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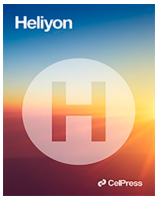

Review article

Unveiling the role of lncRNA ERDR1 in immune cell regulation

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ABSTRACT

Long non-coding RNAs (lncRNAs) are a class of RNA molecules that exceed 200 nucleotides in length and lack the capacity to encode proteins. In recent years, there has been a surge of interest in lncRNA research, leading to the discovery of their diverse structures and functions. This review focused on elucidating the regulatory roles of lncRNA erythroid differentiation regulatory 1 (Erdr1) within immune cells and its involvement in related disorders. By synthesizing findings from recent studies sourced from PubMed, this paper examined the biological functions and underlying mechanisms by which lncRNA Erdr1 influences immune cells and contributes to various diseases. Emerging research highlights that lncRNA Erdr1 exerts significant effects on the functionality of immune cells, particularly T lymphocytes (T cells), natural killer (NK) cells, and macrophages. Furthermore, Erdr1 has been implicated in the mitigation of several diseases, including acne, wound healing, osteoarthritis, melanoma, gastric cancer, obesity, and autism. Given its complex biological functions and mechanisms, Erdr1 presents itself as a promising biomarker and a potential therapeutic target for a range of immune cell-related disorders.

1. Introduction

Non-coding RNAs (ncRNAs), which comprise more than 90 % of the human genome, are essential regulators of cellular metabolism, proliferation, transcription, and post-transcriptional modification processes [1]. Although ncRNAs lack protein-coding sequences, they are categorized into several distinct types, including PIWI-interacting RNA (piRNA), circular RNA (circRNA), small interfering RNA (siRNA), small nuclear RNA (snRNA), microRNA (miRNA), and long non-coding RNA (lncRNA) [2]. In recent years, the discovery of a vast array of lncRNAs has revealed their diverse structures, functions, and sequences [3] (see Table 1).

LncRNAs, defined by their sequences exceeding 200 nucleotides, represent the most substantial class within the ncRNA family [4]. These molecules are recognized as key regulators of cellular physiological activities, particularly in maintaining cell homeostasis and regulating gene expression [5]. LncRNAs interact with miRNAs, modulating their biological functions, including mRNA cleavage and translational repression [6]. Studies have shown that lncRNAs can adopt complex secondary and tertiary structures, enabling them to interact with proteins and DNA to influence gene expression at various levels [7]. In summary, lncRNAs play pivotal roles in numerous cellular processes and hold significant potential for therapeutic applications across a wide range of disorders, including cancer,

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diabetes, obesity, cardiovascular diseases, and inflammation.

The expression of lncRNA erythroid differentiation regulatory 1 (Erdr1) has been shown to be significantly dysregulated in various human diseases, including melanoma, gastric carcinoma, rosacea, psoriasis, osteoarthritis, alopecia areata, alopecia, wound healing, pulmonary fibrosis, and autism. This review aimed to consolidate current knowledge on the diverse disease types and biological functions associated with lncRNA Erdr1.

Moreover, lncRNA Erdr1 isemerges as a keypivotal immunomodulator that plays a role in a variety ofwith multifaceted roles across various immune cells such as cell types, including T cells, NK cells, and macrophages, and plays an important role in. It significantly contributes to immune responses and inflammationry processes by enhancingamplifying signaling pathways, regulating cytotoxicity, influencingcytotoxic activity, guiding cell polarization, and modulating inflammatory response, and participating inresponses. Additionally, Erdr1 influences the functionbehavior of non-immune cells. Its specific, with its precise effects may dependoften contingent on concentration, cell type, and microenvironmental the specific conditions of the microenvironment [8–10].

2. Discovery and characterization of lncRNA Erdr1

Although research on the structure of lncRNA Erdr1 is currently limited, some relevant studies have provided valuable insights. One study has identified lncRNA Erdr1 in serum-free WEHI-3 supernatants from humans and mice, where it is predominantly expressed as a 56-kDa dimer in mammals [17]. Erdr1 is ubiquitously expressed across various tissues and organs, including the liver, brain, intestine, thymus, blood vessels, nerves, and normal human epidermis [18]. Wang et al. have conducted a bioinformatic analysis that identifies a CpG island within the Erdr1 promoter. They have further confirmed the presence of 12 CpG sites within this promoter region, ranging from 896 base pairs (bp) to 842 bp relative to the transcription start site (with +1 marking the transcription start site), using bisulfite DNA sequencing. Furthermore, studies have revealed that Erdr1, a gene located on the Y chromosome, is involved in the negative regulation of cell migration and proliferation, and plays a crucial role in maintaining the somatic stem cell population [19].

3. Regulatory effect of lncRNA Erdr1 on immune cells

3.1. Roles on T cells

T cells, which originate from bone marrow (BM)-derived thymocyte progenitors in the thymus, play a crucial role in maintaining health and preventing disease. These cells are primarily categorized into $CD4^+$ T helper (Th) cells and $CD8^+$ T helper (Th) cells ($CD4^+$ and $CD8^+$ T cells), based on their functions [20]. T cells orchestrate immune responses to pathogens, allergens, and tumors, and are therefore critical in regulating disease processes, including cancer, fibrotic diseases, type 2 diabetes (T2D), and inflammation. Given their central role in immunity, T cells are critical targets in various disease treatments.

