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REVIEW ARTICLE

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G protein coupled receptor in apoptosis and apoptotic cell clearance

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Abstract

Apoptosis is a genetically programmed form of cell death that is substantially conserved across the evolutionary tree. Apoptotic cell elimination includes recognition, phagocytosis, and degradation. Failure to clear apoptotic cells can ultimately cause a series of human diseases, such as systemic lupus erythematosus, Alzheimer's disease, atherosclerosis, and cancer. Consequently, the timely and effective removal of apoptotic cells is crucial to maintaining the body's homeostasis. GPCRs belong to the largest membrane receptor family. Its intracellular domain exerts an effect on the trimer G protein. By combining with a variety of ligands, the extracellular domain of G protein initiates the dissociation of G protein trimers and progressively transmits signals downstream. Presently, numerous G protein-coupled receptors (GPCRs) have been identified as participants in the apoptosis signal transduction pathway and the apoptotic cell clearance pathway. Therefore, studies on the mechanism of GPCRs in the clearance of apoptotic cells is important for the development of GPCRs therapeutics.

KEYWORDS

apoptosis, apoptotic cell clearance, G protein, GPCRs, signal transduction

1 | INTRODUCTION

Apoptosis is a genetically regulated form of programmed cell death that is considered a less severe mode of cell death compared to necrosis, pyroptosis, and ferroptosis.[1] Macrophages and dendritic cells in mammals can phagocytose and degrade apoptotic cells without triggering inflammation.[2] The clearance of apoptotic cells is a highly dynamic process that involves several steps: recruitment, recognition, phagocytosis, and degradation.[3] Failure to clear apoptotic cells properly can lead to chronic autoimmune diseases,[4] like systemic lupus erythematosus and rheumatoid arthritis, and in severe cases, it can cause cancer, Alzheimer's disease, and Huntington's disease.[5] Understanding the mechanism of apoptosis and the process of apoptotic cell clearance is crucial for clinical treatment and the development of drugs related to these diseases.[6,7]

GPCRs, a kind of seven transmembrane protein, is the largest receptor family on the membrane surface.[8] It is widely distributed in various life forms, and more than 800 members have been identified in the human genome

Xinyan Li and Chao Li have contributed equally to this work.

so far. Except for some "orphan receptors" whose ligands remain unidentified, most GPCRs are evolutionarily conservative.[9] They can recognize and bind different extracellular ligands, change the conformation of transmembrane domains, activate heterotrimeric G proteins that interact with intracellular domains, and contribute to the propagation of numerous signal pathways downstream, which is essential for maintaining cell development, organogenesis, and body stability.[10]

Over 200 billion cells undergo physiological turnover via apoptosis every day in a human body. Efficient removal of apoptotic cells helps maintain homeostasis and eliminate abnormal, non-functional, or harmful cells. GPCRs located on the cell membrane surface participates in a multitude of intracellular processes, including driving and controlling actin skeleton rearrangement, mediating/inhibiting apoptosis, eliminating and degrading apoptotic cells, and other biological processes. This review discussed the function of various GPCRs in the signal cascade transduction of apoptosis and apoptotic cell clearance.

1.1 | Apoptosis and apoptotic cell clearance

Apoptosis is determined by the activation of the caspases cascade and the mitochondrial control pathway. The activation of pro- and anti-apoptotic factors in the Bcl-2 family determines whether apoptosis occurs. Apoptosis triggers the transmission of signals to the downstream caspases. The apoptosis inhibitor IAP family prevents apoptosis by blocking the activity of various caspases. Activation of the TNFR family of death receptors (TNFR1/2, Fas, and DR3/4/5) and related ligands (TNF-α, FasL, TRAIL, and TWEAK) promotes apoptosis by facilitating the formation of the death-inducing signaling complex (DISC) and ultimately by activating caspase-8 and caspase-3.[11–15]

