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ESCRT Mechanism-mediated Repair of Plasma Membrane Damage Induced by Regulatory Cell Death*

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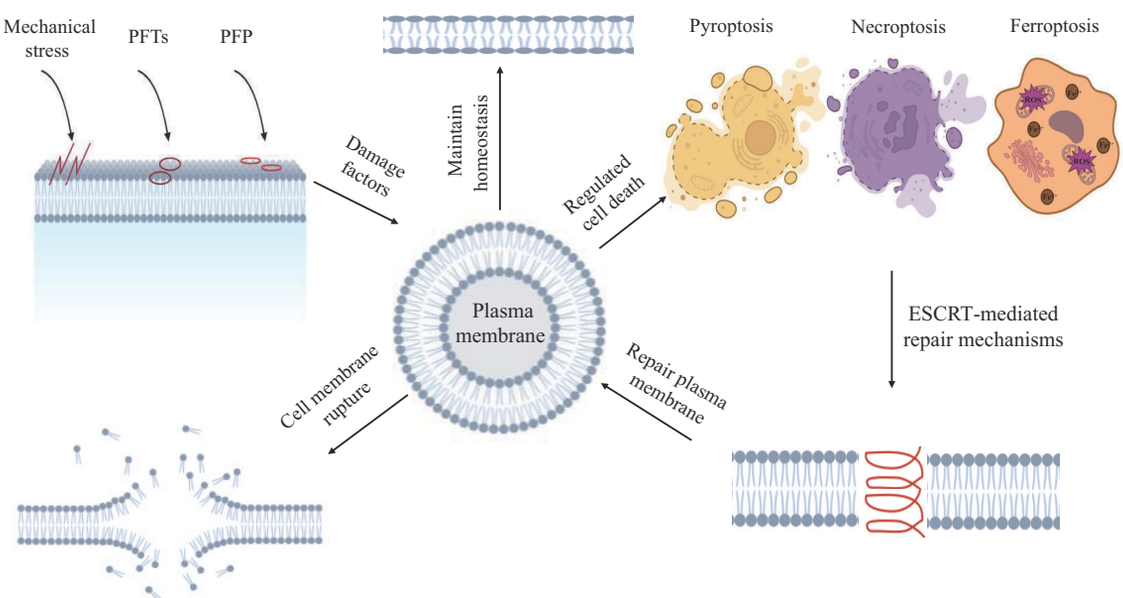
Graphical abstract



Abstract The plasma membrane (PM) plays an essential role in maintaining cell homeostasis, therefore, timely and effective repair of damage caused by factors such as mechanical rupture, pore-forming toxins, or pore-forming proteins is crucial for cell survival. PM damage induces membrane rupture and stimulates an immune response. However, damage resulting from regulated cell death processes, including pyroptosis, ferroptosis, and necroptosis, cannot be repaired by simple sealing mechanisms and thus, requires specialized repair machinery. Recent research has identified a PM repair mechanism of regulated cell death-related injury, mediated by the endosomal sorting complexes required for transport (ESCRT) machinery. Here, we review recent progress in elucidating the ESCRT machinery-mediated repair mechanism of PM injury, with particular focus on processes related to regulated

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cell death. This overview, along with continued research in this field, may provide novel insights into therapeutic targets for diseases associated with dysregulation of regulated cell death pathways.

Key words ESCRT, pyroptosis, ferroptosis, necroptosis, plasma membrane repair
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The plasma membrane (PM) serves as a crucial barrier for communication between the intracellular and extracellular environments, and its integrity is essential for cellular function. This article delves into the role of endosomal sorting complexes required for transport (ESCRT) mechanism in repairing PM damage during regulated cell death, particularly in processes such as necroptosis, pyroptosis, and ferroptosis. We will provide a detailed analysis of ESCRT-mediated membrane repair mechanisms and discuss their importance in maintaining cellular homeostasis and regulating cell death.

The PM regulates the flow of matter, energy, and information between the interior of a cell and the external medium, thereby playing a major role in regulating cellular function. Accordingly, maintaining the structural integrity of the PM is essential for cell homeostasis. The cytoplasmic membrane is a crucial component of the cell. It functions as a direct barrier separating the intracellular and extracellular environments. This membrane contains protein sensors and receptors, which are capable of inducing cell responses by transducing extracellular signals. Additionally, it contains transport channels for inorganic ions and small water-soluble organic molecules. These channels facilitate the movement of these substances across the membrane. Furthermore, the cytoplasmic membrane is involved in the transportation of nutrients and large molecules into and out of the cell. This is achieved through processes such as endocytosis and exocytosis.

The main component of the PM is a lipid bilayer with a thickness of approximately 5−10 nm. The primary structural lipids are glycerophospholipids (phosphatidylserine and phosphatidylcholine), sterols, and sphingolipids (sphingomyelin)[1]. The enrichment of sphingolipids and sterols, such as cholesterol, confers the membrane with resistance to mechanical stress. Glycerophospholipids with small head groups (such as phosphatidylethanolamine and phosphatidic acid) are tapered within the membrane to induce a curved structure; the shape of the lipid determines the shape of the membrane. Proteins are the second main component of the PM, and can be divided into integral and peripheral proteins. Depending on the cell type, the lipid-to-protein ratio can vary from 20% to 70%. Carbohydrates, which are located on the extracellular side of the cell membrane, constitute the third major component of the cell membrane.