Erdr1 is notably highly expressed in the thymus, which is predominantly composed of T cells, yet its specific functions within this context remain unclear. Initial research by Kim et al. has revealed that recombinant Erdr1 significantly reduces the infiltration of $CD4^+$ and $CD8^+$ T cells, thereby markedly attenuating the inflammation associated with the pathogenesis of rosacea [21] (Fig. 1a). However, the precise mechanisms by which Erdr1 influences T-cell functionality remain to be fully elucidated. Further studies by the same group have demonstrated that recombinant Erdr1 suppresses the expression of C-C chemokine receptor 6 (CCR6) by inhibiting the levels of C-C motif chemokine ligand 20 (CCL20), thereby regulating Th17 cell chemotaxis [22] (Fig. 1a). Additionally, it has been found that Erdr1 enhances T-cell antigen receptor (TCR) signaling sensitivity in T cells by increasing calcium (Ca^{2+}) flux [23]. Another investigation has demonstrated that Erdr1 induces the differentiation of regulatory T (Treg) cells and upregulates the expression of CD25, CD69, and cytotoxic T-lymphocyte-associated protein 4 (CTLA4), which are classical markers of Treg cell activation [24].

In the aforementioned studies, Erdr1 has been identified as a modulator of the TCR signaling pathway in T cells. However, the underlying mechanism of this process remains unclear. To address this issue, researchers have investigated the effects of Erdr1 on T cells from lymph nodes under TCR stimulation. Initially, $CD4^+$ T cells in the lymph are labeled with carboxyfluorescein succinimidyl ester (CFSE) to monitor changes in the number of TCR-induced $CD4^+$ T cells. Flow cytometry is then employed to analyze CD69 expression and the proportion of $CD4^+$ T cells in lymph following Erdr1 treatment under TCR stimulation. The results show significant differences in CD69 levels and the number of $CD4^+$ T cells compared to the control group, with statistical significance ($p < 0.05$).

Further analysis has assessed Ca^{2+} influx and the expression levels of phosphorylated phospholipase C gamma 1 (PLCγ1) in $CD4^+$ T

Table 1
Roles of lncRNA Erdr1 on some diseases.

Disease	Therapeutic target	Mechanism	Expression	Reference
Atopic dermatitis			Up-regulated	[11]
Psoriasis	T cell	Suppress keratin 14, recombinant s100 calcium binding protein A8 (S100A8), IL-17, IL-22, and CCL20	Down-regulated	[12]
Rheumatoid arthritis	Treg cell	Activate TCR pathway	Up-regulated	[13]
Myelodysplastic syndromes	NK cell	Activate JNK pathway	Up-regulated	[14,15]
Heart disease	Macrophages	Activate prostaglandin E2 (EP2) receptor	Down-regulated	[16]

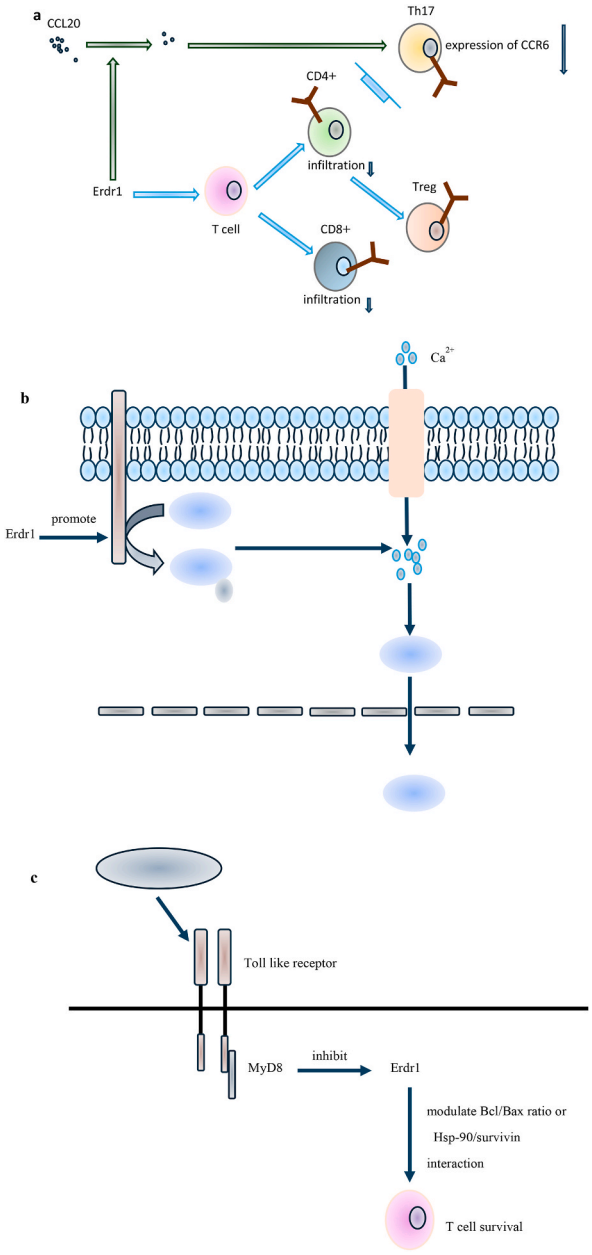

Fig. 1. Regulatory effect of lncRNA Erdr1 on T cells. (a) Effect of Erdr1 on T-cell differentiation. (b) Erdr1 regulates the $CD4^+$ T-cell response to TCR by augmenting the PLCγ1/Ca^{2+}/NFAT signaling pathway. (c) Microbes diminish Erdr1's capability to induce T-cell apoptosis by interacting with TLR on the cell surface.