Phagocytes recognize "Eat me" signals (e.g., phosphatidylserine PS, calreticulin, annexin1, etc.) from apoptotic cell ectopics via phagocytosis receptors (TIM4, MERTK, BAI1, CD36, etc.) on their surface.[16,17] This initiates a downstream signaling response through ELMO and DOCK activation of the GTPase RAC1, which enhances actin remodeling, promotes cytoskeletal rearrangement, and engulfs the apoptotic cell to form a phagosome. The Rab GTPase protein family regulates the maturation process in phagosomes.[18] Phagolysosomes are formed when mature phagosomes fuse with lysosomes via Ca^{2+}-dependent SNARE complexes (composed of VAMP7 and Syntaxin 7). A vast number of proteases, nucleases, and hydrolases in the lysosome facilitate the breakdown of apoptotic cells in the phagosome.[19]

2 | GPCRs PROMOTE APOPTOSIS

GPCRs can be referred to as "orphan receptors" if no corresponding endogenous ligands have been found. The GPCRs family contains more than 100 orphan receptors. Research has shown that the transcription level of the orphan receptor GPR160 is higher in the prostate cancer cell line PC-3 than that in normal prostate tissue cells, and knockdown of GPR160 can lead to apoptosis and growth arrest of prostate cancer cells and thymus free mouse cancer cells in vitro.[20] Another orphan receptor, GPR4, was recently found to be proton-activated, and studies have shown that treatment with 1-methyl-4-phenylpyridine ion (MPP) and hydrogen peroxide (H_2O_2) in GPR4 over expression cells increased and decreased the expression of BAX and BCL-2, respectively. When GPR4 antagonists were used to knock down GPR4 expression and CRISPR/Cas9 to knock out GPR4 expression, the ratio of Bax/Bcl-2 and the production of ROS were reduced, and knock out of GPR4 reduced phosphatidylinositol diphosphate (PIP2) and Ca^{2+}. The results suggest that GPR4 deletion might improve calcium signal transduction mediated by the caspase dependent mitochondrial apoptosis pathway by regulating PIP2.[21] Recently, many GPCRs, including N-formyl peptide receptor (FPR), have been found in cells lacking inhibitory proteins, such as β stimulation of 2-adrenergic, angiotensin II (type 1A), and vasopressin V2 receptors, which will open a series of apoptosis signals, such as cell spheroidization, annexin positive, and caspase activation, to mediate cell apoptosis. Activation of the apoptotic response, initiated by G protein signaling, involves the activation of phosphatidylinositol 3-kinase, mitogen-activated protein kinase, and c-Src, and leads to the release of cytochrome c from the mitochondria, which eventually activates caspase 9 and caspase 3[22] (Figure 1).

2.1 | GPCRs inhibit apoptosis

Coincidentally, GPCRs were found not only to induce apoptosis, but also to inhibit it. Overexpression of CD97/ADGRE5 has been observed in various malignant tumor cells,[23] and studies have shown that CD97 can inhibit cancer cell apoptosis and enhance tumor cell viability under apoptosis conditions. Stable overexpression of CD97 reduced endogenous apoptosis induced by serum starvation and stannous sulfur synthase, as well as exogenous apoptosis initiated by tumor necrosis factor (TNF)/cycloheximide. The protection provided by CD97 against cell death was accompanied by the inhibition of caspase activation and the modulation of both anti-apoptotic and pro-apoptotic members of the BCL-2 superfamily.[24]

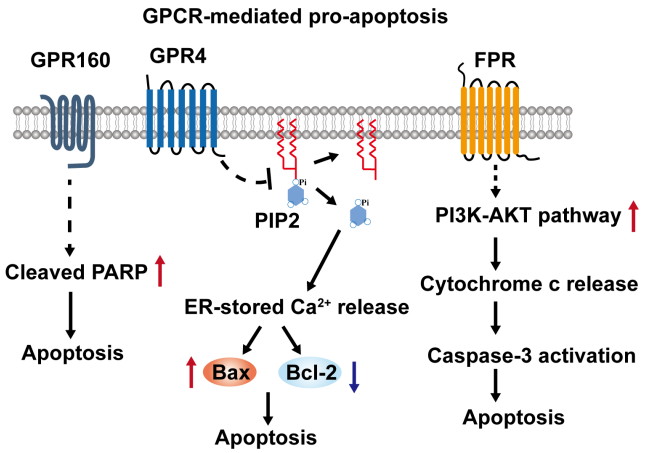

FIGURE 1 Model for promotion of apoptosis by GPCRs. Orphan receptor GPR160 through an undetermined signaling pathway, cleaves PARP and promotes apoptosis; endothelin receptor GPR4, through the classical signaling pathway involving IP3 and DAG as a double messenger, inhibits PIP2 degradation and participates in apoptosis by mediating endoplasmic reticulum calcium signaling; FPR via the classical PI3K-AKT pathway, releases cytochrome c, activates caspase-3, and promotes apoptosis.

