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Review

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REVIEW

EZH2 in non-cancerous diseases: expanding horizons

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Abstract

Enhancer of Zeste homolog 2 (EZH2), a histone methyltransferase within polycomb repressive complex 2 (PRC2), plays a crucial role in epigenetic regulation by silencing gene expression through trimethylation of histone 3 at lysine 27 (H3K27me3). Beyond its well-documented oncogenic functions, emerging research has revealed EZH2's involvement in various non-cancerous pathologies. For instance, EZH2 is critical in regulating immune responses, particularly in modulating T cell differentiation and cytokine production, which affects inflammation and immune homeostasis. EZH2 also controls fibroblast activation and extracellular matrix (ECM) remodeling, influencing critical processes such as cell differentiation, tissue repair and energy homeostasis. Additionally, EZH2's epigenetic regulation of neuroinflammatory processes is linked to neuronal health and survival. Recent advancements in EZH2 inhibitor therapies demonstrate promising potential for treating a range of non-cancerous conditions, with preclinical trials suggesting efficacy in mitigating disease progression. This review highlights the expanding functional scope of EZH2, emphasizing its epigenetic mechanisms and the therapeutic opportunities for targeting EZH2 in non-cancerous diseases.

Keywords EZH2, EZH2 inhibitor, non-cancerous disease, immunological disorder, fibrosis, degenerative disease

Background

Enhancer of Zeste homolog 2 (EZH2) is a key histone methyltransferase that forms the catalytic core of polycomb repressive complex 2 (PRC2). It specifically catalyzes trimethylation of histone 3 at lysine 27 (H3K27me3), leading to gene silencing through chromatin condensation (Margueron and Reinberg, 2011; Pasini and Di Croce, 2016). EZH2's activity is closely linked to polycomb repressive complex 1 (PRC1). PRC1 recognizes H3K27me3 through its canonical partner PHC1/2 and catalyzes histone H2A lysine 119 ubiquitination (H2AK119ub), which helps stabilize H3K27me3 marker and further compacts chromatin (Cao et al., 2002; Kasinath et al., 2021). The interdependence between PRC1 and PRC2 is crucial for maintaining gene repression and proper chromatin architecture. As a crucial epigenetic regulator, EZH2 plays a pivotal role in the maintenance of stem cell pluripotency, cell differentiation, and tissue homeostasis (Beguelin et al., 2013; Spencer Chapman et al., 2023; Xu et al., 2022b). EZH2 also plays critical roles in embryonic development and tissue regeneration, regulating chromatin during these processes to ensure proper cellular fate decisions (Huang et al., 2018; Zhang et al., 2020b). Its dysregulation is commonly observed in cancers, where