cells treated with Erdr1 in the presence of TCR stimulation. The findings reveal that Erdr1 significantly enhances both Ca^{2+} influx and the phosphorylation of PLCγ1. In the final phase of the study, the nuclear factor of activated T cells 1 (NFAT1), nuclei, and actin are fluorescently stained to assess the translocation of NFAT1 into the nucleus, a crucial step in T-cell activation. The results suggest that Erdr1 modulates the $CD4^+$ T-cell response to TCR stimulation by augmenting the PLCγ1/Ca2+/NFAT signaling pathway (Fig. 1b).

These outcomes demonstrate that Erdr1 is critical in stimulating the PLCγ1/Ca^{2+}/NFAT signaling pathway in peripheral $CD4^+$ T cells under TCR influence. The findings highlight the pivotal role of Erdr1 in regulating T-cell activity, providing valuable insights for developing timely interventions and treatments for T-cell-associated diseases.

Additionally, it has been reported that commensal bacteria influence both proinflammatory and anti-inflammatory immune responses [25]. Soto et al. have discovered that symbiotic microbes can suppress Erdr1 expression through a Toll-like receptor (TLR) pathway involving myeloid differentiation factor 88 (MyD88), thereby modulating T-cell survival. Their research has demonstrated that Erdr1 activation leads to the secretion of tumor necrosis factor receptor superfamily (Fas) and caspase 3, triggering apoptosis.

Consequently, they conclude that microbial suppression of Erdr1 reduces its capacity to induce T-cell apoptosis (Fig. 1c). Furthermore, they indicate that Erdr1 can autocrinally induce T-cell apoptosis [26]. Existing studies suggest that Erdr1 influences the B-cell lymphoma-2 (Bcl-2)/Bcl-2-associated X protein (Bax) ratio and the heat shock protein 90 (Hsp-90)/surviving interaction, leading to T-cell apoptosis at high cell densities [27].

Another study has demonstrated that regulating Erdr1 levels in the intestine by early-life microbiota is associated with enhanced histone H3 acetylation. They further find that Erdr1 can promote the growth of intestinal organoids by enhancing the proliferation and activity of $Lgr5^{+}$ intestinal stem cells (ISCs) through the activation of Wnt signaling in intestinal epithelial cells and organoids [28]. Overall, these studies suggest that Erdr1 is a critical regulatory factor for T cells, and targeting the downregulation of Erdr1 may offer a novel therapeutic approach for diseases associated with T-cell apoptosis.

3.2. Roles on macrophages

Research shows that macrophages, the most prevalent immune cells in various malignancies, release a range of cytokines, including tumor necrosis factor (TNF), interleukin (IL)-1β, IL-6, IL-8, IL-12, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Additionally, macrophages secrete chemokines such as CCL1, CXCL2, CCL5, CXCL8, CXCL9, CXCL10, and CXCL11, which are involved in inhibiting tumor growth and migration [29]. Based on their distinct functions, macrophages are classified into two types: classically activated (M1) and alternatively activated (M2) [30]. When macrophages become dysfunctional, they can lead to the uncontrolled production of inflammatory mediators and growth factors, contributing to the development of various conditions, including cancer, abnormal tissue repair, and chronic inflammation [31].

An investigation by Wang et al. has revealed that Erdr1 levels and subcellular localization vary significantly in lipopolysaccharide (LPS)-induced M1 macrophages and IL-4-induced M2 macrophages compared to M0 macrophages, with Erdr1 being downregulated in M1 macrophages and upregulated in M2 macrophages [32]. Previous research has suggested that Erdr1 can either promote or inhibit IL-1β production, depending on the concentration and cell density. Building on this, the study has further demonstrated that Erdr1 promotes IL-1β production at low cell density and suppresses it at high cell density. YAP1 (Yes1 Associated Transcriptional Regulator) isassociated transcriptional regulator) serves as a keycentral effector ofwithin the Hippo signaling pathway. When Elevated levels of Erdr1 level is elevated, facilitate an ERDR1-YAP1 interaction, which subsequently promotes the productionrelease of anti-inflammatory cytokines. WhenConversely, when Erdr1 levels are reduceddecrease, the ERDR1-MID1 interaction inducestriggers the production of pro-inflammatory cytokines. Notably, Erdr1 and Mid1 are closely relatedlinked in gene localization, and they aregenomic positioning as neighboring genes onwithin the PAR region of the sex chromosome (X and Y chromosomes). (X and Y). Together, Erdr1 and Mid1 share a role in regulating contribute to the regulation of YAP1 signaturetarget gene expression, and are both are involved inintegral to the regmodulation of intracellular zinc signaling [33](Fig. 2.). These findings suggest that Erdr1 promotes a pro-inflammatory response at low cell density and inhibits it at high cell density. Furthermore, the authors have reported that conformational changes in Erdr1 enhance IL-1β production, leading to pro-inflammatory polarization, while increased Erdr1 levels reduce IL-1β production, promoting anti-inflammatory polarization [32].