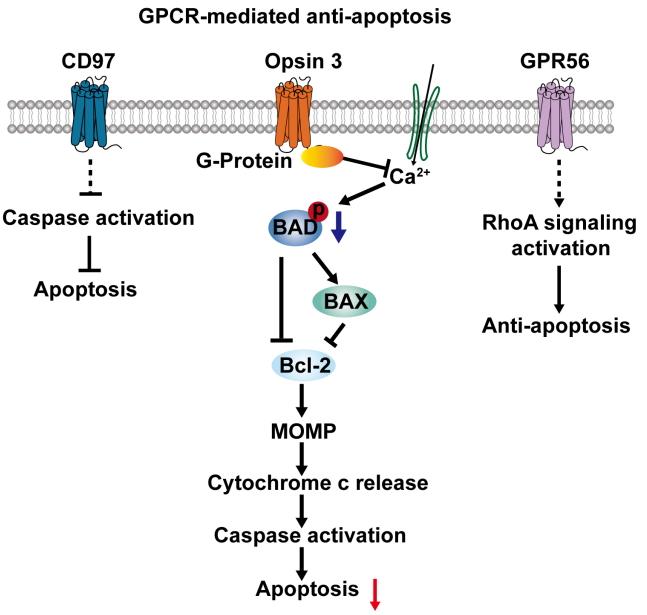

FIGURE 2 Model for inhibition of apoptosis by GPCRs. Adhesion-type GPCR CD97 inhibits caspase activity through an unknown signaling pathway, subsequently influences apoptosis. Orphan receptor OPN3 inhibits calcium flow to the cytoplasm through canonical calcium-dependent G-protein-coupled signaling and the mitochondrial pathway, decreasing the phosphorylation of BAD and ultimately inhibiting apoptosis by reducing caspase activity via the regulation of Bcl2 and cytochrome c release; Adhesion-like GPCR GPR56 mediates high cell adhesion and anti-apoptotic activity through an undefined signaling pathway by activating of RhoA signaling.

Additionally, GPR56[25] has been identified as the latest marker for high ecotype viral integration site expression in acute myeloid leukemia (EVI1 high AML). In GPR56 knockout mice, the number of hematopoietic stem cells (HSCs) in the bone marrow was reduced, and the adhesiveness of primary cells and regeneration ability were impaired. Therefore, GPR56 was found to mediate high cell adhesion and anti-apoptosis activity by activating RhoA signal transduction.[26] OPN3 knockdown by RNAi-OPN3 in human epidermal melanocytes leads to apoptosis. Downregulation of OPN3 markedly reduced intracellular calcium levels and decreased the phosphorylation of BAD. Attenuated BAD phosphorylation and elevated BAD protein levels alter mitochondrial membrane permeability, which triggers the activation of BAX and the inhibition of BCL-2 and raf-1. Activated BAX results in the release of cytochrome c and the loss of mitochondrial membrane potential. Cytochrome c complexes associate with caspase9, forming a post-mitochondrial apoptosome that activates effector caspases including caspase 3 and caspase 7. The release of apoptotic molecules eventually promotes the occurrence of apoptosis[27] (Figure 2).

2.2 | Chronic stimulation of beta AR (adrenergic receptors) induces cardiomyocyte hypertrophy and apoptosis

Adrenergic receptors (ARs) are members of the G protein-coupled receptor superfamily, and in heart failure, chronic catecholamine-stimulated AR may lead to pathological cardiac remodeling, including myocyte apoptosis and hypertrophy. Cardiomyocyte expression includes three types of βAR (β1, β2, and β3)and three types of αAR. Among these, β1Ar is usually the main receptor subtype in Cardiomyocytes, while β2AR signaling is species-specific.[28]

