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REVIEW

Regulatory Mechanism and Drug Therapy of NLRP3 Inflammasome in Recurrent Pregnancy Loss: Research Status and Prospect

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Abstract: Recurrent pregnancy loss (RPL) is a distressing reproductive system disease with complex underlying causes and difficult treatment, making it a common fertility challenge for women of childbearing age. In recent years, the role of inflammasomes in RPL has gradually been recognized. NOD-like receptor family pyrin domain-containing 3 (NLRP3) is a key component of the innate immune system and a central regulator of inflammatory signaling. Accumulating evidence links NLRP3 inflammasome activation to female reproduction. During pregnancy, the assembly and activation of the NLRP3 inflammasome generate pro-inflammatory cytokines and pyroptosis-associated factors that engage in extensive cross-talk with other inflammatory pathways, thereby contributing to RPL through diverse mechanisms, including inflammatory cascades, endometrial receptivity, immune cell differentiation and polarization, pyroptotic cell death, autophagy, and intestinal barrier permeability. A detailed understanding of these intricate interactions may unveil novel therapeutic targets and strategies to mitigate the physiological and psychological burden of RPL on affected couples. However, currently there are still limited RPL therapeutic drugs targeting NLRP3. Developing drugs that precisely target and regulate NLRP3 is expected to promote the development of RPL therapy research. This comprehensive review investigates the complex relationship between NLRP3 inflammasome and RPL, highlighting the central role of inflammation in disease progression. It also summarizes potential drugs targeting NLRP3 inflammasome for the treatment of RPL, providing theoretical basis for potential clinical therapeutic targets.

Keywords: inflammation, endometrial receptivity, immunity, pyroptosis, autophagy, intestinal barrier

Introduction

Recurrent pregnancy loss (RPL) is defined as two or more clinically recognized pregnancy failures before 20–24 weeks of gestation with the same partner.[1,2] Approximately 3–5% of women of reproductive age are affected by RPL, and the probability of a successful subsequent pregnancy decreases significantly with each additional miscarriage.[3,4] RPL has been identified as a sentinel risk marker for a variety of obstetric complications—including preterm birth, fetal growth restriction, placental abruption, and stillbirth in future pregnancies—as well as a predictor of long-term health issues such as cardiovascular disease and venous thromboembolism.[5] With global fertility rates declining markedly, RPL has emerged as a major concern in reproductive medicine, imposing considerable economic and psychological burdens on affected couples and exerting a significant impact on healthcare systems and society at large.[6]

The pathogenesis of RPL is highly complex. Beyond well-established causes such as chromosomal abnormalities, uterine anatomical defects, thrombophilic disorders, endocrine dysfunctions, infections, sperm quality issues, and lifestyle factors, up to 50–60% of RPL cases remain idiopathic, with no identifiable cause, namely idiopathic RPL (iRPL) or unexplained RPL (URPL).[7,8] Although RPL caused by factors such as fetal genetic abnormalities and maternal anatomical abnormalities can never disappear, the substantial proportion of unexplained cases underscores the urgent need to explore additional etiologies and therapeutic approaches.[9]

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Inflammasomes are multiprotein complexes formed by the assembly of various proteins, functioning as danger receptors or sensors and serving as crucial components of the innate immune system. They have been causally linked to inflammation triggered by metabolic disorders and are involved in the pathogenesis and progression of various autoimmune and metabolic diseases. Commonly studied inflammasomes include NLRP1, NLRP3, NLRP6, NLRC4, and AIM2. Among them, the NLRP3 inflammasome is one of the most extensively and widely investigated. During early pregnancy, In early pregnancy, in order for the embryo to successfully implant and maintain pregnancy status, the mother must maintain an immune homeostasis with the fetus carrying paternal antigens and promote invasion of physiological trophoblast cells.[10] Pregnancy loss in this period is often attributed to a breakdown in maternal–fetal immune tolerance and to acute or chronic inflammation at the maternal–fetal interface or in the placenta.[11] Recent studies have emphasized that NLRP3 may be associated with RPL.[12] The NLRP3 inflammasome can recognize various pathogenic microorganisms and signal molecules related to injury. During early pregnancy, its abnormal activation and activation can disrupt the balance of the inflammatory factor network in the body, leading to immune disorders and oxidative stress at the maternal fetal interface, as well as disrupting the balance of pyroptosis and autophagy in pregnancy related cells, ultimately resulting in adverse pregnancy outcomes.[13,14] Although an increasing number of researchers in the field of reproductive medicine have recognized the potential association between NLRP3 and RPL and have conducted research on it, there is still a lack of systematic reviews focusing on the mechanistic role of NLRP3 inflammasome and its targeted therapeutic strategies specifically in the context of RPL. This gap poses a significant barrier to the comprehensive understanding of the RPL pathophysiological network and the establishment of effective clinical treatment frameworks. Meanwhile, the development of selective NLRP3 inhibitors continues to attract considerable interest. A variety of small-molecule inhibitors and naturally occurring bioactive compounds targeting NLRP3 have been reported. However, effective inflammasome inhibitors specifically applicable to clinical studies in RPL remain in the early stages of development, and many preclinical investigations on these candidate compounds urgently require systematic summarization and evaluation.

In this review, we summarize the evidence implicating NLRP3 inflammasome activation in RPL through its effects on inflammatory signaling, endometrial receptivity, immune cell differentiation and polarization, pyroptotic cell death, autophagy, and intestinal barrier permeability. We also discuss the therapeutic potential of targeting the NLRP3 inflammasome in RPL, reviewing the efficacy and safety of emerging NLRP3-directed pharmacologic agents and offering theoretical guidance for future clinical interventions.