The cell membrane can bend toward or away from the cytoplasm, resulting in a positive or negative curvature, respectively[2]. Membrane curvature is an important parameter that defines the morphology of cells, organelles, and local membrane subdomains. The generation and maintenance of curvature are essential for mediating transportation of molecules across the membrane and maintaining cell function. Phosphatidylcholine and phosphatidylserine are cylindrical lipids that form flat monolayers. Lipids with a smaller polar headgroup than phosphatidylcholine, such as phosphatidylethanolamine, phosphoric acid, diacylglycerol, and cardiolipin, have a roughly conical shape, and therefore exhibit negative curvature causing the monolayer to bend and bring the headgroups into closer proximity. Conversely, lipids with a larger head group-to-acyl chain ratio, such as in lysophosphatidylcholine or phosphatidylinositol phosphate, have an inverted conical shape[3].

The structural flexibility of the PM makes it a relatively weak cell barrier compared to other cellular structures, such as cell walls in prokaryotes and plant cells. Thus, the PM is susceptible to damage even during normal physiological processes such as muscle contraction[4], and contributes to the development of several diseases including diabetes[5], muscular dystrophy[6-7], and acute kidney injury[8]. There are many experimental methods for introducing extracellular substances into cells, including microinjection and electroporation, which also cause artificial damage to the PM.

Thus, the susceptibility of the PM to damage has led to repair mechanisms receiving considerable research attention.

Inability to rapidly repair membrane damage leads to permeation and ion imbalance, ultimately resulting in cell death. To counteract these negative effects, repair mechanisms are induced to maintain cell integrity. Skeletal muscle cells and cardiomyocytes are classic examples of cells capable of undergoing extensive cycles of PM destruction and repair because of their high mechanical activity. Similarly, intestinal epithelial cells and skin fibroblasts are resistant to mechanical and chemical disruption of the PM[9]. Lack of PM repair is associated with several diseases such as muscular dystrophy. Furthermore, weight loss has been observed in patients with muscular dystrophy, which suggests a link between repair defects and disease phenotypes such as in dysferlin-deficient muscular dystrophy, where progressive muscle loss occurs if repeated membrane lesions cannot be repaired.

Most cells undergo PM damage owing to mechanical or chemical stress. The diameter of the cell membrane damage determines the specific repair mechanism that is induced. Membrane damage <1 nm in diameter caused by electroporation or protein-induced lipid disorders can be repaired spontaneously, whereas damage larger than a few nanometers requires active membrane repair mechanisms. For such membrane ruptures, the membrane tension reaction prevents spontaneous membrane resealing. For example, the cell membrane cannot simply be resealed after damage caused by pore-forming toxins (PFTs), pore-forming proteins, or laser beams, which cause the cell membrane to form stable pores[10].

ESCRT has been shown to be involved in endocytosis and budding in cell membrane repair[11]. Membrane tension is defined as the force per unit length acting on a membrane cross section and regulates many important biological processes[12]. The primary function of wound-induced exocytosis in membrane repair is to decrease membrane tension, allowing the bilayer to reseal. The ESCRT-III complex has been shown to be recruited to the cell membrane when membrane tension is reduced[13].

During the iron death process of other types of lysed cell death, the loss of plasma membrane integrity allows cellular contents to enter the extracellular space, thereby causing an inflammatory response. As an important or even ultimate defense, cells can initiate mechanisms to repair or isolate and remove damaged membranes. Recent studies have shown that activation of the ESCRT-III mechanism leads to membrane repair by shedding damaged portions of the cell membrane, thereby preventing various types of lysogenic cell death, including necrotic apoptosis, pyroptosis, and iron-death. ESCRT is an evolutionarily conserved mechanism originally thought to be part of the so-called vesicle protein sorting mutant in yeast. In mammalian cells, the ESCRT-III complex consists of 12 subunits: charged multivesicular body protein 1A (CHMP1A), CHMP1B, CHMP2A, CHMP2B, CHMP3, CHMP4A, CHMP4B, CHMP4C, CHMP5, CHMP6, CHMP7, and increased sodium tolerance-1 (IST1).

In this article, we outline the factors that affect cytoplasmic membrane damage and review ESCRT-mediated membrane repair mechanisms, with particular focus on the processes associated with regulated cell death. To provide new research ideas and strategies for the treatment of diseases caused by dysregulation of regulated cell death pathways.

1 Damage factors

In regulated cell death, mechanical injury and toxin exposure are two major factors among the various causes of plasma membrane damage. They not only disrupt the structural integrity of cell membrane but also activate the ESCRT-mediated repair mechanisms, particularly in processes such as necroptosis, pyroptosis, and ferroptosis. Many factors induce PM damage, including mechanical rupture, pathological conditions, and toxin exposure, resulting in the formation of pores of different sizes and shapes. Two types of wounds can occur: (1) lipidic pores, which are simple holes in the lipid membrane that can spontaneously close, and (2) non-lipidic pores, which are pores formed by pore-forming proteins or molecules that cannot close spontaneously and thus require dedicated repair mechanisms[14]. PM damage is associated with a variety of diseases, such as diabetes, muscular dystrophy, and acute kidney injury, highlighting the importance of PM integrity.

1.1 Mechanically−induced wounds

Mechanical stress can induce damage when applied to the cytoplasmic membrane[15]. Physical damage mainly occurs based on transient disruption of the PM structure, therefore, this strategy is frequently employed for the delivery of hydrophilic molecules into cells. Electroporation is a common

method of inducing physical damage, in which electric field pulses applied for microseconds to milliseconds randomly form small hydrophilic pores with a radius of 1−10 nm in the PM. These pores are metastable and typically have a lifetime of milliseconds to seconds[16]. Other physical methods of breaking the PM barrier include using various mechanical tools, applying shear force, exposure to ultrasound, and the insertion of micropipettes directly into the cell. Mechanically created wounds at the PM have micron-scale dimensions, thus, the cells can be resealed by an active repair process[17-18].

