechanisms of membrane repair and how the size of the wound and the resulting calcium entry activates preferentially one or another mechanism adapted to the magnitude of the injury.

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Introduction

Plasma membrane (PM) integrity is the most essential condition to ensure cell homeostasis. The PM of cells is constantly exposed to mechanical or biochemical threats that jeopardize its integrity. Intrinsic properties of the PM are important to confer resistance to wounds as a preventive mechanism against membrane injury. Proteins from the cytoskeleton and from the extracellular matrix are main actors to confer such resistance to plasma membrane. But as we will concentrate on repair mechanisms, the role of these proteins will not be discussed here.

A leaky PM can be a consequence of diverse events and especially mechanical trauma or attack by pore forming toxins. Several cell types are particularly susceptible to PM trauma: for instance, neurons, that have little self-renewal; muscle cells that are exposed to mechanical stress; and cells from intestinal track or from the immune system that are exposed to chemical and biochemical attacks. Those cells strongly rely on PM repair mechanisms for their survival.

Pathological conditions, for example stroke or heart attack events or ischemia–reperfusion episodes lead indirectly to acidosis, oxidation and swelling of the cell due to massive entry of sodium ions, all contributing to PM damage and disruption [1,2••,3•]. Several genetic diseases, like muscular dystrophies, have also been associated with defective PM repair mechanisms. It is therefore of major importance to understand membrane repair mechanisms not only to achieve therapeutic strategies for orphan genetic diseases, but also to improve the quality of aging tissues subjected to membrane injury.

Two types of wounds can occur: a simple hole made in a lipid membrane (referred to as 'lipidic' pores) may close spontaneously [4,5]. The rules concerning healing of these have been outlined in our previous review [6]. They involve the physical properties of the membrane (somehow linked to its composition), which will determine whether a pore in the membrane will close spontaneously or will require additional energy and active repair mechanisms. Other pores made by pore forming proteins or molecules (referred to as 'non-lipidic' pores) cannot close spontaneously and require dedicated mechanisms of healing.

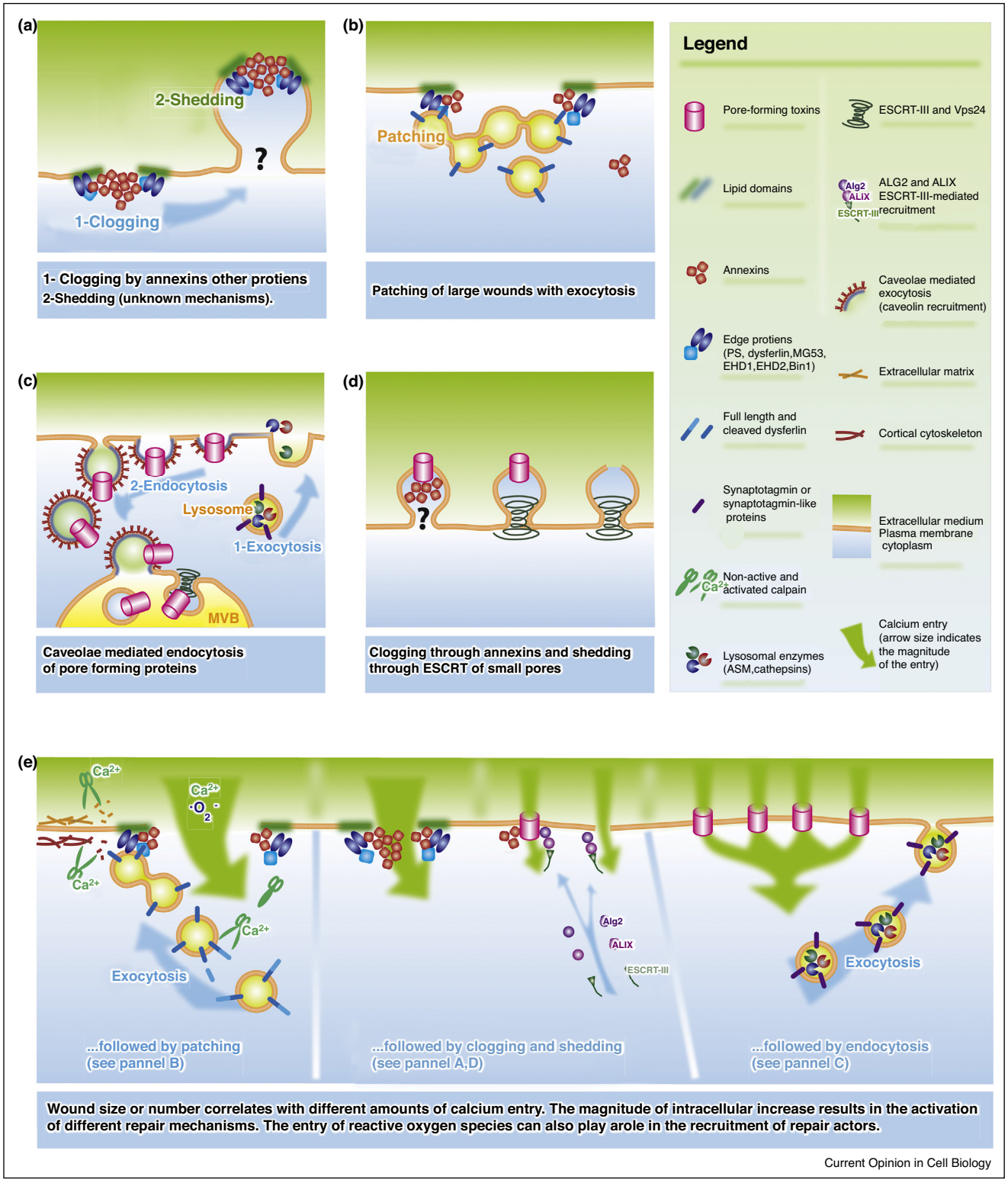
Here, we provide an overview of the known repair mechanisms, how they are differentially activated depending on the size or the nature of the wounds (lipidic or non lipidic) and how calcium entry, the major activator of PM wound repair, stimulates each of them specifically. The different known repair mechanisms are illustrated in Figure 1.

Repairing wounds through clogging or patching

Clogging by protein aggregation/annexins

The first mechanism of PM wound repair involves protein aggregation that is thought to clog the wound. Although the size of the concerned wounds has not been formally measured, the methods used (mostly laser wounding) and

Figure 1



Models for calcium-dependent repair of small to large wounds. Different repair mechanisms have been described to deal with wounds of different sizes and nature. These mechanisms include: **(a)** clogging small or medium size holes with annexins, followed by shedding; **(b)** patching of large wounds with fusion of intracellular vesicles at the wound site; **(c)** endocytosis of large number of small wounds made by pore-forming toxins. **(d)** clogging by annexin aggregation and/or extracellular shedding of a discrete number of small wounds in an ESCRT-III dependent manner (this