Overview of the NLRP3 Inflammasome

Structure and Function

The NLRP3 inflammasome is encoded by the cold-induced autoinflammatory syndrome 1 (CIAS1) gene. The NLRP3 protein comprises an N-terminal pyrin domain (PYD), a central nucleotide-binding and oligomerization (NACHT) domain, and a C-terminal leucine-rich repeat (LRR) domain.[15] As a member of the NOD-like receptor (NLR) family, the NLRP3 inflammasome assembles with NLRP3 as the sensor, apoptosis-associated speck-like protein containing a CARD (ASC) as the adaptor, and pro-caspase-1 as the effector.[16] Upon recognition of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), these components undergo a series of signaling events to form a multiprotein complex. This activates the innate immune response, leading to maturation and release of pro-inflammatory cytokines and chemokines, induction of pyroptotic cell death, and regulation of immune cell differentiation and systemic immune homeostasis.[17]

Priming and Activation

The canonical activation pathway of NLRP3 inflammasome is mainly believed to be related to two signals.[18]

Signal 1 (Priming): Engagement of pattern recognition receptors such as tumor necrosis factor receptor (TNFR), Toll-like receptors (TLRs) or interferon receptor (IFNR) by PAMPs or DAMPs triggers nuclear factor-κB (NF-κB) – dependent upregulation of NLRP3 as well as pro–IL-1β and pro–IL-18, thereby establishing a transcriptional "priming" state.[19,20]

Signal 2 (Activation): Diverse cellular perturbations—K^+ efflux,[21] Ca^{2+} flux,[22] Cl^- efflux, mitochondrial reactive oxygen species accumulation, or lysosomal damage[23]—then provoke NLRP3 oligomerization. This drives recruitment of ASC and pro–caspase-1 into a macromolecular inflammasome complex.[24] Caspase-1 is auto-processed into its enzymatically active form, which cleaves pro–IL-1β and pro–IL-18 into their mature cytokines and induces gasdermin D–mediated pyroptosis.[25]

In mice, noncanonical activation pathways exist whereby lipopolysaccharide (LPS) triggers caspase-11 (and its human orthologs caspase-4 and caspase-5), directly promoting NLRP3 assembly and subsequent pro-inflammatory cytokine release.[26] Although canonical and noncanonical pathways can intersect under certain conditions, their precise molecular interplay remains to be fully elucidated.[27]

A third, "alternative" activation route has also been described in human and porcine monocytes.[28] In this pathway, a single TLR ligand suffices to activate NLRP3 via a TLR4 – TIR-domain-containing adaptor inducing interferon-β (TRIF) – Recombinant Receptor Interacting Serine Threonine Kinase 1 (RIPK1) – Fas-associated with death domain protein (FADD) – caspase-8 signaling axis, bypassing typical hallmarks of inflammasome activation such as ASC speck formation, pyroptosis, and K^+ efflux.[29,30] Despite requiring NLRP3, ASC, and caspase-1 signaling, this alternative route proceeds independently of the two-signal paradigm characterizing canonical and noncanonical activation (Figure 1).

Mechanism of NLRP3 Inflammasome in RPL

NLRP3 Inflammasome and Endometrial Receptivity

Successful establishment and maintenance of pregnancy require immune tolerance at the maternal–fetal interface, enabling peaceful coexistence between the mother and the semi-allogeneic fetus.[31] There are a large number of inflammatory mediators at the maternal fetal interface. Normal levels of inflammatory mediators are beneficial for the mother to resist and eliminate foreign pathogens, but excessive cytokine release is undoubtedly catastrophic for the establishment of endometrial receptivity and embryo implantation.[32] Failure to establish maternal–fetal interface homeostasis—rooted in deficient endometrial receptivity—is a primary cause of miscarriage, since aberrant receptivity leads to faulty implantation and subsequent fetal loss.[33] Indeed, approximately 75% of pregnancy failures are traced to abnormal embryo implantation, and up to two-thirds of these are attributed to impaired endometrial receptivity.[34]

Endometrial stromal cells can respond to estrogen and progesterone, and differentiate into functional decidual cells under the stimulation of cyclic adenosine monophosphate (cAMP), various paracrine and autocrine inducers produced locally in the uterus.[35] Unlike many mammals, human decidualization is spontaneous and cyclic, driven by the menstrual cycle's estradiol and progesterone fluctuations rather than direct embryonic signals.[36] Decidual cells that undergo decidualization become larger, more rounded, with enlarged nuclei, expanded endoplasmic reticulum (ER) and Golgi apparatus, and accumulated lipids and glycogen in the cytoplasm.[37]

The ER is an important organelle that controls protein quality, regulating protein synthesis and transmembrane protein secretion.[38] Accumulation of misfolded proteins triggers endoplasmic reticulum stress (ERS), characterized by disrupted trafficking, calcium homeostasis, and oxidative-stress regulation.[39] The unfolded protein response (UPR)—mediated by IRE1, PERK, and ATF6 pathways—attempts to restore ER function.[40,41] All three UPR branches can activate NF-κB, upregulating genes encoding pro-inflammatory cytokines and thereby modulating the cellular inflammatory response.[42] A basal level of ERS and UPR is necessary for successful implantation; however, uncontrolled ERS/UPR can amplify inflammation, impair endometrial receptivity, and precipitate miscarriage.[43]

In endometrial cells from RPL patients, ERS/UPR pathways are aberrantly activated, leading to upregulation of the Thioredoxin-interacting protein (TXNIP) /NLRP3 axis.[44] This increases NLRP3 inflammasome assembly and IL-1β production in decidual cells, exacerbating local inflammation. Mucin-1 (MUC-1), a key regulator of decidualization and trophoblast invasion and a biomarker of endometrial receptivity, can specifically inhibit NLRP3 activation by disrupting TLR signaling.[45] In RPL patients, MUC-1 expression is downregulated in both endometrium and decidua, while NLRP3 inflammasome components and Caspase-1–dependent IL-1β and IL-18 are significantly elevated.[46,47] These findings underscore that abnormal activation of NLRP3 inflammasome is associated with reduced endometrial receptivity in RPL patients, and its excessive secretion of inflammatory mediators is also involved in the pathological process of abnormal