Both β1 and β2AR can be coupled to stimulatory GS proteins to activate adenylyl cyclase and cAMP production. cAMP-dependent protein kinase A (PKA) phosphorylates various substrates, leading to accelerated cardiac relaxation, and β1AR primarily plays a role in regulating the heart rate and contractility in mice. In contrast, activation of β2AR can couple to both Gs and Gi, which causes a small increase in myocyte contraction, followed by a sustained decrease. Later studies revealed that chronic stimulation of β1AR induces apoptosis in myocytes; however, the pro-apoptotic effect of β1ARs in adult rat myocytes seems to be blocked by PKA inhibition, whereas the activation of β2ARs has anti-apoptotic effects.[29] Interestingly, inhibition of the Gi pathway activates β2AR signaling from anti-apoptotic to pro-apoptotic in mouse adult myocytes, suggesting that β2AR to Gs signaling can cause myocyte apoptosis when β2AR is coupled to Gi.

2.3 | BAI-1 activates ELMO/DOCK180/Rac pathway to mediate apoptotic cell clearance

Previous studies have indicated that Rac can be activated by mammalian ELMO and DOCK180 proteins,[30] as well as their homologues in *C. elegans*. Additionally, it has been found that the Docker domain of DOCK180, which is responsible for activating Rac by functioning as a guanylate exchange factor, is conserved among known members of the DOCK180 protein family in yeast and metazoans.[31] In order to play the role of an upstream regulator of Rac in cells, DOCK180 must combine with ELMO. Research has shown that CED-12/ELMO contains a group of evolutionarily conserved ARM repeat sequences that can promote DOCK180-mediated Rac activation and plasma membrane skeleton rearrangement, as well as complete phagocytosis.[30] However, the upstream components of ELMO/DOCK180 during phagocytosis are still unclear.

The N-terminal protein interacting with ELMO1, which is necessary for the ELMO-Dock180 complex to target on the membrane, and the HF7C yeast strain (His, Trp, Leu) was used to screen a mouse seven-day embryonic library using pGBT10-N-term ELMO1 (residues 1–558) as bait. After screening of 1.1×107 colonies for growth on selective SCM plates (Trp, Leu, His with 5 mM 3-amino-1,2,4-triazole), and additional specificity/selection steps, the library plasmids were rescued and sequenced. BAI-1 is an adhesive protein and was named a brain-specific angiogenesis inhibitor because its extracellular segment can inhibit angiogenesis in angiogenesis experiments. It is expressed in both human monocytes and macrophages. The ability of J774 macrophages to stably express BAI-1 to ingest and phagocytose apoptotic cells is enhanced compared to the experimental group, and in vitro simulation experiments have proven that BAI-1 interacts with phosphatidylserine.[32] However, there are specific conditions for BAI-1-mediated enhancement of phagocytosis. In J774 cells expressing BAI-1, ELMO1 must be stably knocked out with shRNA to promote the clearance of apoptotic cells compared with the control group, indicating that ELMO1 expression is necessary for BAI-1-mediated phagocytosis. In LR73 cells transfected with BAI-1, the level of Rac GTP increased first and then returned to the basal level, proving that the expression of BAI-1 could activate the activity of Rac GTP. When ELMO, Dock180, and BAI-1 were simultaneously expressed in LR73 cells, the uptake of apoptotic cells reached the maximum, revealing that BAI-1 mediated the elimination of apoptotic cells through the ELMO1/DOCK180/Rac signaling pathway. On the other hand, three experiments were conducted by injecting siRNA into macrophages to mediate BAI-1 knockdown, BAI-1 knockout, and adding soluble BAI1 TSRs with apoptotic thymocytes, which further supported BAI-1 as an upstream activator of ELMO/DOCK180/RAC[33] after binding with phosphatidylserine of plasma membrane eversion, mediating the activation of Rac, and promoting the rearrangement of plasma membrane skeleton, completing the degradation of apoptotic cells[33] (Figure 3).