Nanoparticles (NPs) can also cause mechanical damage, although the interaction between NPs and biomembranes is complicated. NPs show increased permeability of biofilms[14] and can induce hemolytic activity in a concentration- and size-dependent manner[19-20]. In addition, surface tension has been suggested to mediate the toxic effects of NPs. Recent molecular dynamic simulations have shown that NPs can induce the formation of pores in the lipid bilayer under surface tension but cannot in a non-tensioned lipid bilayer. Gold NPs can form pores in cell membranes; however, once formed, the pores in the membrane can enhance the permeability of the double layer, leading to toxic effects in cells[21]. Both carbon NPs and large particles interfere with pore-formation by strengthening or weakening the biofilm. The cytotoxicity of NPs is closely related to their size; smaller NPs may be more harmful than larger NPs as they have the potential to kill cells *via* cytolysis at high surface tension (*e.g*., in permeable swelling)[22].

1.2 PFTs

The general mode of action of bacterial PFTs involves the following steps: (1) bacterial pathogens secrete toxins, (2) toxin binding to the target cell membranes, (3) toxin oligomerization on the membrane, and (4) transmembrane pore formation. One remarkable feature of bacterial PFTs is the conversion of the toxin from a water-soluble monomeric state to an oligomeric transmembrane pore *via* an array of structural/conformational changes. The most prominent structural change is reorganization of the pore-forming motifs and their insertion into the hydrophobic environment of the membrane lipid bilayer. PFTs can be classified according to the structural motifs employed to generate transmembrane pore architecture; α-PFTs use α-helices to form transmembrane pores whilst β-PFTs generate β-barrel pores[23]. Common PFTs and their sources are detailed in Table 1[23-24].

Table 1 Pore−forming toxins and their sources [25−26]

Type	Name	Source
α-PFTs	Colicins	*Escherichia coli*
	Cry toxin	*Bacillus thuringiensis*
	Cytolysin A	*Escherichia coli, Salmonella enterica,* and *Shigella flexneri*
	Actinoporins	Sea anemones
β-PFTs	α-hemolysin	*Staphylococcus hemolysins*
	The bi-component leukocidins γ-hemolysin	
	β-hemolysin	
	δ-hemolysin	
	Phenol-soluble modulins (PSM)	
	The panton valentine leucocidin (PVL)	
	LukED	
	LukGH/AB	
	Aerolysin	*Aeromonas hydrophila*
	Perfringolysin O (PFO)	*Clostridium perfringens*
	Vibrio cholerae cytolysin	*Vibrio cholerae*
	Listeriolysin O (LLO)	*Listeria monocytogenes*
	Intermedilysin (ILY)	*Streptococcus intermedius*
	Streptolysin O (SLO)	*Streptococcus pyogenes*

1.3 Pore−forming proteins

Immune cells use pore-forming proteins, including complement, perforin, perforin-2, granulysin, gasdermins (GSDMs), and mixed lineage kinase domain-like pseudokinase (MLKL), to induce cell death in microorganisms and host cells. Some of these proteins induce inflammation[27-29]. After proteolytic cleavage or activation by phosphorylation, the pore-forming protein oligomerizes and binds to membrane lipids, thereby destroying membrane integrity.

Pore-forming proteins are also observed in regulated cell death processes. During regulated necrosis, assembly of necrosomes induces autophosphorylation of receptor-interacting serine/threonine-protein kinase 3 (RIP3). Phosphorylated RIP3 then recruits and phosphorylates MLKL, leading to its oligomerization and translocation to the PM. MLKL oligomers rupture the PM by generating cation channels, leading to cell necrosis. Caspase-1 is activated by the inflammasome during pyroptosis. Activated caspase-1 cleaves gasdermin D (GSDMD) to generate the N-terminal fragment, which is oligomerized and translocated to the PM, resulting in rupture through non-selective pore formation[30].

Cytotoxic T cells and hepatocytes produce porin, perforin, and complement component 9 (C9). Perforin forms transient pores on the target PM to facilitate the rapid entry of granzymes during killer cell attacks[31-32]. C9 also forms pores and participates in the final step of membrane attack complex (MAC) assembly[33]. The perforin-like protein contains an MAC domain, which is also found in the complement MAC that kills extracellular bacteria, and perforin-1, used by cytotoxic T cells and natural killer cells that kill virus-infected cells. The MAC domain has been identified as the killer domain of perforin, and is responsible for polymerization, membrane insertion, and pore formation. It may have similar functions in perforin-like molecules in macrophages. The pore-forming proteins and their physiological functions are listed in Table 2[27].