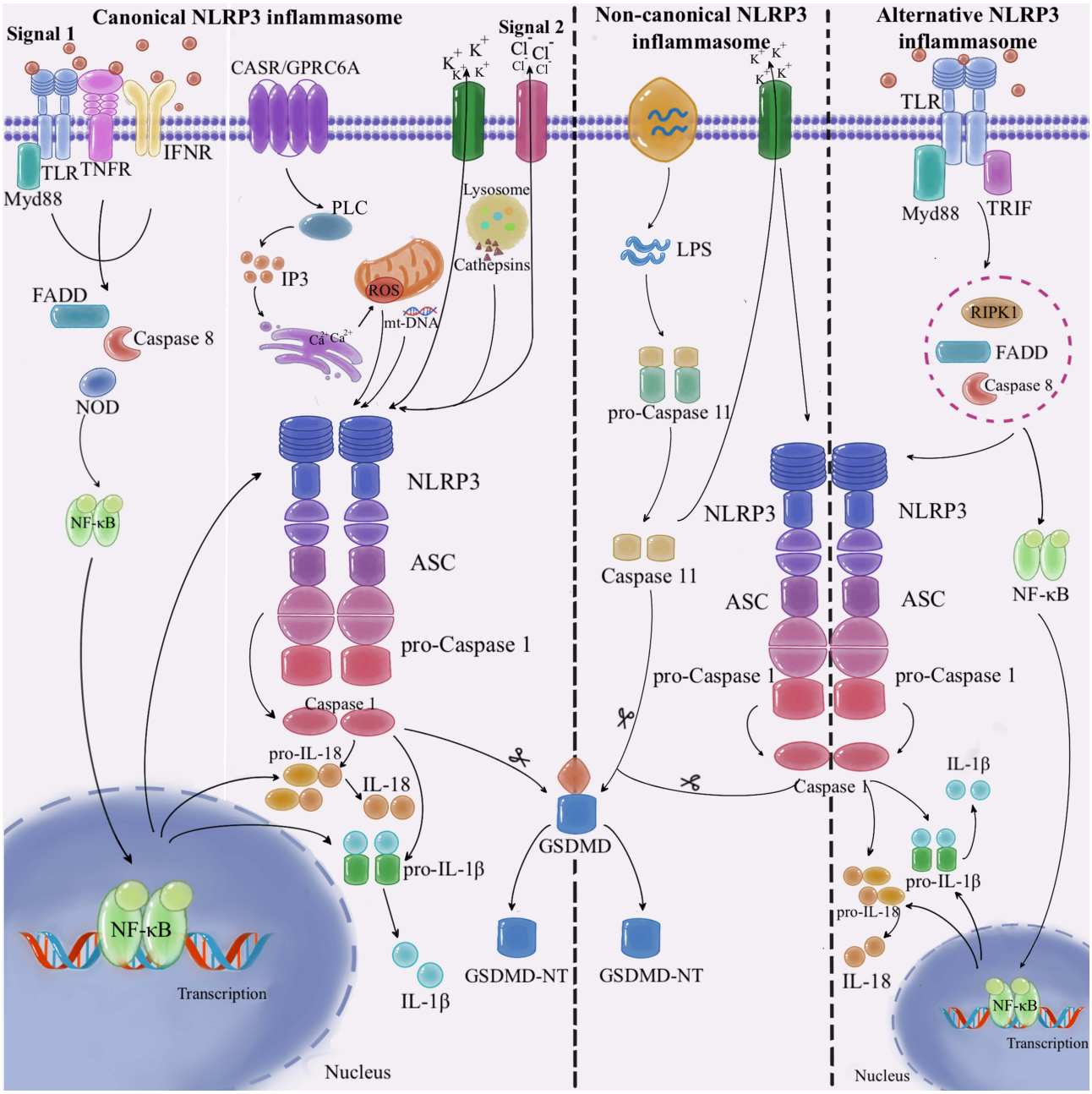

Figure 1 Three Pathways of NLRP3 Inflammasome Activation: (Left) Canonical Pathway: The priming signal constitutes the initial step. Pattern recognition receptors (PRRs) such as TLRs, TNFR, and IFNR, stimulated by exogenous agents, indirectly activate the priming signal through endogenous molecules, leading to NF-κB activation. NLRP3 is deubiquitinated by NF kB as a post transcriptional modification, promoting the secretion of Pro-IL-1B and Pro-IL-18. The activation signal of NLRP3 inflammasome is activated by stimuli including K^+ efflux, Cl^- efflux, altered Ca^{2+} signaling, mtDNA production, ROS release, or lysosome damage. Subsequently, NLRP3 protein oligomerization is activated, and its assembly with ASC and pro-caspase-1 is completed, forming a complete NLRP3 inflammasome. Caspase-1 is thereby activated, leading to the maturation of IL-1β and IL-18, induction of membrane pore formation, and pyroptosis. (Middle) Non-canonical Pathway: NLRP3 inflammasome activation is primarily initiated by LPS stimulation. LPS directly activates caspase-11 in mice (or caspase-4 and caspase-5 in humans). Activated caspase-11 induces K^+ efflux, which subsequently triggers NLRP3 inflammasome assembly and IL-1β/IL-18 maturation through the same downstream mechanisms as the canonical pathway. Concurrently, activated caspase-11 cleaves GSDMD, resulting in pyroptosis. (Right) Alternative Pathway: Only a single signal is required. TLR ligands alone are sufficient to activate the NLRP3 inflammasome via the TLR4-TRIF-RIPK1-FADD-caspase-8 signaling axis, without any features of typical and atypical NLRP3 inflammasome activation pathways, such as ASC spot formation, induction of cell pyroptosis, and intracellular K^+efflux.

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Abbreviations: ASC, Apoptosis-associated spek-like protein containing a CARD; CaSR, Calcium-sensing receptor; IFNR, Interferon receptor; FADD, Fas-associated with death domain protein; GSDMD, Gasdermin D; IL, Interleukins; IP3, Inositol Trisphosphate; LPS, Lipopolysaccharide; mtDINA, mitochondrial DNA; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor family pyrin domain-containing 3; NOD, Nucleotide-binding oligomerization domain; PLC, Phospholipase C; RIPK1, Recombinant Receptor Interacting Serine Threonine Kinase 1; ROS, Reactive oxygen species; TLR, Tolllike receptors; TNFR, Tumor necrosis factor receptor; TRIF, TIR-domain-containing adaptor inducing interferon-β.

receptivity in RPL patients. As a pattern recognition receptor, the unique feature of NLRP3 inflammasome is that it can recognize and respond to various stimuli, providing more platforms for the activation of caspase-1 and the maturation and secretion of IL-1 β and IL-18, thereby affecting the establishment of the implantation window period and exacerbating the inflammatory response at the maternal fetal interface, participating in the occurrence and development of RPL.[48]