Gong et al. have demonstrated that Erdr1 inhibits the infiltration of inflammatory cells, including macrophages, via the transforming growth factor-β (TGF-β)/Smad signaling pathway [34]. Another study has found that Erdr1 expression is significantly increased in prostaglandin E2 (EP2) receptor 2-deficient macrophages compared to normal ones, suggesting that Erdr1 regulates macrophages through EP2 modulation. This finding is further supported by evidence showing that Erdr1 enhances macrophage migration and cardiac repair by improving the EP2 signaling pathway [16].

Recent research by Li et al. has reported that the level of lncRNA Gm47283/Gm21887 (Erdr1) is elevated in resistin-like molecule α (RELMα)-deficient animals. Since RELMα is a macrophage-secreted protein, the findings suggest that lncRNA Gm47283/Gm21887 inhibits macrophage release of RELMα, thereby affecting eosinophil chemotaxis [35]. Collectively, these studies indicate that Erdr1 is a potential therapeutic target for modulating macrophage function, offering promising avenues for the treatment of inflammation-related diseases.

3.3. Roles on NK cells

NK cells, as innate lymphocytes, form the first line of defense and play a critical role in combating the early phases of infections and malignancies [36]. These cells are capable of releasing a variety of cytokines, such as interferon-γ (IFN-γ), perforin, TNF-α, TNF-γ, and

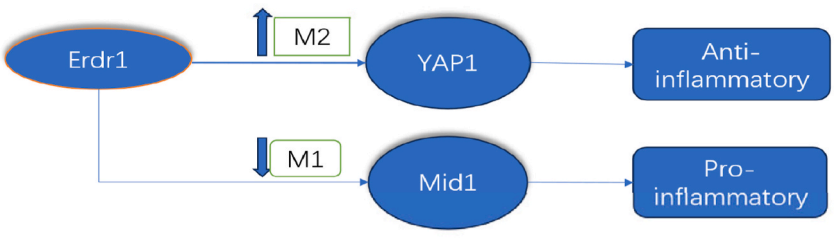

Fig. 2. Erdr1 and YAP1/Mid1.

IL-2, as well as chemokines like CCL3, CCL4, and CCL5, to modulate the immune response and eliminate infected or transformed cells [37]. Consequently, NK cells have been employed in clinical trials as part of immunotherapeutic strategies.

Research on NK cells is comparatively less extensive than the studies conducted on T cells and macrophages. However, Lee et al. have reported that NK cell cytotoxicity is significantly enhanced when treated with 10 ng/mL Erdr1 and co-cultured with the human leukemia cell line K-562 for 10 h. Erdr1 enhancesaugments the cytotoxicitycytotoxic capacity of NK cells by promotingstimulating the secretion of lytic granules. Theis study also highlightsunderscores the importancecritical role of immune synapse formation forin NK cell-mediated toxicity, particularly dependentemphasizing its reliance on actin recombination.remodeling. ERDR1 stimulatesfacilitates the accumulation of actin by NK cells at immune synapses, which may work synergistically within NK cells, potentially enhancing cytotoxic effects in conjunction with the Fas/FasL pathway to promoteoptimize NK cell killingtargeting and destruction of target cells. ([34).]. Numerous studies suggest that NK cells are promising targets for cancer therapy, as they are activated by tumor cells to release cytokines and chemokines, subsequently leading to tumor cell destruction through adhesion, granule polarization, degranulation, and cytokine secretion [38]. Therefore, Erdr1 may have a substantial impact on tumor cell functions. However, the molecular mechanisms underlying the effects of Erdr1 on NK cells remain unclear and warrant further investigation.

3.4. Roles on cytokines secreted by immune cells

Research has shown that Erdr1 can regulate the secretion of cytokines such as IL-18 and TGF-β by immune cells, playing a crucial role in the progression of various diseases, including inflammation and cancer.

3.5. IL-18

IL-18, a key marker of innate immune activation and a member of the IL-1 cytokine family, is synthesized by various immune cells, including macrophages, Langerhans cells, as well as non-immune cells such as intestinal epithelial cells, osteoblasts, endothelial cells, and keratinocytes [39]. Along with its receptor, IL-18R, IL-18 plays a significant role in both innate and adaptive immunity by promoting IFN-γ secretion from Th1 cells, non-polarized T cells, NK cells, B cells, and macrophages [40]. Extensive research has demonstrated IL-18's involvement in infectious, metabolic, and inflammatory diseases.

Studies have highlighted Erdr1's potential in treating inflammation through its regulation of IL-18. Kim et al. have first identified a significant inverse correlation between IL-18 and Erdr1 levels in patients with rosacea, suggesting a negative interaction between these two factors [21]. Further research has revealed that Erdr1 suppresses IL-18 levels in synovial tissue and inhibits cell migration by preventing extracellular-regulated kinase 1/2 (ERK1/2) phosphorylation in collagen-induced arthritis (CIA) model in DBA/1J mice [13]. Additionally, recombinant Erdr1 has been shown to alleviate psoriasis by modulating the expression of CCL17, which is regulated by IL-18, thereby reducing Th20 cell distribution in psoriatic lesions [41]. Another study has demonstrated Erdr1's role in melanoma progression, where it suppresses tumor cell migration, invasion, and growth both in vitro and in vivo, partly by significantly downregulating Hsp-90 through the inhibition of IL-18 levels [42]. Collectively, these findings underscore Erdr1's crucial role in modulating IL-18 levels, with significant implications for the treatment of inflammation and cancer (Fig. 3).