2.4 | GPR132 combines with extracellular lactate to activate PKA-AMPK pathway and promote the continuous uptake of apoptotic cells

In addition to BAI-1, phagocytosis and degradation of macrophages are also influenced by metabolism and its products. One such example is apoptosis-induced macrophage proliferation (EIMP), which is affected by lactic acid.[34] Recent research has shown that lactic acid, produced by glycolysis driven by phagocytosis, can stimulate macrophages to continuously ingest apoptotic cells.[35,36] This phenomenon has been observed in vascular smooth muscle cells as well.[37] Lactic acid is also linked to the NAD^+-dependent deacetylase SIRT1, which can deacetylate MYC protein to maintain its stability.[38–40] Therefore, it is suggested that lactic acid (EIL) produced by the clearance of apoptotic cells may promote EIMP by SIRT1-mediated deacetylation of MYC protein.[41] This hypothesis was supported by immunoprecipitation experiments, which demonstrated that during phagocytosis, LDHA-dependent lactate production increased MYC protein expression and promoted EIMP. EIL stabilized MYC protein by reducing its acetylation, which occurred after MYC transcription. Further experiments confirmed this view: EIL activated SIRT1, which can stabilize MYC expression and promote EIMP through deacetylation. Previous studies have shown that AMPK in nonimmune tissues such as skeletal muscle is activated by lactic acid through nicotinamide phosphoribosyltransferase rescue, increasing the level of NAD^+ and activating SIRT1. Therefore, further studies have demonstrated that EIL can activate AMPK, increasing the NAD^+/NADH ratio and activating the MYC-EIMP pathway mediated by SIRT1. In order to elucidate the mechanism by which extracellular lactic acid (EIL) activates AMP-activated protein kinase (AMPK), it was initially important to determine whether ATP levels significantly changed upon the addition of apoptotic cells. Since the ATP levels remained unchanged, further investigation revealed the presence of a G protein-coupled lactate receptor, GPR132, which was found through consultation of relevant literature. This receptor had previously been proven to play a role in activating the

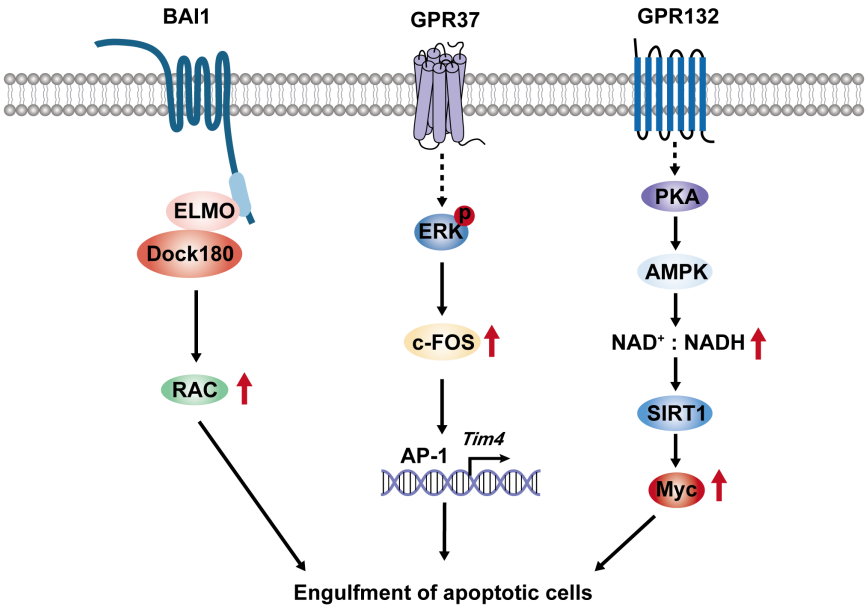

FIGURE 3 Model for GPCRs to affect apoptotic cell clearance. Angiotensin BAI1, through the classical G protein signaling pathway, binds to ELMO/DOCK180 to form a complex, transmits the signal to the downstream cascade, activates of Rac, promotes plasma membrane backbone rearrangement, and completes the phagocytosis of apoptotic cells; endothelin receptor GPR37, through the canonical MAPK/ERK signaling pathway, activates the phosphorylation of ERK, which is regulated by the PASP- ERK-AP1 signaling axis, promotes Tim4 expression, and facilitates phagocytosis; Orphan receptor GPR132 interacts with extracellular lactate through the canonical AMPK-PKA G-protein signaling pathway, which regulates the ratio of NAD^+ to NADH, leading to SIRT1-mediated deacetylation and stabilization of Myc proteins, ultimately promoting phagocytosis.