NLRP3 Inflammasome and Cell Differentiation and Polarization Phenotypes

At the maternal–fetal interface, $CD4^+$ T-cell subsets—particularly Th1/Th2 and Th17/Treg—play pivotal roles in balancing allogeneic immune rejection and tolerance.[47] Th1 and Th17 cells secrete pro-inflammatory cytokines such as IFN-γ, IL-17A, IL-6, IL-2, and TNF-α, thereby amplifying local inflammation and activating immune responses.[49] In contrast, Th2 and Treg cells produce immunosuppressive cytokines including IL-4, IL-10, and transforming growth factor-β (TGF-β), which inhibit effector immune cells and promote tolerance.[50] After successful embryo implantation, immune cell differentiation at the maternal–fetal interface typically shifts toward an immunosuppressive profile to protect the semi-allogeneic embryo from maternal attack.[51]

NLRP3 inflammasome–derived IL-1β and IL-18 are potent drivers of Th1 and Th17 polarization.: IL-1β, IL-18, and IFN-γ promote Th1 differentiation, while IL-1β together with TGF-β favors Th17 lineage commitment.[52,53] In a study,[54] the upregulated expression levels of NLRP3 inflammasome in peripheral blood and decidua tissues of RPL patients and mouse models were confirmed to be positively correlated with Th1 and Th17 cells, and negatively correlated with Th2 and Treg cells. However, the application of Caspase-1 inhibitor YVAD in RPL mouse models can rescue the immune cell imbalance caused by this inflammatory change, significantly downregulating the Th17/Treg differentiation ratio, strongly confirming that abnormal activation of NLRP3 is a key factor that interferes with the balance of immune cell differentiation and mediates the development of RPL.

Decidual macrophages constitute the second-largest immune population at the maternal–fetal interface after NK cells and polarize into pro-inflammatory M1 or anti-inflammatory M2 phenotypes.[55] M1 macrophages produce high levels of TNF-α, IL-1β, and IL-6, promoting inflammation and Th1 responses; M2 macrophages secrete IL-10 and TGF-β, clearing apoptotic cells and supporting tissue remodeling.[56] From placental maturation to the end of pregnancy, a predominance of M2 macrophages is characteristic of a healthy pregnancy, whereas excessive M1 polarization or reduced M2 activity contributes to RPL.[57] Metabolic reprogramming from oxidative phosphorylation to glycolysis underlies M1 polarization. The NLRP3 inflammasome can upregulate fructose-2,6-bisphosphatase-3 (PFKFB3) via IL-1β–dependent signaling, enhancing glycolytic flux and driving macrophage differentiation toward the M1 phenotype.[58] This provides a mechanistic link by which NLRP3 activation skews macrophage polarization and contributes to the inflammatory milieu underlying RPL.

NLRP3 Inflammasome and Pyroptosis

Activation of the NLRP3 inflammasome is commonly accompanied by programmed inflammatory cell death, known as pyroptosis.[59] While physiological levels of pyroptosis help the host eliminate pathogens, excessive pyroptosis amplifies inflammation and contributes to autoinflammatory disorders.[60] In the canonical pathway of NLRP3 inflammasome activation, inflammasome assembly induces autocatalytic cleavage of pro–caspase-1 into active caspase-1, which then cleaves gasdermin D (GSDMD) protein to release its N-terminal pore forming domain (GSDMD-N), causing cell membrane perforation, while promoting the maturation and secretion of IL-1 β and IL-18, initiating inflammatory cell aggregation, and inducing pyroptosis.[61] In the noncanonical pathway, lipopolysaccharide (LPS) binds directly to caspase-4/5/11, triggering GSDMD cleavage independently of caspase-1; GSDMD-N rapidly forms membrane pores, releasing excessive pro-inflammatory cytokines and chemokines and initiating pyroptosis.[62] It has been observed that women with unexplained recurrent spontaneous abortion (URPL) have abnormally increased rates of pyroptosis in their decidua cells, which is directly related to the increased expression of NLRP3, caspase-1, and GSDMD in their decidua tissue.[63] In addition, Cheng et al[64] also confirmed that abnormal activation of the NLRP3/caspase-1/GSDMD pathway can exacerbate cell pyroptosis in the placental trophoblast layer, causing excessive cell death, hindering the proliferation and invasion of trophoblast cells, and ultimately leading to adverse pregnancy outcomes.

NLRP3 Inflammasome and Trophoblast Autophagy Homeostasis

Autophagy is a highly conserved programmed cell recycling mechanism present in eukaryotic cells, which can occur in the decidua and trophoblast cells of pregnant women and and is essential for decidualization, trophoblast proliferation and invasion, vascular remodeling, and maternal–fetal immune tolerance.[65] Both insufficient and excessive autophagy can cause trophoblast dysfunction and immune imbalance at the maternal–fetal interface, making it a key factor in RPL pathogenesis.[66] Emerging evidence reveals complex, bidirectional crosstalk between inflammasome activation and autophagy, necessary for balancing protective and harmful inflammation.[67]

Lee et al[68] found that in an LPS-induced inflammatory mouse model of early pregnancy, NLRP3 inflammasome activation and IL-1β levels were markedly increased in trophoblasts, accompanied by upregulation and phosphorylation of the autophagy regulator TBK1. Inhibition of TBK1 with amlexanox reversed LPS-induced NLRP3 activation via suppression of the upstream mammalian target of rapamycin complex 1 (mTORC1) pathway, indicating there is a tight relation and mutual regulatory mechanism between NLRP3 inflammasome activity and autophagy under inflammatory state at the maternal fetal interface.