Table 2 Pore−forming proteins and their physiological functions [34]

Name	Physiological function
Complement	Lytic bacteria and opsonized cells
Perforin	Eliminates infection and cancer cells
Perforin-2	Enhances the ability to eliminate invading bacteria
Gasdermins	Recruit immune cells and activate responses to infection and sterile danger signals
Mixed lineage kinase domain-like (MLKL)	Cell death caused by caspase inactivation involving infection, inflammation, septicemia, ischemic lesion, and neurodegeneration
Granulysin	Kills intracellular bacteria, fungi, and parasites intracellularly and possibly extracellular

2 ESCRT−mediated repair mechanisms

The ESCRT mechanism plays a crucial role in response to PM damage. After mechanical injury, the ESCRT-III complex is rapidly recruited to the site of damage, helping to seal the wound and restore membrane integrity. In toxin-induced damage, the ESCRT mechanism is also involved in the repair process, preventing the uncontrolled release of cellular contents. In the process of regulated cell death, the integrity of the plasma membrane is key to cell survival. The ESCRT-III complex plays an essential role in this process. Here are the specific roles of the ESCRT-III complex in membrane repair in different types of regulated cell death. Necroptosis: ESCRT-III repairs plasma membrane damage caused by the MLKL protein, limiting the spread of cell death. Pyroptosis: ESCRT-III limits the secretion of pro-inflammatory cytokines after inflammasome activation, modulating the immune output of pyroptotic cells. Ferroptosis: ESCRT-III repairs the damaged plasma membrane, limiting the entry of cell death-inducing factors, thus playing an important role in cell death and cancer therapy.

Recent evidence has highlighted the role of the ESCRT machinery in PM repair. ESCRT assembles into multi-subunit machinery in the cytosol and drives the membrane scission required in most physiological and metabolic processes involving lipid bilayer membrane dissociation, including the generation of multivesicular bodies (MVBs), cytokinesis, PM damage repair, nuclear membrane remodeling,

autophagy in the endocytosis pathway, cytokinetic abscission, formation of viral replication compartments, lysosome repair, nuclear pore-quality control, and nuclear envelope repair[11]. ESCRT also plays an important role in PM repair following pyroptosis, necroptosis, and ferroptosis[35].

ESCRT-III is an important eukaryotic membrane remodeling machine that plays a role in the membrane remodeling of organelles[36]. ESCRT-III-mediated PM repair mechanism is shown in Figure 1.

Using deep-etching electron microscopy, Skowyra *et al*.[37] found that stimulation of lysosomes in U2OS and macrophage cells by silica particles resulted in ESCRT-III aggregation on endolysosome vesicle structures. Furthermore, small areas with low densities of immunolabels were clustered, indicating that ESCRT-III mainly targets discrete areas of the organelle membrane. Jimenez *et al*. [38] showed that ESCRT-III proteins specifically recruited to the wound sites induced by a laser beam and accumulated until wound closure. Quantitative analysis of wound closure kinetics coupled with mathematical modeling suggested that ESCRTs are involved in the repair of small wounds. Real-time imaging and correlative scanning electron microscopy identified extracellular buds and shedding at the site of ESCRT recruitment. Scheffer *et al*. [39] reported the Ca^{2+}-dependent accumulation of the ESCRT-III-VPS4 complex following creation of a large focal injury to the cell membrane. The authors also identified the role of ALG2 as the initiator of sequential ESCRT-III-VPS4 complex assembly, which facilitates the scission and repair of the injured cell membrane. Lack of ALG2, ALIX, or VPS4B prevented the shedding and repair of the injured cell membrane. Similarly, Sønder *et al*.[40] showed that, following injury to the PM of invasive breast cancer cells and Ca^{2+} flux into the cytoplasm, annexin A7 formed a complex with ALG2 to facilitate the proper recruitment and binding of ALG2 and ALIX to the damaged membrane. ALG2 and ALIX assemble the ESCRT-III complex, which helps to excise and shed the damaged portion of the PM during wound healing. Radulovic *et al*. [41] reported that recruitment of ESCRT-III complex subunits was prominently influenced by the ESCRT-I components TSG101 and ESCRT-III-binding protein ALIX, in various lysosomal membrane injury events. Interference with ESCRT recruitment abolishes lysosome repair and causes irreversible lysosome damage, which is lethal to cells. Furthermore, Shukla *et al*. [42] showed that the Ca^{2+}-binding regulatory protein ALG2 binds directly to negatively charged membranes in a Ca^{2+}-dependent manner. By monitoring the colocalization of ALIX with ALG2 on negatively charged membranes, the authors also show that ALG2 recruits ALIX to the membrane and that ALIX recruitment to the membrane orchestrates the downstream assembly of late-acting CHMP4B, CHMP3, and CHMP2A subunits along with the AAA ATPase VPS4B. At the site of damage, the ESCRT-III subunits CHMP3, CHMP2A, and CHMP2B, and the ESCRT-III-related protein CHMP1A appear to co-localize with CHMP4B-positive spots, with maximum levels of CHMP4B observed during wound closure. ESCRT recruitment is rapid, occurring as early as 30 s to 4 min post-injury, followed by wound repair within minutes of the damage. Recruitment of CHMP4B to the sites of damage is an energy-independent process, whereas both membrane repair and ESCRT-mediated shedding are energy-dependent. Furthermore, the ATPase responsible for the disassembly of ESCRT-III polymers, VPS4, is also localized to the site of damage[43]. In yeast and non-neuronal mammalian cells, nuclear relocation of CHMP7 recruits the ESCRT-III proteins CHMP4B, CHMP2B, and VPS4 to promote nuclear envelope repair[44].