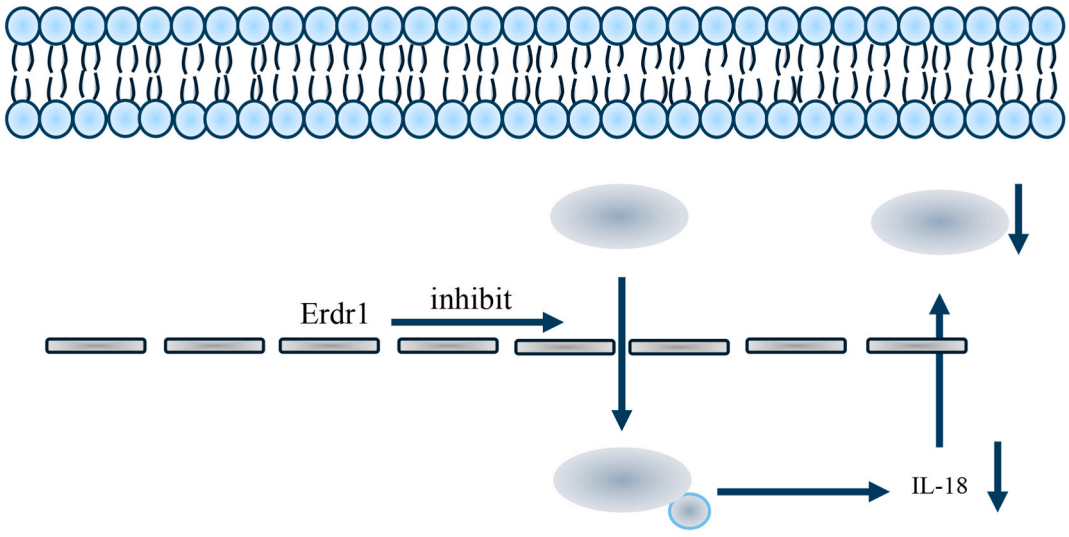

Fig. 3. Regulatory effect of lncRNA on IL-18. Erdr1 inhibits ERK1/2 phosphorylation to reduce the level of IL-18, and then the expression level of Hsp-90 is reduced.

3.6. TGF-β

TGF-β consists of three isoforms: TGF-β1, TGF-β2, and TGF-β3 [43]. It plays a crucial role in regulating cell proliferation, differentiation, apoptosis, and migration [44]. Recent studies have linked elevated TGF-β expression to various conditions, including metabolic disorders, immune system dysfunction, fibrosis, and cancer [45]. Additionally, TGF-β is vital in immune responses and in maintaining immune homeostasis by influencing the proliferation, differentiation, and survival of immune cells [46]. Due to its wide-ranging functions, TGF-β is regarded as a potential therapeutic target for various diseases.

Erdr1 has been reported to influence TGF-β levels through several mechanisms. Wang et al. have discovered that TGF-β can induce the overexpression of Methyl CpG Binding Domain Protein 2 (Mbd2) via the TGF-β/Smad signaling pathway. Mbd2, in turn, increases TGF-β expression by suppressing Erdr1, which contributes to the amelioration of idiopathic pulmonary fibrosis (IPF) [45] (Fig. 4). Furthermore, research by Gong et al. has found that Erdr1 can reduce inflammatory cell infiltration by elevating TGF-β expression, thereby enhancing collagen production [34]. These findings suggest that Erdr1 is a promising target for enhancing wound healing and treating conditions like acne by modulating TGF-β levels. However, the molecular mechanisms underlying this process remain to be fully elucidated.

4. Roles of lncRNA Erdr1 on diseases related to immune cells

4.1. Inflammation

Deregulated inflammatory responses can result from various causes, including infections, toxins, trauma, post-ischemic injury, and autoimmune conditions [47]. Inflammation is essential for maintaining tissue homeostasis, involving complex molecular mechanisms mediated by an array of cytokines [48]. This process is associated with several disorders, including obesity, cancer, and coronary atherosclerotic heart disease [49]. Inflammatory responses are triggered by activating receptors on both immune and non-immune cells [50]. Identifying effective therapeutic targets to modulate immune cells offers a promising strategy for managing inflammation.