Oxidative stress—defined by excessive reactive oxygen species (ROS) relative to antioxidant defenses—is normally balanced during healthy pregnancy.[69] However, pathological oxidative insults to trophoblasts disrupt proliferation and invasion, impair placental development, and contribute to spontaneous abortion, iRPL and fetal dysplasia.[70] An abnormal oxidative stress state has been reported in the placental tissues of patients with RPL. Oxidative stress is one of the major triggering factors for NLRP3 inflammasome activation, while the accumulation of ROS during NLRP3 inflammasome activation further exacerbates oxidative stress. Although the specific mechanisms underlying the oxidative stress–NLRP3 axis in the context of RPL remain unexplored, the close association between the two is undeniable. ROS generated under oxidative stress can trigger excessive autophagy in trophoblasts.[71] Li et al[72] observed that in an in vitro model of oxidative damage to human placental trophoblast cells, the expression of NLPR1, NLRP3, pro-IL-1 β, and IL-1 β significantly increased, while the expression of autophagy related factors microtubule associated protein light chain 3II (LC3-II), myosin like BCL2 binding protein-1 (Beclin-1), Autophagy (ATG) 5, and ATG7 was upregulated, and the expression level of ubiquitin binding protein 62 (p62) was downregulated, and autophagy was overactivated. Intriguingly, treatment with the NLRP1 agonist MDP further amplified oxidative stress and inflammation, increasing NLRP3 but suppressing Beclin-1, ATG5, ATG7, and the LC3-II/LC3-I ratio while elevating p62, indicating autophagy inhibition. Conversely, NLRP1 knockdown reduced NLRP1, NLRP3, and IL-1β levels but restored autophagy marker expression. These results indicate that excessive ROS induced oxidative stress in the gestational trophoblast layer increases the level of NLRP3 inflammasome, thereby upregulating autophagy in trophoblast cells. But obviously, there is a bidirectional regulatory effect between inflammasomes and autophagy: overactivated inflammasomes can trigger autophagy defects, but inhibiting inflammasome activation under oxidative stress can actually increase autophagy levels in a compensatory manner. With the deepening of research, the multiple regulation between inflammasomes and autophagy has gradually been recognized, and the direction of inflammatory response seems to depend on the cell types involved and the specific conditions that induce inflammation, inflammasome activation, and autophagy.[73–75]

NLRP3 Inflammasome and Gut Barrier Permeability

Immune cells and inflammatory mediators can traverse a compromised intestinal barrier and exacerbate systemic inflammation and local inflammation at the maternal fetal interface.[76,77] During pregnancy, gut-derived immune factors not only enter the systemic circulation through the intestinal mucosa but can also be transported by dendritic cells to the placenta, where they exert direct effects.[78] Tersigni et al[79] observed that women with RPL exhibit increased intestinal permeability alongside elevated expression of caspase-1, IL-1β, and NLRP3 in endometrial tissues. They speculated that NLRP3 activation may be linked to gut barrier dysfunction and subsequent amplification of endometrial immune responses, ultimately precipitating RPL. It's worth noting that heightened gut permeability in RPL may facilitate the exposure of the endometrium to the infiltration of peripheral immune cells, triggering further NLRP3 inflammasome activation; in turn, the inflammatory stimulation generated by the activation of NLRP3 inflammasomes will further enhance the permeability of intestinal blood vessels to intensify the immune response, thereby promoting the occurrence and development of RPL. Although the "gut–endometrium axis" hypothesis has gained support in recent years,[80–82] the

precise molecular mechanisms by which NLRP3 modulates barrier integrity and drives maternal–fetal inflammation remain to be elucidated. Further investigation into NLRP3's role in gut permeability will be crucial for advancing our understanding of RPL pathogenesis and for identifying novel therapeutic targets.

Taken together, the NLRP3 inflammasome contributes to RPL via multiple interconnected pathways. Mapping these pathways not only provides mechanistic insights for RPL etiology but also reveals potential molecular targets for precise prevention and treatment (Figure 2).

Current Status of NLRP3 Inflammasome–Targeted Therapeutics in RPL Prevention and Treatment

Aspirin

High-mobility group box-1 protein (HMGB1), a DAMP that directly primes the NLRP3 inflammasome, is closely related to pregnancy decidualization and embryo implantation.[83] Aspirin has been shown to downregulate HMGB1 levels, thereby suppressing aberrant NLRP3 activation in the decidua and at the maternal–fetal interface of URPL mice.[63] This reduces local inflammation, attenuates endothelial cell pyroptosis-induced impaired angiogenesis, and improves both implantation and live-birth rates in URPL models. Current research generally suggests that taking aspirin at a daily dose of 50–150 mg during pregnancy is both safe and effective for preventing pregnancy complications such as preeclampsia and antiphospholipid syndrome, but there is still considerable controversy regarding the recommended dosage, optimal time for administration, and gestational age at which treatment should be discontinued;[84] although it is primarily used for thrombophilia-associated RPL, it is often combined with other agents for immune-mediated or unexplained RPL.[85]

Metformin

Preeclampsia (PE), characterized by new-onset hypertension after 20 weeks' gestation with multisystem involvement, is a risk factor for RPL.[86] As an NF-κB pathway inhibitor, metformin markedly suppresses NLRP3 activation and mitochondrial injury in LPS-stimulated human chorionic trophoblast models via inhibition of the TLR4/NF-κB/PFKFB3 axis.[87] This reduces placental inflammation, trophoblast pyroptosis, and excessive glycolysis. As a commonly used hypoglycemic and anti-inflammatory drug in clinical practice, metformin is often used as a combination therapy for RPL, and its safety for pregnant women is worthy of recognition,[88] but gastrointestinal side effects may increase with prolonged use,[89] and the long-term effects of continuous metformin use during pregnancy on offspring are still uncertain.[90]

Low-Molecular-Weight Heparin (LMWH)

LMWHs, derived from unfractionated heparin (UFH; average MW 4,000–6,000 Da), exert both anticoagulant and anti-inflammatory effects.[91] In a study, participants co cultured TEV-1 trophoblast cells and RAW264.7 macrophages stimulated by LPS to simulate the abnormal inflammatory environment at the RPL maternal fetal interface. It was found that LMWH could inhibit the expression of NLRP3 inflammasome in this model, alleviate LPS induced inflammatory response, and thus infer that LMWH may improve the abnormal inflammatory state at the RPL maternal fetal interface by blocking the activation of NLRP3 inflammasome, and enhance the activity of trophoblast and macrophages.[13] Other studies show LMWH suppresses NLRP3 via PI3K/AKT signaling, reducing pregnancy loss and inflammasome activation in PE mouse models, restoring trophoblast differentiation, and improving cell proliferation.[92] At present, the use of LMWH for the treatment of RPL is still controversial, and its clinical data are conflicting.[93,94] Meanwhile, the potential bleeding side effects and allergic reactions associated with the use of LMWH require strict monitoring of its dosage and duration. Therefore, further research is needed on the incidence of complications and appropriate gestational time periods for LMWH treatment of RPL.