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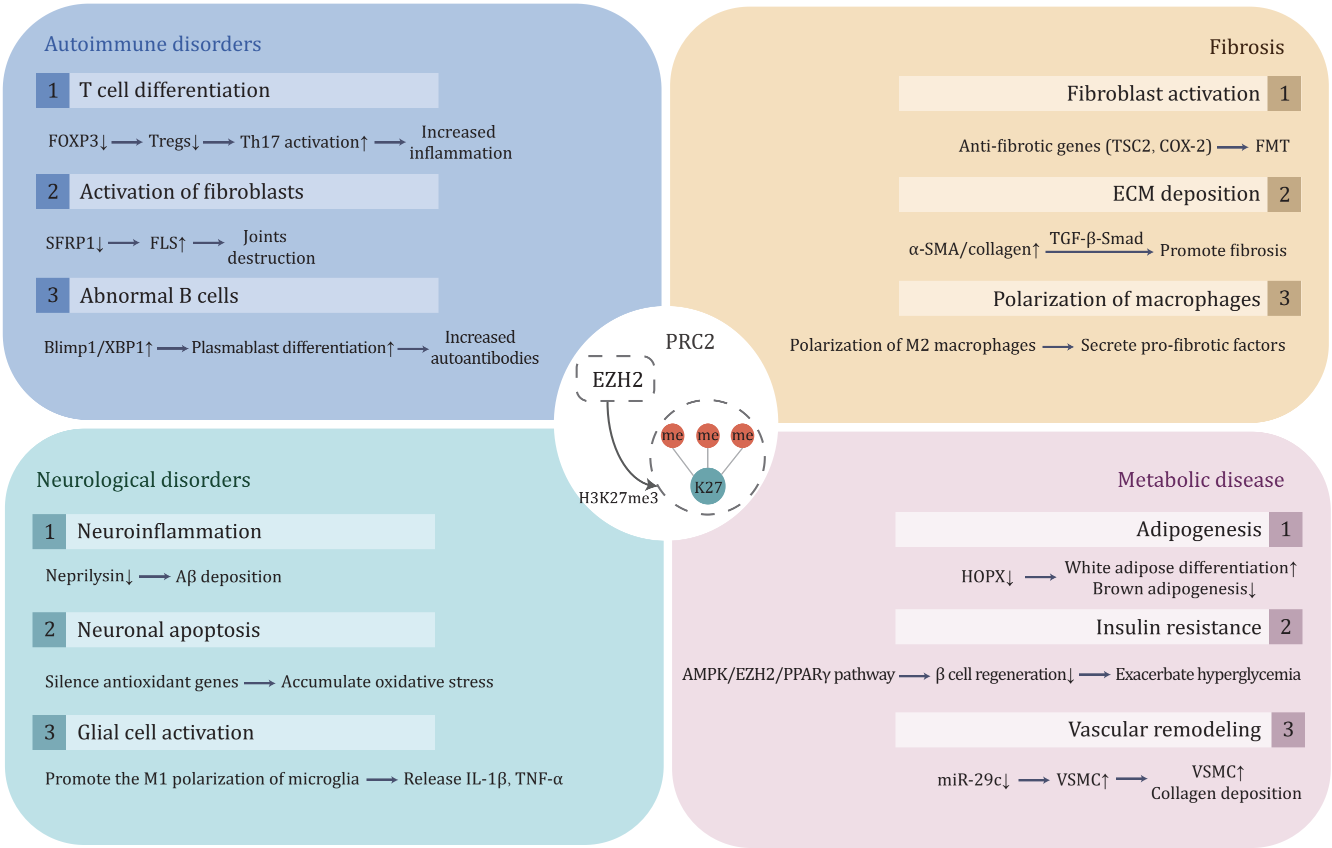

Figure 1. EZH2-mediated epigenetic regulation in non-cancer diseases. The figure depicts how EZH2, as part of the PRC2 complex, influences the molecular processes underlying autoimmune disorders, fibrosis, neurological diseases, and metabolic diseases. In each category, key pathways affected by EZH2 through H3K27 trimethylation, contributing to disease progression are shown.

overexpression of EZH2 is linked to poor prognosis and therapeutic resistance by repressing tumor suppressor genes, facilitating cell proliferation, and enabling immune evasion (Chase and Cross, 2011; Kempkes et al., 2024; Zeng et al., 2022). Recent comprehensive reviews also emphasize the therapeutic potential of targeting EZH2 in cancer, where inhibitors of EZH2 are currently being investigated in clinical trials (Li et al., 2021a). In 2020, FDA-approved Tazemetostat for the treatment of epithelioid sarcoma (ES) and relapsed or refractory (R/R) follicular lymphoma (FL) (Hoy, 2020). Generally speaking, the growing body of research has highlighted the importance of EZH2 as a therapeutic target in cancer, offering new insights into the possibilities of modulating epigenetic regulators for clinical benefit.

In recent years, mounting evidence suggests that EZH2 is also critically involved in the pathogenesis of several non-cancer diseases, making it a versatile regulator in human health and disease. In fact, epigenetic regulation has emerged as a key mechanism in the development of non-cancerous diseases. For instance, EZH2-mediated repression of key immune regulatory genes leads to abnormal immunological activation in autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) (Ding et al., 2022; Xu et al., 2022a). In fibrotic diseases, such as pulmonary and cardiac fibrosis, EZH2 promotes fibroblast activation and extracellular matrix (ECM) deposition (Zhang et al., 2023b). In addition, EZH2 has been linked to neuronal survival and synaptic plasticity in neurological disorders including Alzheimer's disease (AD) and Parkinson's disease (PD) (Dibaj et al., 2024; Sardoiwala et al., 2020), suggesting its potential involvement in neuroprotection. Despite the growing understanding of EZH2's role in non-cancerous diseases, research in this area is still in infancy. There is a critical need to further investigate the mechanisms by which EZH2 contributes to the pathogenesis of these diseases, as well as to explore the potential of EZH2 inhibitors in non-oncological therapeutic applications.