Ca^{2+} flux during ferroptosis induces activation of the ESCRT-III-dependent membrane repair machinery, which counterbalances the kinetics of cell death and modulates the immunological signature of ferroptosis[45]. Westman *et al*.[46] showed that ESCRT-III stabilizes the damaged membrane areas of epithelial cells and maintains epithelial integrity. Pashkova *et al*. [47] found that ESCRT-III may coordinate late ESCRT-driven membrane remodeling events. Nguyen *et al*.[48] observed that CHMP1B first polymerizes into a single-stranded helical filament, shaping membranes into moderate-curvature tubules. Subsequently, IST1 assembles a second strand on CHMP1B, further constricting the membrane tube and reducing its diameter to near the fission point. Each constriction step thins out the underlying bilayer, thereby lowering the barrier to membrane fission. Alqabandi *et al*.[49] used a combination of techniques in biomimetic systems and purified proteins to study CHMP2A and CHMP2B affinities and their effects on membranes. The results showed that CHMP2B binding was enhanced in the presence of PI(4, 5)P2

lipids. In contrast, CHMP2A did not show lipid specificity and required CHMP3 to bind significantly to membranes. On the micrometer scale and at moderate bulk concentrations, CHMP2B formed a reticular structure on the membranes, whereas CHMP2A (+CHMP3) bound homogeneously. Unexpectedly, CHMP2A and CHMP2B induced different mechanical effects on membranes: CHMP2B strongly rigidified them, whereas CHMP2A (+CHMP3) had no significant effect. Using high-speed atomic force microscopy and electron microscopy, Maity *et al*. [50] showed that VPS4 constricts and cleaves the ESCRT-III CHMP2A-CHMP3 helical filaments *in vitro*. Constriction starts asymmetrically and progressively decreases the diameter of the CHMP2A-CHMP3 tubular structure, coiling the CHMP2A-CHMP3 filaments into dome-like end caps, which revealed that VPS4 actively constricted ESCRT-III filaments and cleaved them prior to completing the disassembly.

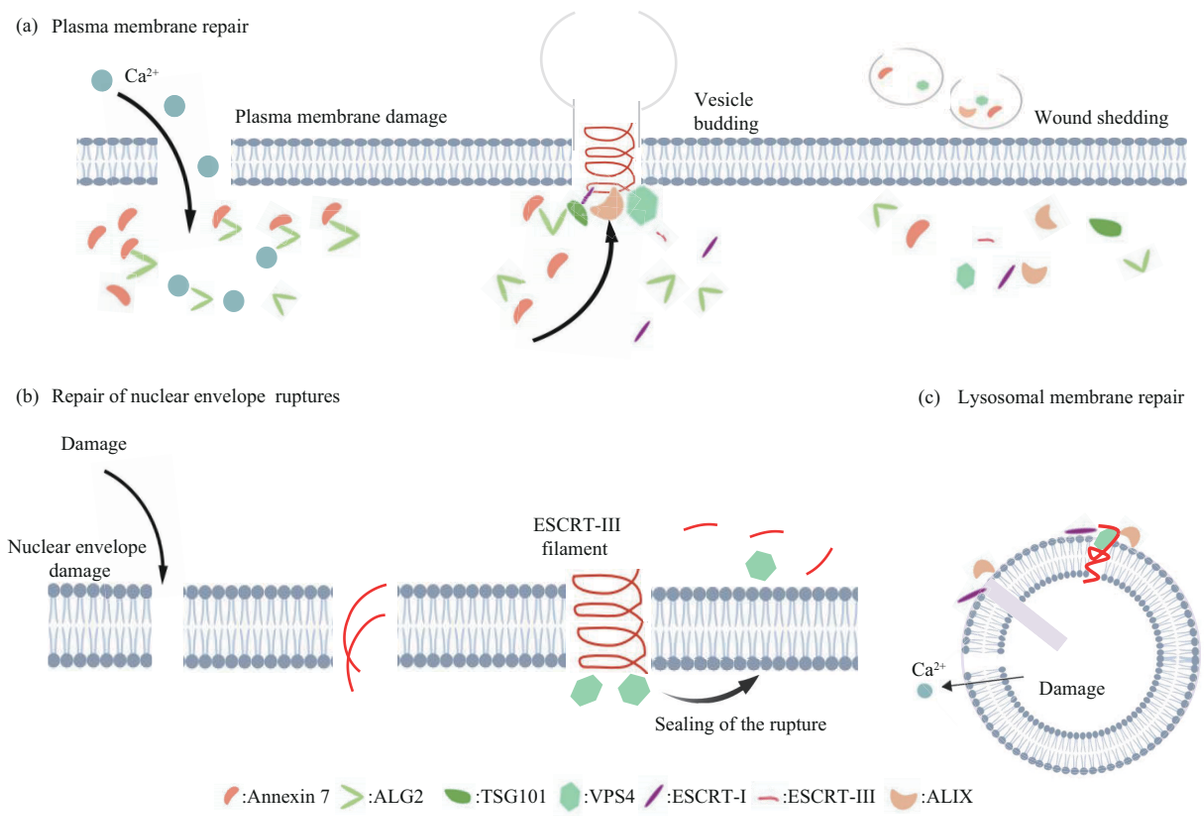

Fig. 1 ESCRT−III mediated repair mechanisms

Plasma membrane damage induces Ca^{2+} influx into the cytoplasm. This leads to the recruitment of annexin A7, which forms a complex with the Ca^{2+} sensor ALG2, thereby promoting its recruitment and localization at the wound site. This is followed by the recruitment of ALIX and TSG101 in an ALG2-dependent and Ca^{2+}-dependent manner. The ESCRT-III complex is further recruited by ALIX and ESCRT-I, and together with VPS4, leads to membrane repair and shedding of damaged parts of the cell membrane[11].

Cell-selected repair strategies appear to depend on the extent of damage, spatial location of damage and cell type. Individual eukaryotic cells can rapidly repair their plasma membrane after injury through a process that restores internal homeostasis and prevents cell death.