lactate-mediated PKA-AMPK pathway in inflammatory macrophages. Silencing SLC16a1, the gene encoding for GPR132, led to a partial reduction in MYC protein expression. Furthermore, when the inhibitors and activators of GPR132 were added, it was observed that silencing of GPR132 mediated the reduction of MYC expression, and that this reduction could be saved by the inhibition of LDHA. Additionally, a reduction of EIMP was observed when macrophages were incubated with apoptotic cells. GPR132 mRNA increased in a LDHA-dependent manner when macrophages were incubated with apoptotic cells. In order to explore the role of GPR132 as a signal molecule for PKA, macrophages were incubated with exogenous lactic acid, which resulted in an increase in the phosphorylation of CREB (cAMP response element binding protein), a target of PKA and a marker of PKA activity. Additionally, macrophages incubated with apoptotic cells exhibited an increase in pCREB, which was reduced by LDHA-KO and restored by exogenous lactic acid. Moreover, GPR132 silencing reduced pCREB and pAMPK in exposed macrophages. Finally, treatment of macrophages with PKA inhibitors resulted in a reduction of pAMPK activation, MYC protein expression, and EIMP as determined by cell count measurements. The above mentioned experimental data support the notion that extracellular lactic acid can increase the NAD^+ to NADH ratio via the GPR132-PKA-AMPK pathway, leading to the deacetylation and stabilization of Myc protein mediated by SIRT1 and promoting EIMP[34] (Figure 3).

2.5 | GPR37 combines with PASP to promote phagocytosis in the ERK-AP1 signal axis

The process of pinocytosis in macrophages on apoptotic cells is crucial in resolving inflammation. The absence of pinocytosis has been linked to various chronic diseases, for instance, asthma and atherosclerosis. It is important to recognize that intercellular factors, like soluble mediators like TGF-b, PGE2, IL-10, LXA4, and RvD1, control the growth of lymphocytes and the resolution of inflammation. These factors have been shown to increase phagocytosis and resolution of inflammation.[42–44] Furthermore, all cells release extracellular vesicles (EVs) containing mRNA, proteins, and non-coding mRNA, which neighboring cells can absorb, thereby promoting the proliferation of phagocytes. However, the specific mechanism remains unclear. It has been reported in scientific literature that the supernatant obtained following high-speed centrifugation and the removal of EVs does not promote the proliferation of lymphocytes after incubation. This suggests that EVs play a crucial role in cellular processes. Further experiments in mice have demonstrated that the

injection of efferocytosis-enhancing EVs (Effero-EVs) resulted in a significant increase in the efficiency of clearing apoptotic cells, and the injection of a neutral sphingomyelinase 2 (nSCase2) inhibitor, GW4869, reduced the number of EVs in mouse peritoneal exudate and increased the accumulation of neutrophils, indicating that endogenous EVs can regulate the clearance of apoptotic cells and contribute to the resolution of inflammation.[45,46] The binding rate of phagocytes and apoptotic cells was found to be stronger in the presence of EVs, and flow cytometry analysis revealed that Effero-EVs treated Mfs increased the cell surface expression of the efferocytosis receptor Tim4. To better understand the mechanism by which EVs mediate the upregulation of Tim4, protein mass spectrometry was performed on Effero-EV treated Mfs and a control group. Nine proteins known to play a role in inflammation elimination were identified from the up-regulated proteins, with a focus on the protein PASP. PASP is known to bind to the protein-coupled receptor GPR37 outside the cell, and PASP immunostaining and nanoflow cytometry confirmed that PASP is located on the surface of EVs.[47] An experiment using siRNA to block GPR37 showed that this action stopped the upregulation of Tim4, which is controlled by effero-ev, which find out if PASP sends signals through this pathway. Past studies have demonstrated that GPR37 agonists can activate the ERK signaling pathway,[47,48] and the AP-1 transcription factor is regulated by ERK.[49] AP-1 is one of the transcription factors that bind to the Timd4 promoter, making it an essential component of the pathway. To further investigate the role of PASP-GPR37-ERK-AP1 signal axis in regulating Tim4 expression and Mf efficiency (Figure 3).