This review summarizes the multifaceted role of EZH2 in non-cancerous diseases, focusing on its epigenetic regulation of immune modulation, tissue remodeling, metabolic pathways, and neurological conditions (Fig. 1). It also discussed the therapeutic potential of EZH2 inhibitors in these disorders, with strategies ranging from systemic to localized delivery and combination therapies to enhance efficacy. These insights underscore EZH2's promise as a critical target for developing treatments across a wide spectrum of diseases.

EZH2 in autoimmune diseases

Our diverse immune system developed to complete the primary function of protecting hosts from infectious agents. However, the autoimmune diseases, which are failure to distinguish self from non-self are often referred to as a breakdown of immune tolerance. EZH2 plays a pivotal role in the pathogenesis of autoimmune disorders by regulating immune cell differentiation or inflammatory pathways, and interacting with miRNAs and lncRNAs, etc. Preclinical studies with EZH2 inhibitors like EPZ-6438 and DZNep show promise in reducing inflammation and tissue destruction. These findings underscore the potential of EZH2 inhibitors as therapeutic agents in autoimmune diseases.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by synovial inflammation, bone loss, and progressive joint destruction (Smith and Berman, 2022; Smolen et al., 2016). Fibroblast activation is the leading cause of synovial inflammation (Gravallese and Firestein, 2023). The increasing amount of experimental evidence suggests that EZH2 involves in the pathology of RA by abnormally activating fibroblast-like synoviocytes (FLS), which accelerates joint damage (Araki et al., 2018; Xiao et al., 2020; Xu et al., 2022a). In FLS from RA, EZH2 is overexpressed, induced by pro-inflammatory cytokines such as TNF-α, acting through NF-κB and JNK pathways. In addition, the expression of EZH2 was negatively regulated by miR-26b-5p, which was low-expressed in FLS from RA patients (Hu et al., 2021). EZH2 silences genes that inhibit synovial fibroblast activation, such as SFRP1, which suppresses Wnt signaling pathway—a key player in joint destruction and inflammation in RA (Trenkmann et al., 2011). Moreover, EZH2 interacts with long non-coding RNAs (lncRNAs) such as lnc-IL7R, promoting cell cycle progression and inhibiting FLS apoptosis through repression of cell cycle inhibitors p16 and p21 (Ye et al., 2017). Other regulatory mechanisms involve that EZH2 inhibits miR-22-3p expression by binding to its promoter, which results in increased expression of pro-inflammatory and matrix-degrading molecules such as CYR61, contributing to tissue destruction (Chang and Zhou, 2022). A recent study showed that EZH2 shRNA decreased the RA symptom score in a collagen-induced arthritis mouse model, by repressing bone ferroptosis and attenuating the osteoblast-osteoclast imbalance (Piao et al., 2024).

As a key feature of RA, synovial inflammation is characterized by a large presence of activated CD4$^+$ T cells. The differentiation of naïve CD4$^+$ T cells into various T cell subsets, including T helper 1 (Th1), T helper 17 (Th17), and regulatory T cells (Tregs), is highly dependent on environmental and epigenetic regulation. Accumulating studies show that EZH2 plays a critical role in immune cell regulation, particularly in the differentiation of Tregs. In RA, reduced EZH2 expression in CD4$^+$ T cells is linked to defective Tregs formation, further exacerbating the autoimmune response. EZH2 inhibition in T cells diminishes Foxp3 expression, a key transcription factor for Tregs development, promoting RA's inflammatory environment (Cooles et al., 2022; Xiao et al., 2020). Even when it was shown that EZH2 was essential for maintaining mature Tregs (DuPage et al., 2015), it should be noted that neither naïve nor Treg exhibit any H3K27me3 occupancy at the Foxp3 locus, indicating that EZH2 may indirectly control Foxp3. To investigate the mechanism of EZH2 regulation on Foxp3, more research is required (Wei et al., 2009).

