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# THE ROLE OF PHOSPHOLIPID SCRAMBLASES IN AUTOIMMUNE TISSUE DAMAGE: MECHANISMS OF PHOSPHATIDYLSERINE EXPOSURE AND IMMUNE ACTIVATION

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## Abstract

Phospholipid scramblases are membrane proteins that disrupt lipid asymmetry, crucially exposing phosphatidylserine (PS) on the cell surface. Three major human scramblase families – the phospholipid scramblases (PLSCR), the TMEM16/anoctamin family, and the XKR (XK-related) family – have been characterized. PLSCR proteins (especially PLSCR1) were initially identified as Ca^2+-dependent scramblases, but their physiological role remains debated. TMEM16F (ANO6) is a Ca^2+-activated ion channel/scramblase essential for rapid PS externalization, as shown by TMEM16F knockout models and in Scott syndrome (a bleeding disorder). XKR family members (notably XKR8) are caspase-activated scramblases that irreversibly externalize PS during apoptosis. In apoptosis, scramblases mediate the hallmark PS "eat-me" signal for phagocytic clearance. Dysregulated scramblase activity or apoptotic clearance can trigger autoimmunity: for example, XKR8 deficiency in mice causes lupus-like disease, and human systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) patients exhibit altered scramblase expression and PS exposure. Here, we review recent biochemical and immunological studies of PLSCR, TMEM16, and XKR proteins, focusing on their lipid-translocation mechanisms, roles in apoptotic PS exposure, and links to autoimmunity (SLE, APS). We emphasize advances from the last decade and analyze how aberrant PS scrambling contributes to inflammatory diseases.

**Keywords:** Phospholipid scramblases,phosphatidylserine externalization, TMEM16F, apoptosis, autoimmune diseases, tissue inflammation,immune dysregulation, efferocytosis

## Introduction

Normal eukaryotic cells maintain an asymmetric distribution of phospholipids: aminophospholipids like PS and phosphatidylethanolamine are confined to the

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inner leaflet of the plasma membrane by ATP-dependent flippases. Phospholipid scramblases are proteins that collapse this asymmetry by bidirectional lipid translocation, rapidly externalizing PS and other lipids. The exposure of PS on the outer membrane leaflets serves two key signals: (1) in platelets, it provides a catalytic surface for blood clotting; (2) in apoptotic cells, it acts as an "eat-me" signal for phagocytosis. Several scramblase families have been identified. Early work implicated a $Ca^{2+}$-dependent scramblase activity in red blood cells and platelets, later attributed to TMEM16F (ANO6). A group of proteins named XKR (XK-related) were discovered through their $Ca^{2+}$-independent scramblase activity in apoptosis. The phospholipid scramblase (PLSCR) family (PLSCR1–4) was also proposed as lipid scramblases, though recent studies question their direct role in scrambling. These scramblases are central to processes such as apoptosis and coagulation and, when dysfunctional, contribute to disease. In particular, failure to clear apoptotic cells – due in part to inadequate PS exposure – is a well-recognized factor in autoimmune diseases like SLE. This review surveys the major scramblase families (PLSCR, TMEM16, XKR), their biochemical mechanisms of lipid translocation, roles in PS exposure during apoptosis, and connections to autoimmunity (SLE, APS). We emphasize recent peer-reviewed findings (past 5–10 years) in biochemistry and immunology, aiming for a comprehensive, publication-level analysis.