3 | DISCUSSION

Apoptotic and apoptotic cell clearance play a vital role in maintaining homeostasis.[50] From the beginning of apoptosis to the recognition, encapsulation, and degradation of phagocytes, this is a tightly regulated process, and GPCRs play a positive and negative role in the signaling of this process.[51] With the progress of research, it was found that different GPCRs would bind to different signaling molecules, start upstream signaling pathways, and finish the process of apoptotic cell death.[51] The discovery and in-depth study of more and more GPCRs have gradually revealed their important role in clearing apoptotic cells. As the most numerous cell surface receptors, GPCRs are involved in many biological processes such as behavioral regulation, immunomodulation, and maintenance of homeostasis. Among these processes, GPCRs involved in apoptosis and efferocytosis are only some, but more GPCRs involved in apoptotic cell clearance may be identified with further research.

In addition to GPCRs, receptor tyrosine kinases (RTKs) are the largest class of enzyme-linked receptors that simultaneously bind to ligands and phosphorylate target proteins residues.[52] Such a structure is similar to that of the α subunit, where GPCRs can bind to ligands, and the β and γ subunits, which bind to G proteins and transmit signals downstream. The RTKs have been shown to play an important role in the regulation of apoptosis, such as the expression of EphA2, a receptor tyrosine kinase of the Eph family, which leads to an increase in apoptosis.[53] GPCRs can interact with the extracellular domains of RTKs, promote the aggregation of RTKs, enhance the kinase activity of RTKs, increase the efficiency of RTKs signaling, and regulate the signaling pathways of GPCRs to achieve the cross regulation and integration of signals. It also regulates the signaling pathway of GPCRs to achieve cross-regulation and integration of signals.[54] The new mechanism of interaction plays a crucial role in many physiological and pathological processes. For example, in tumor cells, GPCRs interact with RTKs to promote the proliferation and metastasis of tumor cells. In the nervous system, this interaction regulates neuronal development and synaptic plasticity. Therefore, an in-depth exploration of the role of GPCRs in apoptosis and apoptotic cell clearance may provide new insights into the function of interactions with RTKs.

Studying how GPCRs regulate apoptosis is of great significance for better understanding the pathogenesis of many diseases and identifying potential therapeutic targets. To use GPCRs as a therapeutic target for diseases caused by apoptosis, we need to learn more about how GPCRs send apoptosis signals and find its target site.[51] Because mammals are rich in a wide variety of GPCRs, many of which are still referred to as orphan receptors because no specific ligand has yet been discovered, this research is still limited. Many diseases are caused by the abnormal clearance of apoptotic cells,[55] and GPCRs can also contribute to disease development by interfering with apoptosis.[56] However, the majority of studies have concentrated on the pathways that mediate apoptosis, including GPR160, GPR4, FRP, and others, with minimal research examining the role of GPCRs in mediating the clearance pathway of apoptotic cells. Because of the specificity and complexity of this process in mammals, studying GPCRs that may play a role in mammalian apoptotic clearance is challenging. Impediment of apoptotic cell clearance can lead to autoimmune diseases and even cancer. Researching how GPCRs work in the clearance of apoptotic cells in lower model organisms will help us understand the effects in mammals and give us ideas for how to treat many diseases.

At present, there is a lack of research on the role of GPCRs in apoptosis, whether these GPCRs can also transmit signals independently in a variety of signaling pathways, may also act as cell surface receptors for the binding of a variety of small molecules and acid compounds in the human body, and respond to a variety of signaling molecules by activating transcriptional networks or signaling cascades, and participate in many metabolic pathways in the body (such as bile acid synthesis, glycolipid and water metabolism, energy expenditure, etc.),[57,58] and regulate the inflammatory response, affecting the clearance of apoptotic cells. In general, the regulatory role of GPCRs in apoptosis and related diseases has attracted more and more attention,[58] and its impact on apoptosis is more and more closely related to the treatment of a variety of malignant tumors, opening up more options for the treatment of related diseases.

AUTHOR CONTRIBUTIONS

Xinyan Li, Chao Li, Yang Kang, Rui Zhang, Peiyao Li, Qian Zheng, Hui Wang, Hui Xiao, and Lei Yuan wrote the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

No new data. Data sharing not applicable to this article as no datasets were generated or analyzed during the current article.

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