To sum up, targeting EZH2 with specific inhibitors shows promise as a therapeutic approach for RA, as the abnormal activation and proliferation of FLS was repressed by EZH2 inhibitors. However, it is pivotal that EZH2 inhibitor was specifically delivered to the target FLS, given the fact that Tregs differentiation was suppressed by EZH2 inhibition. Nonetheless, epigenetic modulation by EZH2 inhibitors presents a novel avenue for RA treatment.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a common autoimmune rheumatic disease characterized by the presence of nuclear autoantibodies and inflammation of multiple organs (Durcan et al., 2019). The pathogenesis of systemic lupus erythematosus is multifactorial, including genetic, environmental, and hormonal factors (Tsokos et al., 2016). These involved factors lead eventually to dysfunction of B and T cells to produce autoantibodies, which enter tissues, form immune complexes, and cause tissue inflammation (Tsokos, 2020, 2024). Compared with healthy controls, EZH2 expression was higher in CD4$^+$ T cells and B cells in SLE patients. CD4$^+$ T cell disorders contribute to the disease's pathogenesis by promoting excessive autoantibody production and tissue damage. Elevated levels of EZH2 and H3K27me3 in CD4$^+$ T cells in SLE result from overactivated mTORC1 and reduced miR-26a and miR-101 expression, which disrupts T cell balance and promotes endothelial adhesion (Iwata et al., 2023; Zheng et al., 2020). Epigenetic modifications by EZH2 further drive CD4$^+$ T cell overactivation. B cell lymphoma 6 protein (BCL-6) binds to the promoter region of miR-142-3p/5p in CD4$^+$ T cells in SLE and recruits EZH2 and HDAC5, which leads to the increasing H3K27me3 and the reducing H3K9/K14ac, respectively (Ding et al., 2020, 2022). Furthermore, in CD8$^+$ T cells, upregulating CD38 expression leads to EZH2 acetylation through inhibiting cytotoxicity-related transcription factor RUNX3, which impairs CD8$^+$ T cell-mediated cytotoxicity and increases infection risk (Chakraborty and

Mehrotra, 2020; Katsuyama et al., 2020). Despite this, EZH2 inhibitors have shown promise in lupus models by improving immune tolerance.

Another important factor in the pathophysiology of SLE is aberrant Tfh cell activation. Increased E4BP4 has been demonstrated to bind directly to Bcl6 promoter region, drawing in EZH2 and HDAC. This increases H3K27 trimethylation and decreases H3 acetylation, which in turn inhibits Tfh cell growth and Bcl6 transcription (Wang et al., 2020b).

EZH2 also involves in abnormal B cell maturation and autoantibody production in SLE. Dysregulated immune activity in peripheral blood mononuclear cells (PBMCs), including abnormal B cell transcription factors, cytokines, B cell-T cell interactions, and toll-like receptor (TLR) pathway activation are implicated in SLE pathogenesis. Elevated EZH2, particularly in plasmablasts, correlates with disease activity and autoantibody levels (Iwata et al., 2023; Yang et al., 2023; Zheng et al., 2023). mTORC1 activation in B cells, along with methionine, induces EZH2 expression, which leads to H3K27me3-mediated repression of BACH2, promoting the expression of BLIMP1 and XBP1, and driving plasmablast differentiation (Zhang et al., 2020a). EZH2 inhibitors have been shown to suppress autoantibody production and germinal center formation, suggesting that EZH2 promotes B cell proliferation and inhibits apoptosis, ultimately leading to excessive plasma cell activity and autoantibody production in SLE.

Inflammatory bowel disease

In addition to rheumatoid-related diseases, EZH2 also plays an important role in other autoimmune disorders. Inflammatory bowel disease (IBD) is a prevalent health issue characterized by chronic gastrointestinal inflammation that manifests as relapsing episodes, encompassing Crohn's disease (CD), ulcerative colitis (UC), and IBD unclassified (Bruner et al., 2023; Khor et al., 2011). The pathogenesis of IBD is complex, heterogeneous, and multifactorial, encompassing host genetics, gut microbiota, environmental factors, and disruptive immune homeostasis (Guan, 2019; Mukherjee et al., 2024). EZH2 has been found to be a significant epigenetic regulator of intestinal immune homeostasis. Recent studies have shown that EZH2 modulates Tregs function by interacting with Foxp3, and its deficiency in these cells leads to increased inflammation and autoimmunity (Bamidele et al., 2019; Sarmento et al., 2017). Nevertheless, it has been demonstrated that EZH2 enzymatic activity inhibition encourages the production of MDSCs, but Th17 and Treg cells might not be essential for GSK343-mediated relief of DSS-induced colitis (Zhou et al., 2019). Additionally, EZH2 controls the expression of pro-inflammatory cytokines like TNF-α and IL-6, helping to restrain excessive inflammatory responses in the gut (Zhou et al., 2021).