PM repair is a conservative cellular response that actively reseals damaged areas to prevent cell death and maintain homeostasis. Terasaki *et al*. [51] demonstrated that intracellular vesicles are recruited by extracellular Ca^{2+} influx signaling to the site of the damage, to form “patches” that repair damaged cell membranes. They originally proposed various models of membrane repair. (1) Thermodynamic resealing can occur spontaneously if less tension is generated by disordered arrangement of membrane phospholipids

at the wound edge. This process is the most likely route of resealing for membrane breaks ≤1 μm in diameter. (2) Exocytosis contributes to repair by trafficking intracellular vesicles to the wounded area, where they fuse with the injured membrane to form a repair patch. (3) Wound constriction is another repair mechanism, which is mediated by caveolae. During this process, the caveolae cluster to fuse around larger wounds, leading to wound constriction and the intracellular fusion of caveolar endosomes. (4) Lysosomal exocytosis promotes ceramide-induced endocytic vesicle formation and lesions are actively removed from the membrane. (5) Exocytosis of an intracellular patch and fusion to the wound site may cause extracellular release or “shedding” of the wound site. (6) Endocytosis of wounds may also help to repair membrane damage through invagination of caveolar vesicles and subsequent intracellular fusion of the caveolae[52-54].

The ESCRT-III complex plays a pivotal role in membrane repair and remodeling, particularly in response to plasma membrane damage. It is recruited to sites of injury, where it aids in sealing wounds and restoring membrane integrity. Studies have shown that ESCRT-III accumulation at damage sites is both Ca^{2+}-dependent and energy-dependent, with proteins like ALG2 and ALIX facilitating its recruitment. The complex’s action is not limited to plasma membranes, it also repairs the nuclear envelope and organelle membranes. ESCRT-III’s function in membrane repair is conserved across eukaryotic cells, indicating its fundamental importance in cellular homeostasis. Additionally, ESCRT-III’s role extends to modulating cell death pathways, such as ferroptosis, by stabilizing membranes. The complex’s ability to reshape membranes into tubules and facilitate fission highlights its multifaceted involvement in membrane dynamics. Overall, the ESCRT-III complex is a critical component of cellular mechanisms that maintain membrane integrity and counteract cell death following membrane damage.

According to the Nomenclature Committee on Cell Death, cell death can be divided into accidental cell death (ACD) and regulated cell death (RCD)[55]. ACD is a passive and uncontrolled process, whereas RCD is an active and controlled process. The ESCRT-III complex plays a unique role in suppressing various types of RCD such as necroptosis[56], pyroptosis[57], and ferroptosis[58] by repairing damaged PMs[59]. Gregor *et al*.[60] reported the role of ESCRT proteins in the repair of cellular membrane damage, particularly in cell death mediated by cytotoxic T cells. The study indicates that the ESCRT complex plays a crucial role in the repair of membrane damage, limiting apoptosis mediated by cytotoxic T cells and natural killer (NK) cells, thereby reducing sensitivity to T cell-mediated cytotoxicity.

Pyroptosis, a type of RCD, critically depends on the formation of PM pores by members of the GSDM protein family, most often *via* inflammatory caspase activation[61]. Pyroptosis is morphologically characterized by chromatin condensation, DNA fragmentation, nuclear integrity, DNA laddering, pore formation, cell swelling, and osmotic lysis. The formation of pores in the cell membrane reduces structural integrity, resulting in the release of cellular contents, increased permeability, and induction of inflammatory reactions, eventually resulting in cell membrane rupture and dissolution[62]. GSDMs represent a family of proteins that comprises 6 members in humans (GSDM A, B, C, D, E (also known as DFNA5) and PJVK (also known as DFNB59)), and 10 members in mice (GSDM A1-3, C1-4, D, E, and PJVK)[63].

Using high-resolution atomic force microscopy, Mulvihill *et al.*[64] observed that once N-GSDMD becomes inserted into lipid compositions, it assembles arc-, slit-, and ring-shaped oligomers, each of which can form transmembrane pores. Arc- and slit-shaped oligomers fuse into larger ring-shaped oligomers. Over time, enterocytes (inflammatory cytokines) are released from the pores. Similarly, GSDME and GSDMA3 also showed pore-formation ability[65-66].

The passive transport of molecules through GSDM pores also leads to osmotic imbalance, cell bursting, and death, which allows for the nonspecific release of larger damage-associated molecular patterns from cells[27, 39].

Rühl *et al*.[57] demonstrated that calcium influx through GSDMD pores signals the initiation of membrane repair by recruiting the ESCRT machinery to damaged membrane areas. ESCRT-III-dependent membrane repair limits proinflammatory cytokine (interleukin-1β) secretion and pyroptosis after inflammasome activation. The research by Espiritu *et al*.[67] reveals that ESCRT-dependent membrane repair negatively regulates pyroptosis downstream of GSDMD activation. These findings not only attributed

an anti-inflammatory mechanism of membrane repair to ESCRT-III but also provided new insight into general cellular survival mechanisms during pyroptosis. Further support for this mechanism was provided by an animal experiment. Pyroptosis induced in Sprague-Dawley rats that had been exposed to inescapable tail shock was associated with increased mRNA and protein expression of the ESCRT-III protein CHMP4B[68].

During the process of pyroptosis, the integrity of the cell membrane is disrupted, leading to massive Ca^{2+} influx into the cell, which in turn activates and recruits the ESCRT-III complex to the damaged cell membrane. This Ca^{2+} influx-mediated activation and recruitment of the ESCRT-III complex is essential for the repair of damaged cell membranes. Taken together, the ESCRT-III complex plays a critical role in focal death by repairing damaged cell membranes, a mechanism that is important for the regulation of cell death and drug resistance in tumor therapy.