Progesterone

Progesterone is indispensable for implantation and maintenance of pregnancy, optimizing the endometrial environment, promoting trophoblast invasion, and supporting uterine and placental angiogenesis.[95] Luteal phase deficiency (LPD), or

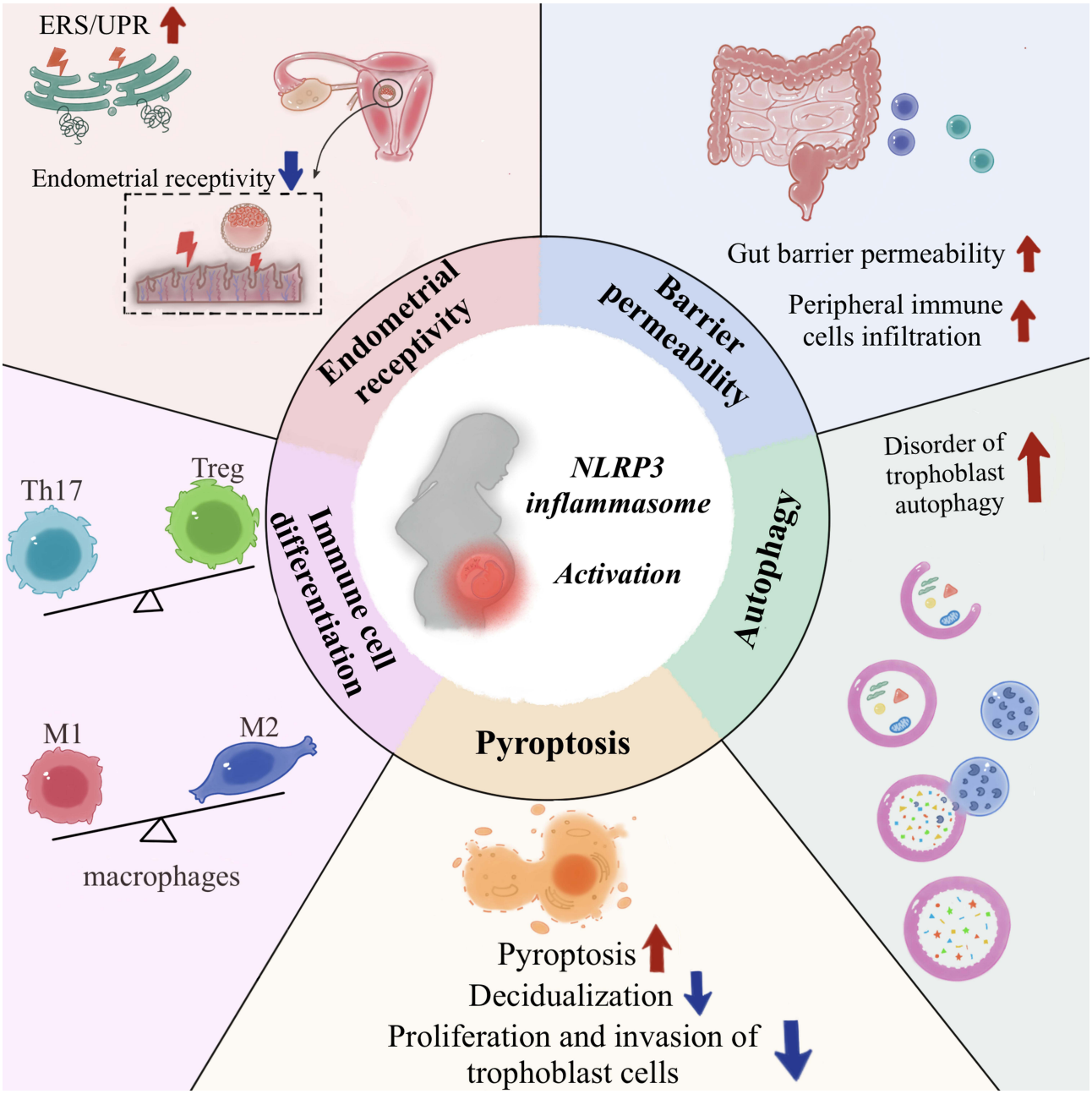

Figure 2 Mechanisms of the NLRP3 Inflammasome in RPL: In endometrial receptivity, the NLRP3 inflammasome participates in ERS events by responding to excessive ERS/UPR activation. This exacerbates inflammatory responses in decidual cells, contributing to impaired endometrial receptivity. In immune cell differentiation, the NLRP3 inflammasome contributes to immune imbalance at the maternal-fetal interface by influencing T-cell differentiation phenotypes and macrophage polarization. Specifically, its overactivation primarily exacerbates inflammation at this interface by increasing the Th17/Treg cell ratio and the M1/M2 macrophage ratio. In pyroptosis, activation of the NLRP3 inflammasome is often accompanied by pyroptosis. Excessive inflammasome activation induces pronounced pyroptosis in decidual and placental trophoblast cells, amplifying inflammatory responses. This impairs the decidualization process and adversely affects trophoblast cell proliferation and invasion capabilities. In trophoblast autophagy balance, the NLRP3 inflammasome is involved in oxidative stress within the placental trophoblast layer. Overactivation of the NLRP3 inflammasome is closely associated with dysregulation of autophagy in trophoblast cells, and a bidirectional regulatory relationship exists between the two processes. In barrier permeability, increased intestinal permeability in RPL patients exposes the endometrium to peripheral immune cell infiltration, thereby promoting NLRP3 inflammasome activation. Concomitantly, the inflammatory stimuli generated by NLRP3 inflammasome activation further enhance intestinal vascular permeability to amplify immune responses, leading to the development and progression of RPL.
Note: Created by Procreate. The figure is original.
Abbreviations: ERS, Endoplasmic reticulum stress; UPR, Unfolded protein response.

insufficient progesterone secretion during the luteal phase of the menstrual cycle, has been identified as a potential cause of RPL, but the specific mechanism is still unclear.[96] Progesterone inhibits NF-κB activity, thereby reducing NLRP3 activation and downstream inflammation.[97] Although exogenous progesterone is empirically used in RPL, direct

evidence of its effect on NLRP3 is lacking, and there are still inconsistent views on the safety and efficacy of exogenous hormone therapy in RPL.[98] Therefore, well-designed randomized trials are needed to establish its efficacy and safety in modulating inflammasome activity.