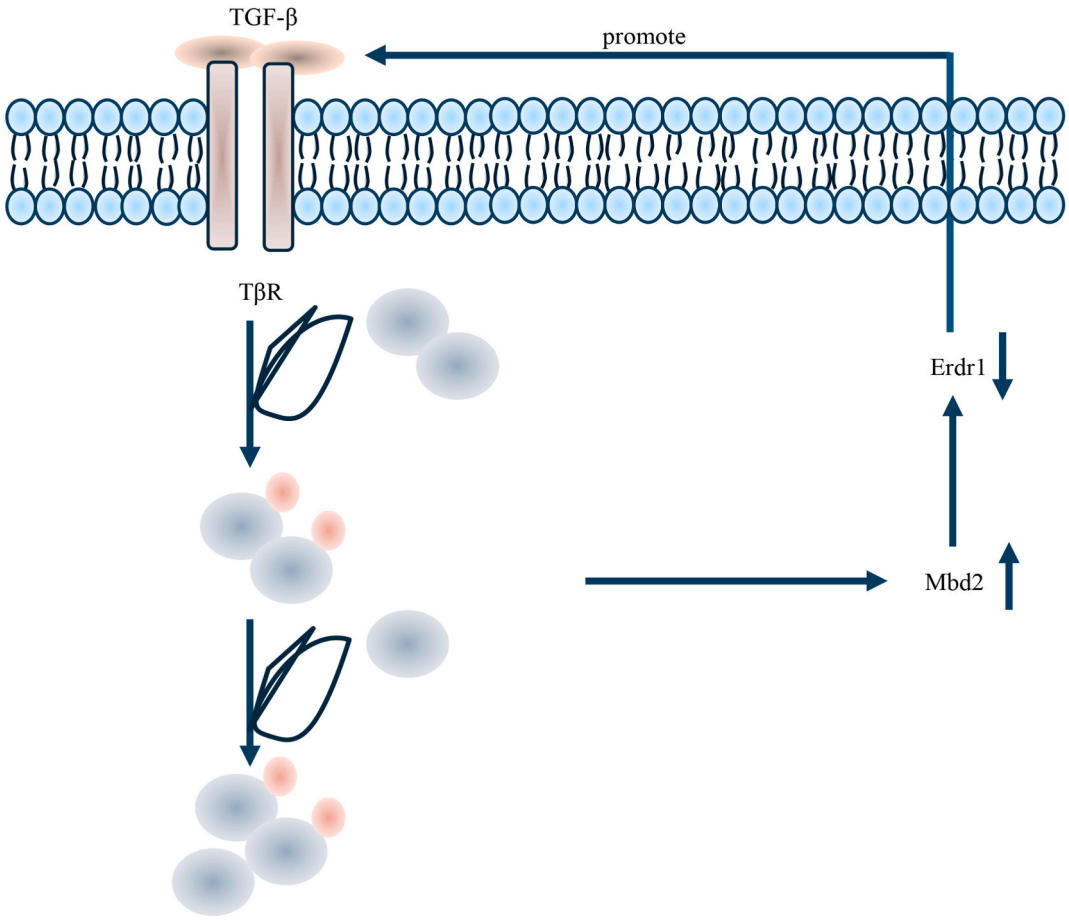

Fig. 4. Regulatory effect of lncRNA Erdr1 on TGF-β/Smad signaling to induce Mbd2 overexpression.

4.2. Skin inflammation

Numerous studies have highlighted the potential of Erdr1 in treating various inflammatory conditions, such as rosacea, psoriasis, osteoarthritis, alopecia areata, and alopecia. For instance, research has shown that Erdr1 can alleviate atopic dermatitis in NC/Nga mice induced by Dermatophagoides farina body extract [11]. Another study has demonstrated that suppressing Erdr1 expression can mitigate the pathogenesis of psoriasis [51]. Additionally, Erdr1 has proven effective in psoriasis treatment by reducing the expression levels of psoriasis-related mRNAs, such as keratin 14 and recombinant S100 calcium-binding protein A8 (S100A8), as well as by downregulating cytokines (IL-17 and IL-22) and the chemokine CCL20 [22]. Through these mechanisms, Erdr1 helps to ameliorate skin inflammation by impacting T cells.

4.3. Rheumatoid arthritis

Erdr1 has also been shown to mitigate the effects of arthritis. Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by pain, swelling, and stiffness, and it is becoming increasingly prevalent in modern society [52]. Discovering novel therapeutic regulators for RA is essential. One study has demonstrated that treatment with recombinant Erdr1 has therapeutic potential for RA by reducing IL-18 levels, which in turn inhibits synovial fibroblast migration in a model of inflammatory arthritis [13]. Additionally, Erdr1 has been found to activate Treg cells under TCR stimulation, thereby inhibiting T-cell proliferation and alleviating RA symptoms [24]. These studies collectively suggest that Erdr1 holds promise in treating RA by modulating IL-18 and T cell activity.

4.4. Cancer

Epidemiological studies have revealed that cancer is responsible for one in six deaths globally in 2020, and projections indicate that cancer incidence can triple by 2070 compared to 2020 [53]. Despite significant advancements in cancer diagnosis and treatment, the disease remains a leading cause of mortality and morbidity [54]. Therefore, early prevention, accurate diagnosis, and effective treatment are crucial for improving outcomes for cancer patients.

4.5. Gastric cancer and MDS

Several studies have underscored Erdr1's potential role in influencing the onset and progression of various cancers, including melanoma, gastric cancer, and bladder carcinoma. Research by June et al. has demonstrated that recombinant Erdr1 reduces the migration and invasion capabilities of SNU-216 gastric cancer cells by activating the c-Jun N-terminal kinase (JNK) pathway. This activation subsequently enhances E-cadherin levels, a molecule known to improve cell adhesion and reduce motility [15]. Yanni Hua et al. have found that JNK expression is elevated in the NK cells of myelodysplastic syndrome (MDS) patients with iron overload compared to those without, highlighting the significance of the JNK pathway in NK-cell function and its potential role in disease treatment [14]. These findings suggest that Erdr1 can exert anti-cancer effects by modulating NK-cell activity.