Ferroptosis is a multistep RCD that is initiated by oxidative perturbations of the intracellular microenvironment, constitutively controlled by GPX4, which can be inhibited by iron chelators and lipophilic antioxidants. Ferroptosis is characterized by excessive iron accumulation and lipid peroxidation, morphologically by loss of PM integrity, cytoplasmic swelling (oncosis), swelling of cytoplasmic organelles, moderate chromatin condensation, the presence of smaller than normal mitochondria with condensed membranes, reduction or vanishing of the mitochondrial crista, and outer mitochondrial membrane rupture[69]. The accumulation of ESCRT-III subunits (*e. g*., CHMP5 and CHMP6) in the PM is increased by the release of classical ferroptosis activators (*e. g*., erastin and Ras-selective lethal small molecule 3), which rely on endoplasmic reticulum stress and calcium influx[70]. Importantly, knockdown of CHMP5 or CHMP6 by RNA interference sensitized human cancer cells (PANC1 and HepG2) to lipid peroxidation-mediated ferroptosis *in vitro* and *in vivo*. These findings suggest that ESCRT-III confers resistance to ferroptotic cell death, allowing for cell survival under stress conditions. The study by Pedrera *et al.* [45] investigates how ferroptotic pore-induced Ca^{2+} flux and ESCRT-III activation regulate cell death kinetics. The research indicates that the formation of ferroptotic pores leads to Ca^{2+} influx and the activation of ESCRT-III, which is crucial for the process of cell death. In summary, the ESCRT-mediated mechanism of ferroptosis repair involves the activation and recruitment of the ESCRT-III complex, which restricts the entry of cell death-inducing factors by repairing damaged cell membranes, thereby playing an important role in cell death and cancer therapy.

Necroptosis is a modality of RCD triggered by perturbations in extracellular or intracellular homeostasis, which critically depends on MLKL, RIPK3, and occasionally the kinase activity of RIPK1[70]. MLKL is the only effector exclusively implicated in necroptosis and is the most downstream component of the pathway reported to date. The three-dimensional structure of inactive MLKL comprises two domains, an N-terminal, four-helix bundle domain (4HB) and a C-terminal pseudo-kinase domain (psK) bridged by a flexible brace region[70-71]. Intensive research in recent years has demonstrated that the 4HB domain of MLKL acts as the killer domain, whereas the psK domain and the brace region are critical to maintaining the cell death-inducing capacity of MLKL. Gong *et al*. [72-73] showed that MLKL-dependent Ca^{2+} influx and phosphatidylserine exposure on the extracellular side of the PM preceded the loss of PM integrity. Moreover, the ESCRT-III machinery was required for the formation of PM bubbles and sustained cell survival when MLKL activation was limited or reversed.

In summary, the ESCRT-III complex plays a central role in regulated cell death by repairing damaged plasma membranes, balancing cell death pathways, modulating immune responses, and regulating the secretion of cytokines, thereby exerting a core function in both cell death and immune regulation.

3 Pathological implications of ESCRT in PM repair

The ESCRT-mediated PM repair function is not only of significant importance in cell biology but also plays a key role in the development and progression of various diseases. Here is the role of the ESCRT-mediated membrane repair mechanism in different pathological processes.

Pyroptosis, ferroptosis, and necroptosis are the conservative processes of cell death. Disorder of these

process is associated with various diseases, including immunodeficiency, neurodegeneration, and cancer[74], hence elucidating the ESCRT-mediated PM repair mechanism can provide new treatment targets.

ESCRT-mediated PM repair function provides a possible treatment for Alzheimer's disease (AD). Amyloid β-protein (Aβ) plays a key role in AD, and its abnormal deposition is the key to AD incidence. Therefore, reducing Aβ content and weakening its neurotoxicity can mitigate the symptoms of AD[75]. Fruhmann *et al*.[76] confirmed that upon deletion of the *Bro1* gene, ESCRT could down-regulate Aβ expression by enhancing the membrane repair function. In addition, during nuclear membrane repair, CHMP4B is regulated by ESCRT-III accessory proteins. Recruitment of CHMP7 and the nuclear envelope protein LEMD2 to the site of injury also plays a role in repair[77].

ESCRT-III-mediated tumor resistance membrane repair is a potential target for cancer treatment[59]. Isermann *et al*. [78] showed that nuclear deformation and rupture may drive the genomic instability of invasive cells and promote the progression of cancer. The ESCRT-III subunit and VPS4B are recruited to the nuclear envelope (NE) fracture site during nuclear rupture to help restore its integrity. Inhibition of NE repair may provide a new treatment strategy against cancer, specifically by targeting invasive cancer cells.

Cytotoxic T lymphocytes (CTLs) and natural killer cells kill virus-infected and tumor cells through the polarized release of perforin and granzymes. ESCRT proteins are recruited to CTL accumulation sites in target cells immediately following perforin release. Inhibition of the ESCRT machinery in cancer-derived cells enhances their susceptibility to CTL-mediated killing[79].

Apoptosis-inducing factor mitochondria-associated 2 (AIFM2, also known as FSP1 or PRG3) is an endogenous ferroptosis suppressor; AIFM2-dependent ESCRT-III recruitment in the PM facilitates ferroptosis resistance through the activation of a membrane repair mechanism that regulates membrane budding and fission. Importantly, the genetic inhibition of the AIFM2-dependent ESCRT-III pathway increases the anticancer activity of sorafenib in a xenograft tumor mouse model[80].