Mcc950

MCC950, a diarylsulfonylurea derivative, is currently considered a specific small molecule inhibitor that selectively blocks NLRP3 inflammasome activation.[99] Palmitic acid (PA) is the most abundant saturated fatty acid in the blood, which can directly activates NLRP3 via TLR/NF-κB or ROS-mediated autophagy disruption.[100] During pregnancy, high concentrations of PA can cause defects in maternal decidualization and placental inflammation, leading to pregnancy complications such as poor endometrial receptivity, preeclampsia, and miscarriage.[101] In PA-induced mouse models of placental inflammation, MCC950 significantly reduced NLRP3 expression and IL-1β levels, alleviating maternal–fetal inflammation.[102] Although experiments have confirmed the safety of MCC950 during human pregnancy, and in vitro toxicity studies of MCC950 have not found significant toxicity. However, in an experiment to treat rheumatoid arthritis, the elevated serum liver enzyme levels in the MCC950 treatment group still added a concerning risk of liver toxicity to the clinical use of MCC950.[103] But in this study, the high-dose application and sampling time of MCC950 should be considered as one of the factors leading to liver toxicity of MCC950. It is necessary to further explore the specific regulatory mechanism of MCC950 in RPL, and further refine experiments to clarify the balance between the safe dosage and efficacy of MCC950. The serum liver enzyme levels of experimental patients should be closely monitored to consider whether medication can continue without significant liver damage deterioration.

β-Hydroxybutyrate (BHB)

As the main ketone body, BHB is not only an energy substrate that maintains metabolic homeostasis, but also a signaling molecule that regulates fat breakdown, oxidative stress, and neuroprotection.[104] It is one of the antagonists of NLRP3 inflammasome and its content increases in normal pregnant women and newborns.[105] After adding ATP to activate NLRP3 inflammasome in LPS induced human trophoblast cells, administering a quantitative amount of BHB can inhibit the co localization of NLRP3 and ASC, hinder the activation of caspase-1, and reduce the level of IL-1 β, thereby affecting the platform construction of NLRP3 inflammasome activation and the inflammatory response of trophoblast cells. Next, in mouse model experiments, BHB was shown to reduce placental inflammation and embryonic absorption rate in LPS induced maternal fetal interface inflammatory mice.[106] In this study, it is not difficult to see the positive role of BHB in the NLRP3 inflammasome related pathway in human trophoblasts. However, this phenomenon was not observed in the inflammatory human placenta induced under the same conditions, indicating that the intervention of BHB on NLRP3 inflammasome may be related to different sites or cell types. At the same time, the safe administration concentration and administration time of BHB also need to be further clarified.

Hyperoside

Hyperoside (quercetin-3-O-β-D-galactopyranoside, Hyp), a flavonol glycoside from Hypericum and Crataegus species, possesses anti-inflammatory and antioxidant properties, is an important natural product.[107] Antiphospholipid syndrome (APS) or positive antiphospholipid antibodies (aPL) are high-risk causes of RPL, and their main pathogenic mechanism is to interfere with early placental formation by reducing trophoblast cell proliferation, invasion of the decidual spiral artery, and increasing trophoblast cell apoptosis and thrombus formation, leading to miscarriage.[108] In an animal model of aPL induced abortion, Hyp targets and inhibits the purinergic ligand-gated ion channel 7 (P2X7)/NLRP3 signaling pathway, which has a protective effect on aPL induced miscarriage and may provide a feasible drug strategy for the treatment of RPL.[109] However, there is currently no evaluation of the efficacy of hyperoside in patients with RPL. It is necessary to conduct research on Hyp in the future to understand its mechanism of inhibiting NLRP3 inflammasome in RPL patients and the safety of its use.

Preimplantation Factor (PIF)

PIF, is a linear peptide involved in reproductive regulation, secreted by living embryos and distributed in mammalian embryos, placental tissue, and peripheral blood of pregnant women.[110] PIF is closely related to pregnancy maintenance and plays an important role in embryo implantation, trophoblast invasion, and immune regulation at the maternal fetal interface.[111] Synthetic PIF suppresses the first priming signal of NLRP3 via TLR4 inhibition and reduces K^+ efflux by modulating Kv1.3b channels, blocking the second activation signal.[112,113] Research has shown that PIF can prevent LPS induced fetal loss by targeting NLRP3 inflammasome to regulate inflammatory response,[114] but there is currently no research report on the RPL population. It is worth noting that before designing RCT studies for women with RPL, it is necessary to investigate the safety and incidence of side effects of exogenous synthetic PIF supplementation.

α-Lipoic Acid (ALA)

ALA, a water-soluble and lipid soluble metabolic antioxidant, can act as a coenzyme to participate in acyl transfer in the metabolism of substances in the body, and can eliminate free radicals that accelerate aging and disease.[115] ALA is a super antioxidant with the most functions and strongest activities among all antioxidants. It can not only reduce the oxidation of antioxidants such as glutathione and vitamin C,[116] but also help diabetes patients balance blood sugar.[117] In addition, it can also play an anti-inflammatory role by regulating the NF kB signaling pathway.[118] Combined ALA and progesterone therapy has improved threatened miscarriage outcomes without fetal harm.[119] In iRPL patients, three-month ALA treatment reduced endometrial NLRP3 expression and caspase-1, IL-1β, and IL-18 levels.[120] This result encourages larger randomized controlled trials targeting ALA for the treatment of RPL by regulating NLRP3. Due to the influence of pharmacokinetic characteristics, the half-life and bioavailability of ALA are relatively short, about 30%, greatly limiting its therapeutic effect.[118] In the future, it is necessary to conduct more in-depth research on the regulatory mechanism and safety of ALA in RPL patients, while exploring more innovative formulas to effectively improve the bioavailability of ALA.

miR-138-5p

miR-138-5p is downregulated in decidua from early pregnancy failure patients, leading to NLRP3 overactivation. Subsequent experiments have shown that upregulating miR138-5p can inhibit the activation of NLRP3 inflammasome by suppressing the expression of its target gene G protein coupled receptor 124 (GPR124), thereby improving the immune tolerance mechanism of maternal fetal interface damage, promoting smooth embryo implantation and normal placental development.[121] Multiple microRNAs have been proved to be involved in the occurrence and development of RPL,[122] and their post transcriptional regulation mechanism on NLRP3 inflammatory bodies has gradually become clear,[123] providing an RNA based prevention and treatment idea for RPL (Table 1).