In addition to its effects on NK cells, Erdr1 also influences tumor cells by modulating IL-18 expression. Jung et al. have demonstrated that Erdr1 significantly inhibits tumor cell migration, growth, and invasion in melanoma through the downregulation of IL-18 expression [42]. This positions Erdr1 as a potential regulator of IL-18, presenting a promising therapeutic target in cancer treatment.

4.6. Pulmonary fibrosis

TGF-β1 (transforming growth factor-beta 1) induces global DNA hypermethylation in fibroblasts, accompanied by overexpression of MBD2 (methyl-CPG binding domain protein 2). Overexpressed MBD2 binds specifically to hypermethylated CpG DNA in the Erdr1 promoter region, thereby inhibiting Erdr1 expression. This inhibition enhances the activity of TGF-β/Smads signaling pathway, promotes the differentiation of fibroblasts into myofibroblasts, and aggravates pulmonary fibrosis [55]. As a regulatory factor, Erdr1 can inhibit the differentiation of fibroblasts into myofibroblasts and reduce the formation of myofibroblasts by inhibiting TGF-β/Smads signaling pathway, thus playing a protective role in pulmonary fibrosis. In summary, Erdr1 plays a protective role in pulmonary fibrosis by inhibiting fibroblast differentiation and regulating TGF-β/Smads signaling pathway.

5. Other diseases

5.1. Obesity

Obesity, a metabolic disorder, is linked to a wide range of complications, including hypertension, T2DM, fatty liver disease, vascular disease, tumors, reproductive disorders, and obstructive sleep apnea [56,57]. With the rise in economic development, the prevalence of obesity has surged, underscoring the urgent need for innovative treatment approaches. Recent research has associated the expression of lncRNA Gm21887 (Erdr1) with obesity, suggesting it as a potential target for therapeutic intervention [35].

5.2. Heart disease

Heart disease continues to be a leading cause of hospitalization, especially among older adults in the United States, highlighting the

urgent need for effective treatment strategies [58]. Wu et al. have found that suppressing Erdr1 expression can enhance cardiac function and improve the inflammatory microenvironment. This improvement is linked to the restored migratory capacity of macrophages, facilitated through the EP2 receptor, as observed in both in vivo and in vitro studies [16].

5.3. Neurodegenerative disorders

It has been found that Erdr1 regulates glutathione (GSH) synthesis by interacting with glutamate transporter-associated protein 3-18 (GTRAP3-18). GTRAP3-18 is an endoplasmic reticulum protein capable of binding to excitatory amino acid transporter 1 (EAAC1) and retaining it in the endoplasmic reticulum, thereby inhibiting EAAC1-mediated cysteine uptake. Erdr1 levels were significantly increased in the hippocampus of GTRAP3-18-deficient mice. In vitro experiments, knockdown of Erdr1 led to a decrease in GTRAP3-18 levels, which in turn increased EAAC1 expression and intracellular GSH levels [59].

It is suggested that the down-regulation of Erdr1 can improve the antioxidant capacity by increasing the GSH level. Oxidative stress is considered to be a key factor in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Erdr1 may play a role in the prevention and treatment of these diseases by regulating GSH synthesis. Helps slow the progression of neurodegenerative diseases.

6. Discussion

As research on Erdr1 progresses, its role in various diseases becomes increasingly clear. On one hand, Erdr1 exerts critical regulatory functions in immune cells, including T cells, NK cells, and macrophages. The mechanisms by which Erdr1 influences disease treatment through immune cell regulation are complex, involving multiple pathways. For instance, Erdr1 can activate the TCR signaling pathway or the PLCγ1/Ca^{2+}/NFAT signaling pathway, enhancing Ca^{2+} influx to reduce the population of $CD4^{+}$ T cells. Additionally, symbiotic microbes may inhibit Erdr1 expression to induce T-cell apoptosis, though the specific microbes and molecular mechanisms underlying Erdr1's role in promoting T-cell apoptosis remain unidentified. Beyond T cells, Erdr1 enhances NK-cell cytotoxicity and cytokine secretion. It also reduces macrophage infiltration by activating the YAP1 and Mid1 signaling pathways or the TGF-β/Smad pathway.

On the other hand, Erdr1's influence extends beyond immune cells to impact cytokines secreted by T cells, NK cells, and macrophages, such as IL-18 and TGF-β, potentially opening new avenues for disease treatment. However, current research on Erdr1 remains limited, and the molecular mechanisms underlying its effects on immune cells, particularly macrophages and TGF-β, are not yet fully understood.

In this review, we explored the role of Erdr1 in various human diseases, with a particular focus on its regulation of T cells, NK cells, and macrophages. While most studies have centered on T-cell regulation by Erdr1, there is a relative scarcity of research concerning its effects on NK cells and macrophages. Future investigations should expand to include these and other immune cells, such as B cells, K cells, dendritic cells, neutrophils, eosinophils, and basophils. Additionally, Erdr1'sErdr1's influence extends beyond immune cells to impact non-immune cells, including human dermal fibroblasts (HDFs) and keratinocytes.

For instance, Erdr1 has been shown to enhance the ability of caspase-3 to induce apoptosis in human keratinocytes exposed to ultraviolet B (UVB) irradiation, mediated through the ERK and mitogen-activated protein kinase (MAPK) pathways [60]. In a study by Gong et al., Erdr1 is found to activate fibroblasts and promote collagen synthesis via the TGF-β/Smad signaling pathway [34]. Wang et al. have further identified Erdr1 as a potential therapeutic target for pulmonary fibrosis by inhibiting fibroblast differentiation [61]. These findings position Erdr1 as a promising target for conditions such as psoriasis, wound healing, and skin cancer. Moreover, Erdr1 has been shown to enhance HDF proliferation and migration by increasing CCL2 production [18].