## Major Scramblase Families

### 1.Phospholipid Scramblase (PLSCR) Family

The PLSCR family (PLSCR1–4) consists of small (~318 aa) type II membrane proteins originally identified by their ability to catalyze $Ca^{2+}$-dependent phospholipid translocation in vitro. PLSCR1 is widely expressed and strongly induced by interferons, suggesting roles in innate immunity. In human cells, IFN-α upregulates PLSCR1 via a STAT1-dependent mechanism, and the PLSCR1 gene is hypomethylated (and thus overexpressed) in SLE patient cells. However,

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the functional scramblase activity of PLSCR1 in vivo is debated. Recent knockout studies found that PLSCR1-deficient cells have normal $Ca^{2+}$-induced PS externalization, whereas TMEM16F-null cells show a profound defect. This indicates that TMEM16F – not PLSCR1 – is the primary $Ca^{2+}$-activated scramblase in cells. Nonetheless, PLSCR1 may influence apoptotic PS exposure indirectly or participate in other signaling pathways (e.g. through interactions with transcription factors and innate immune sensors). PLSCR3 is notable for its role in mitochondria: it can scramble cardiolipin during apoptosis, facilitating cytochrome c release. In this way, certain PLSCR isoforms link internal membrane dynamics to programmed cell death. Overall, while in vitro scramblase activity has been demonstrated, the physiological role of PLSCR proteins in PS translocation remains to be fully resolved.

## 2.TMEM16 (Anoctamin) Family

The TMEM16/ANO family comprises 10 paralogs in mammals, several of which are $Ca^{2+}$-activated. TMEM16F (ANO6) is the best-studied scramblase member. Suzuki et al. (2010) definitively identified TMEM16F as the $Ca^{2+}$-dependent PS scramblase responsible for platelet activation. They showed that TMEM16F-null mice and a human Scott syndrome patient with a TMEM16F mutation have severely impaired $Ca^{2+}$-triggered PS exposure on platelets, leading to reduced thrombin generation. In platelets, TMEM16F expression is high, and its activation by $Ca^{2+}$-fluxes leads to massive PS externalization and procoagulant microvesicle release. In fact, TMEM16F knockout mice phenocopy human Scott syndrome (a bleeding diathesis) with defective coagulation. Biochemically, TMEM16 scramblases are multi-transmembrane ion channels that form a hydrophilic groove through which lipid headgroups can translocate. TMEM16F also influences immune cell function: it can regulate scramblase-mediated PS exposure on activated immune cells and dying cells, affecting coagulation, cell–cell fusion, and possibly immune signaling. Notably, TMEM16F also exhibits ion

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channel activity, which may link membrane potential and ionic conditions to lipid scrambling. Other TMEM16 paralogs have different activities (e.g. TMEM16A is a $Cl^-$ channel without scramblase activity), reflecting divergent functions in physiology. In summary, TMEM16F is a prototypical $Ca^{2+}$-activated scramblase critical for PS externalization in platelets and other cells.

### 3.XKR (XK-Related) Family

XKR proteins (eight in humans: XKR4–XKR8 etc.) are multi-pass membrane proteins that function in caspase-dependent scrambling. The founding member, Caenorhabditis elegans CED-8, and its mammalian ortholog XKR8 were identified as apoptotic scramblases. XKR8 is ubiquitously expressed and contains caspase-3 cleavage sites in its C-terminus. Upon apoptotic stimuli, effector caspases cleave and activate XKR8, triggering rapid and sustained PS exposure on the apoptotic cell surface. Because caspase activation is irreversible, XKR8-mediated PS externalization is also effectively irreversible, marking the cell for clearance. XKR family proteins have no detectable $Ca^{2+}$-binding motifs; instead, they are regulated by proteolysis. For example, a recent study showed that caspase-8 cleavage of XKR8 in osteoclast precursors mediates localized PS exposure to promote cell–cell fusion. In humans, XKR8 is the major apoptotic scramblase in many cell types, although other XKR members (e.g. XKR4) function in specific contexts (XKR4 is expressed in some tissues and also activated by caspases). XKR proteins likely translocate lipids via an intramembrane pathway that becomes exposed upon conformational change (exact mechanism remains under study). Scramblase Classes: In summary, scramblases fall into at least three classes: (1) Caspase-activated (e.g. XKR family), (2) $Ca^{2+}$ - activated (e.g. TMEM16F), and (3) constitutively active or context-specific scramblases (e.g. PLSCR and potentially other minor pathways). All these disrupt membrane asymmetry nonselectively.