Conclusion

In summary, the NLRP3 inflammasome and its associated factors orchestrate multiple key events in the pathogenesis of RPL. Our comprehensive investigation reveals that aberrantly activated NLRP3 inflammasomes in RPL contribute to the impairment of endometrial receptivity by engaging in the endoplasmic reticulum stress response of endometrial cells and subsequently promoting an exaggerated inflammatory response and excessive release of inflammatory mediators within decidual cells. Moreover, the overactivation of inflammasomes aggravates the imbalance of immune cell populations at the maternal-fetal interface, particularly by disturbing the Th17/Treg cell differentiation and the M1/M2 polarization of macrophages, thereby fostering a pro-inflammatory milieu conducive to RPL. The resultant excessive pyroptosis further compromises the proliferation and invasion capacities of trophoblasts. Although the bidirectional regulatory interplay between the NLRP3 inflammasome and autophagy has not been fully elucidated, it is evident that the excessive activation of NLRP3 disrupts the autophagic homeostasis in normal trophoblasts. Additionally, the pathological loop involving NLRP3 overactivation in the endometrium and increased intestinal barrier permeability observed in RPL patients lends intriguing support to the "gut–endometrium axis" hypothesis, offering a novel perspective on the disease's underlying mechanisms. Although the fundamental roles of NLRP3 during pregnancy have been recognized,[48,124] it is not difficult to conclude that the regulation of RPL by NLRP3 inflammasome is diverse, with different activation and

Table 1 Drugs Targeting the Inhibition of NLRP3 Inflammasome and Their Role in the Treatment of RPL

Drug Name	Research Model	Mechanism	Effect	Reference
Aspirin	URPL mouse model	Inhibiting the HMGB1/NLRP3 pathway, reducing the inflammatory response at the maternal fetal interface	Improving vascular damage caused by abnormal endothelial cell necrosis, and increasing implantation and live birth rates.	[63]
Metformin	The LPS-induced HTR-8/SVneo-derived preeclampsia model.	Inhibiting the TLR4/NF-κB/PFKFB3 axis, suppressing NLRP3 activation and mitochondrial damage	Reducing excessive pyroptosis and glycolysis of trophoblast cells and placental inflammation	[87]
Low-Molecular-Weight Heparin	RPL cell model; PE mouse model	Blocking the activation of NLRP3 inflammasome; activating the PI3K/AKT pathway and inhibiting the activation of NLRP3 inflammasome	Improving the abnormal inflammatory state at the maternal fetal interface, enhancing the activity of trophoblast cells and macrophages; Reducing pregnancy loss in PE mice, restoring trophoblast differentiation, and improving cell proliferation.	[13,92]
Progesterone	Monocytes from preeclamptic women and THP-1 cells with hyaluronan	Inhibiting TLR4/NF -κB pathway and obstructing NLRP3 inflammasome activation	Regulating immune balance and improving inflammatory state	[97]
MCC950	Palmitic acid-induced placental inflammation model	Obstructing ASC oligomerization and specifically inhibiting the NLRP3/IL-1β pathway	Reducing placental inflammatory response	[102]
β-Hydroxybutyrate	LPS induced human trophoblast cells and maternal fetal interface inflammatory mouse	Inhibit the co- localization of NLRP3 and ASC, hinder the activation of caspase-1, and inhibit the activation of NLRP3 inflammasome	Reducing the inflammatory response of trophoblast cells and the embryonic resorption rate in model mouse	[106]
Hyperoside	Antiphospholipid antibody induced miscarriage mouse and cell model	Downregulating the expression of P2X7, inhibiting the activation of NLRP3	Reducing the embryonic miscarriage rate, platelet activation, and uterine placental dysfunction induced by aCL, improving inflammatory status, lowering cell apoptosis rate.	[109]
Preimplantation Factor	LPS induced murine model of fetal loss	Inhibiting the expression of NALP-3, ASC and caspase-1, and downregulating the level of NLRP3 inflammasome	Reducing fetal loss and increasing the embryo weight significantly	[114]
α-Lipoic Acid	iRPL patients	Inhibiting the expression of NLRP3 inflammasome	Reducing the inflammatory state of the endometrium	[120]
miR-138-5p	Decidual stromal cells isolated from miscarriage tissue of patients with spontaneous abortion at 6 to 12 weeks of pregnancy	Inhibiting the activation of NLRP3 inflammasome by suppressing the expression of its target gene G protein coupled receptor 124 (GPR124)	Improving the immune tolerance mechanism of maternal fetal interface damage, promoting smooth embryo implantation and normal placental development.	[121]

regulatory mechanisms in different pathological stimuli and cell types. Notably, experimental data remain sparse regarding the influence of NLRP3 on autophagic balance and barrier permeability in RPL, underscoring the need for extensive in vitro and in vivo studies to fill these knowledge gaps. Understanding the multifaceted involvement of the

NLRP3 inflammasome in the pathogenesis of RPL, as well as elucidating strategies to modulate its aberrant activation, is crucial for identifying novel therapeutic targets for the treatment of RPL.

Clinically, RPL management remains largely symptomatic and employs combination pharmacotherapies. The development of drugs targeting NLRP3 is still in its early stages, and there are no relevant drugs recognized as routine clinical drugs for treating RPL. Their efficacy and safety in clinical application are still controversial and uncertain, and further detailed research and consideration are needed. Furthermore, several unresolved questions merit future investigation: the precise bidirectional crosstalk between NLRP3 activation and trophoblast autophagy; whether MCC950's protective effects in palmitate-induced placental inflammation extend to models of decidual dysfunction; and the cell-type–specific variability in β-hydroxybutyrate's inhibitory action on NLRP3.

Our review provides a promising avenue for developing new therapeutic strategies for RPL, emphasizing the importance of further research at all entry points of NLRP3 inflammasome. In parallel, both small-molecule inhibitors and naturally derived bioactive compounds targeting the NLRP3 inflammasome should undergo rigorous, high-quality randomized controlled trials to clarify their safety and efficacy. Meanwhile, under the context of RPL, the potential impact of individualized genetic susceptibility or microbial factors on the abnormal activation of NLRP3 should also be considered as a worthwhile research direction. These research strategies may bring us closer to unraveling the complex pathogenesis of RPL and contribute to the advancement of its clinical management, ultimately benefiting maternal and fetal health.

Data Sharing Statement

No data was used for the research described in the article.

Consent for Publication

All authors approved the final manuscript and the submission to this journal.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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