Interestingly, Erdr1 is not only regulated by immune cells but also exerts influence over them. Li et al. have discovered that levels of lncRNA Gm247283/Gm21887 (Erdr1) are diminished by RELMα, a protein secreted by macrophages, which subsequently alleviates obesity. In addition to these functions, Erdr1 holds promise as a novel biomarker. Gao et al. have identified lncRNA Gm247283 as a biomarker for myocardial infarction, demonstrating its role in regulating prostaglandin-endoperoxide synthase 2 (Ptgs2) expression by binding to miR-706 and affecting ferroptosis in myocardial infarction [35]. Moreover, a study by Woo et al. have reported significantly lower levels of Erdr1 in patients with hair loss compared to healthy individuals, further suggesting Erdr1 as a potential biomarker for hair loss disorders [62].

In addition to regulating IL-18 and TGF-β, Erdr1 also influences other vital cytokines and chemokines, such as Bcl-2, Bax, CCL2, and CCR5. Research has shown that Erdr1 can reduce Bcl-2 expression while increasing Bax levels, leading to apoptosis in melanoma cells [63]. Furthermore, after treatment with ingenol mebutate, a significant decrease in Bcl-2 expression is observed alongside an increase in Erdr1, indicating a strong correlation between Erdr1 and Bcl-2 [64]. Mango et al. have found that Erdr1 modulates CCR5, inhibiting cell apoptosis [65]. Another study has demonstrated that Erdr1 enhances CCL2 production, which subsequently inhibits the migration and growth of HDFs [18].

This review underscored Erdr1's potential in treating a range of conditions, including inflammation, cancer, obesity, and heart failure. Beyond these diseases, Erdr1 is also implicated in brain-related disorders. Notably, an increase in Erdr1 expression has been detected in the cerebral cortex of tubby mice [66]. Analysis of 317 differentially expressed genes between Ts1Cje and disomic mice has revealed significant changes in Erdr1 expression in the cerebellum [67]. Trent et al. have reported notable alterations in Erdr1 expression in genetic mouse models of neurodevelopmental disorders [68]. In a study by Winkler et al., a significant reduction in Erdr1 levels is observed in Pianp-deficient mice, which exhibit anxiety, repetitive behaviors, severely impaired social interactions, and spatial learning deficits [69]. These findings suggest that Erdr1 may be a potential target for brain disorders, including autism and

neurodevelopmental disorders. However, the mechanisms underlying Erdr1's regulatory role in these conditions remain to be elucidated.

Previous studies have established the interaction between the immune and neural systems. For instance, Pooler et al. have reported that the paraventricular hypothalamus controls the flow of monocytes and lymphocytes from secondary lymphoid organs to the BM [70]. Additionally, research by Carotenuto et al. has indicated that glymphatic impairment may contribute to multiple sclerosis [71]. Based on these findings, it can be hypothesized that Erdr1's beneficial effects on brain disorders can be mediated through immune cell regulation, a hypothesis that warrants further investigation.

In additionFurthermore, Erdr1 could be utilizedholds promise as a potential biomarker, especiallyparticularly valuable in monitoringtracking immune cell-relatedassociated diseases such as, including autoimmune disordearses, cancer, and inflammatory diseases.conditions. Measuring Erdr1 expression levels can also be tested within blood or other biological samples to assesscould provide insights into disease statusprogression and treatment effectiveness. Based on theefficacy. Given its pivotal role of Erdr1 in regmodulating immune cell function, drugs that target Erdr1-targeting therapies, such as small molecule inhibitors or activators, are being developed to enhanceeither boost or inhibit the activity ofsuppress specific immune cells by regulating Erdr1, such as bycell activities. For instance, enhancing the activity of Treg cells to treatcell activity through Erdr1 modulation may offer therapeutic benefits in autoimmune diseases, or by promoting the activity ofwhile stimulating effector T cells to enhancecould strengthen anti-tumor immunity.

In summary, Erdr1 emerges as a critical target in the treatment of various diseases. With its promising therapeutic potential, Erdr1 is anticipated to transition into clinical use once key challenges in its application are addressed. However, the current understanding of the molecular mechanisms by which Erdr1 influences immune cells, particularly NK cells and macrophages, remains incomplete, posing a barrier to its clinical integration. Therefore, further investigation into these mechanisms is essential to fully harness Erdr1's potential for therapeutic use. It is expected that with continued research and resolution of these challenges, Erdr1 will advance into clinical settings, offering new avenues for disease treatment.

CRediT authorship contribution statement

Aihua Shu: Writing – review & editing, Supervision, Investigation, Formal analysis, Data curation, Conceptualization. **Xu Tian:** Writing – original draft, Data curation, Investigation, Project administration, Writing – review & editing. **Jie Yue:** Writing – review & editing, Writing – original draft, Software, Resources. **Yuxia Jiang:** Writing – original draft. **Yifei Liu:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Resources, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Data and code availability statement

No new data was generated for the research described in the article.

Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because his is a review article, based on published findings, and does not involve the use of patient data.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2025.e42085.

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