ESCRT-III machinery is a key component in counteracting MLKL-induced PM injuries in cells undergoing necroptosis[81]. Stroke model rats showed evident brain injury, concomitant with the downregulation of ESCRT-III subunits and the up-regulation of necroptosis-relevant protein expression. Post-ischemic administration of polymyxin B could alleviate brain injury, accompanied with restoration of the levels of ESCRT-III subunits and suppression of necroptosis-relevant proteins. Polymyxin B can reduce necroptosis in the stroke model rat brain by enhancing the ESCRT-III machinery and suppressing the RIPK1/RIPK3/MLKL pathway[82].

The ESCRT complex plays a crucial role in regulating cell death processes, especially in the repair of the PM. In AD, the ESCRT complex helps alleviate symptoms by reducing the deposition and neurotoxicity of Aβ. In cancer therapy, ESCRT-III-mediated membrane repair is a potential target, and its inhibition may slow down cancer progression. ESCRT proteins are involved in the killing mechanisms of CTLs and NK cells, enhancing the clearance of virus-infected cells and tumor cells. AIFM2-dependent ESCRT-III promotes resistance to iron mutation, and its inhibition can enhance the effectiveness of anticancer drugs. In necrotic cells, the ESCRT-III mechanism counteracts MLKL-induced PM damage, and polymyxin B alleviates brain injury by enhancing the ESCRT-III mechanism. Therefore, the ESCRT complex plays a key role in various cell death processes, offering new strategies for the treatment of related diseases.

4 Conclusion and prospects

The ESCRT-mediated PM damage repair mechanism plays a central role in maintaining cellular homeostasis and regulating cell death. Future research needs to further elucidate the molecular details of the ESCRT mechanism to develop new therapeutic strategies targeting diseases caused by regulated cell death.

Since initial discovery, the field of ESCRT protein research has progressed, and a large number of ESCRT-mediated PM repair-driven processes, as well as ESCRT-interacting proteins, have been described. Extensive efforts have been made to understand the structural and dynamic behavior of ESCRT-mediated assembly of PM repair machinery in different cellular processes, all of which highlight the orchestrated nature of ESCRT proteins. Small differences in point mutations and ESCRT protein expression levels can

have serious consequences on organelle and cell function, tissue integrity, and can lead to lethal pathology.

Although a large fraction of the processes driven by ESCRT-mediated PM repair mechanisms have been studied, the exact molecular mechanisms by which the multi-subunit ESCRT mediates membrane repair of regulated cell death-induced injuries have not been elucidated. During regulated cell death, it is unclear whether other membrane repair mechanisms also play a role in repairing damaged cells. Since the ESCRT mechanism involves several proteins, the uncertainty of the requirement for individual components of the mechanism for cell survival, presents a challenge in the future development of targeted treatment of disease. Further studies are also warranted to determine whether it is possible to develop specific small-molecule compounds to target membrane repair pathways to control survival of cells damaged by regulated cell death and treat diseases caused by regulated death.

Pyroptosis, ferroptosis, and necroptosis have been extensively studied. A comprehensive understanding of the mechanism underlying ESCRT-mediated membrane repair of damage caused by these processes, will provide better targets and methods for their regulation. Although loss of an intact PM causes cell lysis and necrosis, cells can nevertheless endure a certain level of PM damage by triggering ESCRT-mediated repair to ensure cell survival. A review of the current repair mechanisms of ESCRT machinery-mediated regulatory cell death-induced damage provides new insights into new targets for the treatment of diseases associated with cell membrane damage, such as immunodeficiency, neurodegenerative diseases, and cancer.

The ESCRT complex plays a crucial role in regulating cell death, especially in PM repair. In AD, ESCRT contributes to symptom reduction by reducing Aβ deposition and neurotoxicity. In cancer therapy, ESCRT-III-mediated membrane repair is a potential target, and its inhibition may slow cancer progression. ESCRT proteins are involved in the killing mechanism of CTLs and NK cells, enhancing clearance of virus-infected and tumor cells. AIFM2 is dependent on ESCRT-III to promote iron-mutagenic resistance, and its inhibition enhances the effects of anticancer drugs. In necrotic cells, the ESCRT-III mechanism counteracts MLKL-induced PM damage, and polymyxin B attenuates brain damage by enhancing the ESCRT-III mechanism. Thus, ESCRT plays a critical role in a variety of cell death processes, providing new strategies for the treatment of related diseases.

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ESCRT机制介导的调节性细胞死亡引起的质膜损伤修复及其机制*

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摘要 质膜（PM）在维持细胞稳态方面发挥着至关重要的作用。因此，及时有效地修复由于机械破裂、孔形成毒素或孔形成蛋白等原因造成的质膜损伤对细胞存活至关重要。质膜损伤会导致细胞膜破裂并刺激免疫反应。然而，由程序性细胞死亡过程（如焦亡、铁死亡和坏死性凋亡）引起的质膜损伤不能通过简单的封闭机制修复，因此需要专门的修复机制。最新研究揭示了一种由内泡运输所需的排序复合体（ESCRT）机制介导的质膜损伤修复机制。本文回顾了ESCRT机制介导的质膜损伤修复机制的研究进展，特别关注与程序性细胞死亡相关的过程。本综述以及该领域的持续工作可以为治疗由程序性细胞死亡途径失调引起的疾病提供新的见解。

关键词 ESCRT，焦亡，铁死亡，细胞败亡，质膜修复
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