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## 3.Mechanisms in Apoptosis

During apoptosis, cells irrevocably externalize PS and other aminophospholipids to signal phagocytic clearance. This requires coordinated inactivation of flippases and activation of scramblases . As first noted by Segawa and Nagata, apoptosis-induced PS exposure involves caspase-mediated cleavage of both flippases (e.g. ATP11C) and scramblases. XKR8, when cleaved by caspase-3, becomes a potent scramblase; XKR8-deficient cells show drastically reduced PS on apoptotic surfaces. In intact cells, flippases maintain PS inside the cell by actively transporting it inward. During apoptosis, caspase cleavage inactivates these flippases and simultaneously liberates scramblases. In fact, Segawa et al. showed that effector caspases both disable ATP11C (flippase) and activate XKR8 (scramblase), ensuring PS flips out. TMEM16F can also be activated by the $Ca^{2+}$-fluxes that accompany apoptotic signaling, but its contribution to PS exposure in apoptosis appears secondary to XKR8 in most studies. PLSCR1 was initially thought to contribute via $Ca^{2+}$-sensing, but PLSCR1 knockout has minimal effect on apoptotic PS exposure. Once PS is on the cell surface, it is recognized by receptors (Tim-4, MerTK, etc.) on phagocytes. PS exposure is anti-inflammatory – it actively suppresses immune activation during clearance. Thus, scramblase activation in apoptosis normally promotes an immunologically silent removal of cells. Experimental evidence underscores this: cells that fail to expose PS are poorly engulfed and their corpses accumulate. For example, Kawano et al. found XKR8-null apoptotic thymocytes were inefficiently eaten by macrophages. Conversely, healthy cells avoid scramblase activation and keep PS hidden, preventing inappropriate clearance and coagulation. Importantly, persistent or inappropriate PS exposure (as in tumor microenvironments) can suppress immunity and aid immune evasion. In summary, scramblases in apoptosis biochemically collapse lipid asymmetry – mainly via caspase cleavage (XKR) or $Ca^{2+}$-influx (TMEM16F) – to display PS and other lipids, signaling for phagocytic uptake

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**4.Scramblases and Autoimmune Disease**

Defective apoptotic clearance is a key factor in systemic autoimmunity. Normally, phagocytes swiftly remove dying cells, preventing exposure of self-antigens. However, if scramblases fail to externalize PS, or if phagocytes fail to respond, apoptotic cells accumulate and secondary necrosis releases intracellular contents. This can break tolerance and trigger autoantibodies. Systemic lupus erythematosus (SLE) exemplifies this: patients display impaired clearance of apoptotic cells and elevated autoantibodies against nuclear and phospholipid antigens. For instance, monocyte-derived macrophages from SLE patients have reduced phagocytosis of apoptotic cells, and germinal centers in SLE show accumulation of apoptotic debris. In mice, loss of PS receptors (Mer, Tim-4, MFG-E8) causes lupus-like autoimmunity, underscoring the link. XKR8 and Lupus: In 2018, Kawano et al. showed that XKR8 deficiency in mice blunts apoptotic PS exposure, reduces efferocytosis, and leads to lupus-like disease. XKR8-null mice on an SLE-prone background developed high levels of anti-DNA and phospholipid antibodies, glomerulonephritis, and systemic autoimmunity. These findings establish that insufficient caspase-activated scrambling of PS can initiate systemic lupus features. PLSCR1, IFN, and SLE/APS: PLSCR1 is often upregulated in autoimmune patients. In SLE, PLSCR1 mRNA is markedly increased in blood and PBMCs. This may reflect the type I interferon signature of SLE: PLSCR1 is a robust interferon-stimulated gene (ISG). IFN-α directly induces PLSCR1 via STAT1, and PLSCR1 is hypomethylated in SLE patient DNA. The elevated PLSCR1 correlates with increased PS exposure and fibrin turnover in SLE patients, which could contribute to the known hypercoagulability (thrombophilia) in lupus. In antiphospholipid syndrome (APS), PLSCR1 is likewise upregulated: monocytes from APS patients have higher PLSCR1 mRNA, and PS exposure on their cells is increased. Since externalized PS provides a binding platform for antiphospholipid antibodies (especially anti–β2-glycoprotein I) , heightened