EZH2 activity inhibition has been shown to alleviate intestinal inflammation. In murine models of dextran sulfate sodium salt (DSS)-induced colitis, EZH2 inhibition reduces cell apoptosis, lessens the severity of inflammation, and preserves intestinal epithelial barrier function (He et al., 2019; Li et al., 2020a; Zhou et al., 2021). Furthermore, EZH2 has been shown to interact with other epigenetic-related regulatory factors, such as YAP, to modulate the expression of epigenetic regulator like JMJD3, providing additional insights into its regulatory mechanisms in gut inflammation (Zhu et al., 2024).

EZH2 also exhibits dual roles in the treatment of colonic inflammation. On one hand, it can suppress inflammation by regulating Tregs and silencing pro-inflammatory genes (He et al., 2019); on the other hand, EZH2 may exacerbate inflammation by inhibiting anti-inflammatory genes and promoting the overactivation of immune cells. Understanding and balancing the dual functions of EZH2 will be key to designing effective therapeutic strategies (Li et al., 2024c; Sardoiwala et al., 2022).

Psoriasis

Psoriasis is a chronic autoimmune disease characterized by excessive keratinocyte proliferation and inflammatory immune responses (Griffiths et al., 2021). TNFα, IL-17, and IL-23 are key immunological drivers of psoriasis pathogenesis (Gupta et al., 2021; Wu et al., 2024a). Multiple studies have highlighted that the EZH2 expression is upregulated in psoriasis. By encouraging keratinocyte proliferation and the inflammatory environment, EZH2-dependent epigenetic modification of histone H3 lysine-27 leads to psoriasis (Zhang et al., 2020c). The mechanism involves that EZH2 silences miR-125a-5p, which normally inhibits SFMBT1, a factor involved in the TGF-β/SMAD pathway, thus contributing to dysregulating psoriasis in this pathway (Qu et al., 2021). Additionally, blocking EZH2 with inhibitors such as GSK126 can ameliorate imiquimod-induced psoriasiform lesions in mouse models by reducing keratinocyte proliferation and inflammation (Zhang et al., 2020c). Furthermore, IL-17A, a central cytokine in psoriasis pathogenesis, downregulates miR-101, leading to the upregulation of EZH2 expression and further aggravates epidermal hyperplasia (Quah et al., 2024). These findings suggest that EZH2 inhibitors could represent a novel therapeutic approach for managing the disease.

Sjögren's syndrome

Sjögren's syndrome (SS) is a systemic autoimmune disorder primarily characterized by lymphocytic infiltration of exocrine glands, leading to symptoms such as dry eyes and mouth (Zhao et al., 2024). Recent studies have revealed the involvement of EZH2 in the pathogenesis of SS. Increased development of T follicular helper (Tfh) cells, which are known to stimulate B cell activation and antibody production, has been linked to elevated EZH2 expression in $CD4^+$ T cells in patients with primary SS. EZH2 intensifies the autoimmune response by increasing the phosphorylation of STAT3, a crucial transcription factor in Tfh development. Notably, GSK126 increased Th1, Th2, and Th17 differentiation while decreasing Tfh differentiation but not Tregs (He et al., 2022). Inhibition of EZH2 using selective inhibitors, such as GSK343, has been shown to reduce Tfh differentiation, attenuate $CD4^+$ T cell activation, and alleviate glandular inflammation in mouse models of SS. Subsequent research has confirmed that blocking EZH2 activity not only reduces pro-inflammatory cytokine production but also rectifies the Th1/Th2 imbalance, which plays a critical role in SS progression (Zhu et al., 2022). These findings highlight the potential of EZH2 inhibitors to modulate immune cell functions and suppress inflammatory pathways, paving the way for novel treatments targeting epigenetic mechanisms in SS.

As mentioned above, through epigenetic changes, dysregulated EZH2 plays a crucial role in regulating T cell differentiation, especially in the maturation of Tregs and Th cell subsets (Th1, Th17). Besides, the regulation of autoimmune diseases by EZH2 also involves a range of miRNAs and lncRNAs, including tissue damage aggravated by preventing chondrocyte differentiation and secreting pro-inflammatory factors in OA, and joint inflammation and damage brought on by synovial fibrocyte proliferation in RA, etc. Lastly, by controlling the expression of different kinds of cytokines, EZH2 can engage in the differentiation of distinct immune cells, thus influencing the immunological homeostasis of the body (Fig. 2A).

Given its central role in regulating immune responses, targeting EZH2 with specific inhibitors offers a promising therapeutic approach for autoimmune diseases. EZH2 inhibitors, such as EPZ-6438 and DZNep, have demonstrated efficacy in preclinical models of RA, SLE, and OA, reducing inflammation and tissue damage (Table 1). However, the dual role of EZH2 in Tregs and immune cell regulation necessitates precise targeting strategies, possibly involving targeted delivery systems or combination therapies to maximize therapeutic benefits.

EZH2 in fibrotic diseases

Fibrosis is the extensive deposition of fibrous connective tissue, defined by the accumulation of collagen and other extracellular matrix (ECM) components. Fibrotic diseases can affect nearly every organ and tissue. Multiple retrospective studies have demonstrated that EZH2 promotes fibroblast activation and ECM deposition by silencing antifibrotic genes through H3K27me3-mediated epigenetic regulation. Fulfilling EZH2 inhibitors has shown potential to effectively reverse fibrotic markers.

Liver fibrosis

Liver fibrosis, characterized by the excessive accumulation of ECM, is primarily driven by the activation of hepatic stellate cells (HSCs). The activated HSCs transform to myofibroblasts and secrete extracellular matrix proteins, thus generating the fibrous scar (Horn and Tacke, 2024; Kisseleva and Brenner, 2021). KLF14 was found to transactivate peroxisome proliferator-activated receptor γ (PPARγ) promoter, and its decreased expression in activated HSCs was mediated by EZH2-regulated H3K27me3. Treatment with EZH2 inhibitor EPZ-6438 significantly alleviated thioacetamide (TAA)-induced liver fibrosis in rats, suggesting that EZH2/KLF14/PPARγ axis could serve as a promising therapeutic target for liver fibrosis (Du et al., 2021).

EZH2 has been shown to be significantly upregulated in a number of liver fibrosis models, such as Mdr2, bile duct ligation (BDL), and CCl mice (Chen et al., 2022; Jiang et al., 2021; Yuan et al., 2024). The EZH2 upregulation is correlated with the expression of H19 and other fibrotic markers (Li et al., 2023b). Administration of the EZH2 inhibitor 3-DZNeP shown substantial protective effects (Jiang et al., 2021). Both 3-DZNeP and GSK126 markedly inhibited the activation and proliferation of primary HSCs in TGF-β-treated HSCs *in vivo* (Li et al., 2023b). Moreover, it was discovered that administering active vitamin D (1,25-OH Vitamin D3), but not VD3, improved liver function and had anti-fibrotic effects. This is probably because it interacts with CYP2R1 (Zhang et al., 2023a). In terms of alleviating liver fibrosis, 1,25-OH Vitamin D3 and GSK126 worked synergistically. Studies also demonstrated that 1,25-OH Vitamin D3 promoted H3K27 methylation at the DKK1 promoter through the VDR/EZH2 pathway, thereby weakening the inhibitory signals in activated HSCs and reducing hepatocyte autophagy (Yang et al., 2017; Zhang et al., 2023a).

Renal fibrosis

Renal fibrosis contributes to chronic kidney disease (CKD) progression following acute kidney injury (AKI) and other renal insults. It is well established that TGF-β pathway drives the renal fibrogenic process (Jackson et al., 2024). EZH2 is upregulated in fibrotic kidneys and correlates with decreased renal function and increased fibrotic lesions. EZH2 promotes fibrosis through mechanisms like epithelial-mesenchymal transition (EMT), macrophage polarization, and regulation of PTEN/AKT and TGF-β pathways (Nastase et al., 2018; Zhao et al., 2021). Inhibiting EZH2, either genetically or pharmacologically, improves kidney function by suppressing EMT, reducing fibroblast activation, and regulating inflammatory responses. The infiltration and activation of macrophages also underlie the pathogenesis of renal fibrosis