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scramblase activity may amplify pathogenic clotting in APS. Regulatory Balance and Autoimmunity: Normally, PS on apoptotic cells delivers an immunosuppressive "tolerance" signal. Persistent or ectopic PS exposure can have the opposite effect by allowing autoantigen persistence. In SLE/APS, the combination of excessive IFN-driven scramblase expression and defective clearance receptors likely breaks this tolerance. Indeed, many SLE patients have circulating antibodies against apoptotic cell components, including phospholipids. The molecular details are still being elucidated, but it is clear that scramblases sit at the nexus of cell death and self-tolerance. By controlling PS exposure, they influence whether dying cells are immunogenically "silent" or dangerous.

## Discussion

Phospholipid scramblases serve as critical gatekeepers of membrane lipid distribution, with distinct families tailored to physiological contexts $Ca^{2+}$-activated TMEM16F drives rapid PS exposure in live-cell activation (e.g. platelets, muscle), whereas caspase-activated XKR8 mediates PS exposure exclusively in apoptosis. The PLSCR family's role is more enigmatic: although biochemically capable of scrambling, PLSCR1 and relatives may primarily act in signaling or transcriptional regulation rather than as essential lipid transporters, since cells remain competent for PS exposure even without PLSCR1. This underscores that multiple redundant mechanisms exist for PS externalization: TMEM16F dominates in $Ca^{2+}$-triggered scenarios, XKR8 in apoptosis, and constitutive pathways in specific tissues. The immunological implications are profound. Proper scramblase function ensures apoptotic cells are cleared quietly, maintaining tolerance. When scramblases misfire or clearance is blocked, immune homeostasis is disrupted. SLE and APS studies illustrate this: SLE monocytes overexpress PLSCR1 yet paradoxically fail to clear dead cells efficiently, suggesting that scramblase upregulation alone cannot compensate for

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clearance receptor defects. Moreover, chronic PS exposure in tumors exemplifies the flip side: tumors exploit PS to suppress immunity, reminiscent of how apoptotic cells normally signal quiescence. Targeting scramblases (or PS receptors) may thus be therapeutically relevant. For instance, blocking PS signaling in the tumor microenvironment can enhance anti-tumor immunity, while enhancing PS clearance or modulation might help in lupus. Despite advances, many questions remain. The detailed structure-function of XKR and TMEM16 scramblases (now illuminated by cryo-EM) needs to be matched to in vivo regulation. The physiological role of PLSCR3 in mitochondria and of other XKR isoforms (XKR4/9/6) in immune cells warrant more study. The interplay between scramblases and scramblase-regulating lipids or proteins is also underexplored. Crucially, translating these findings to autoimmunity requires understanding human genetic variation: do polymorphisms in XKR8 or TMEM16F contribute to SLE/APS risk? Lastly, it is intriguing that scramblases are themselves potential autoantigens or modulators of innate immunity (e.g. PLSCR1 interaction with TLRs).

## Conclusion

Phospholipid scramblases (PLSCR, TMEM16, XKR) are fundamental determinants of membrane lipid asymmetry with critical roles in apoptosis and immunity. TMEM16F and XKR8 provide the biochemical means for PS exposure under Ca^2+-triggered and apoptotic conditions, respectively. PLSCR family members, while biochemically active, appear to play more regulatory roles. Dysregulation of scramblase activity or apoptotic clearance leads to immune pathology: XKR8 loss causes lupus-like autoimmunity, and upregulated scramblases in SLE/APS patients correlate with thrombosis and autoantibody production. Understanding these mechanisms at a molecular level – as recent structural studies have begun to do – opens avenues for intervening in autoimmune and thrombotic disorders. The last decade's research has clarified

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many aspects of scramblase biology, but further work is needed to exploit this knowledge in the clinic.

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