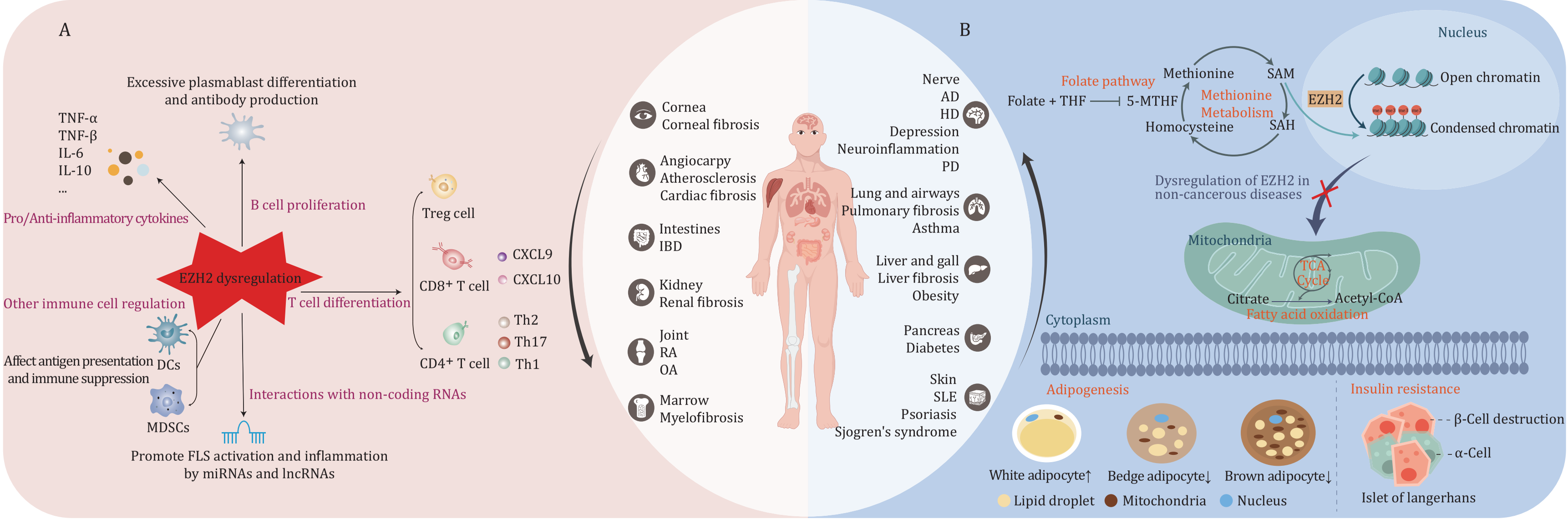

Figure 2. EZH2-mediated epigenetic control of immunity and metabolism in non-cancerous diseases. (A) EZH2 dysregulation also leads to immune responses involving cell differentiation and proliferation, cytokines secretion and so on. (B) EZH2-mediated epigenetic modifications influence metabolic processes such as fatty acid oxidation, adipogenesis and insulin resistance. Abnormal EZH2 expression contributes to a wide range of conditions, including fibrosis, autoimmune diseases and neuroinflammatory diseases. The complex interactions depicted in the figure may indicate thatEZH2 inhibitors could offer potential therapeutic interventions by disrupting these disease-driving pathways. This figure was adapted from online open materials, and redrawn by the authors using Adobe Illustrator.

Table 1. The applications of EZH2 inhibitors in non-cancerous diseases in preclinical researches.

Condition	Target cell	Drug
Liver fibrosis	Hepatic stellate cells	GSK126 (Zhang et al., 2023a), EPZ-6438 (Du et al., 2021), 3-DZNep (Jiang et al., 2021), UNC1999 (Lee et al., 2020), GSK503 (Martin-Mateos et al., 2019), EPZ005687 (Cai et al., 2018)
Pulmonary fibrosis	Individual fibroblasts and myofibroblasts	GSK126 (Le et al., 2021), EPZ-6438 (Wu et al., 2024b), 3-DZNep (Bao et al., 2021)
Renal fibrosis		GSK126 (Yan et al., 2024), 3-DZNep (Zhou et al., 2018), GSK343 (Davis et al., 2022)
Cardiac fibrosis		GSK126 (Aziz et al., 2023)
Systemic lupus erythematosus (SLE)	B cells, T cells and dendritic cells	GSK126 (Katsuyama et al., 2020), 3-DZNep (Rohraff et al., 2019), GSK343 (Yang et al., 2023), GSK503 (Zhen et al., 2020),
Rheumatoid arthritis (RA)	Synovial fibroblasts, B cells, T cells and dendritic cells	GSK126 (Xiao et al., 2020)
Inflammatory bowel disease (IBD)	Intestinal epithelial cells and myeloid-derived suppressor cells (MDSCs)	GSK126 (He et al., 2019), 3-DZNep (Sarmento et al., 2017), GSK343 (Zhou et al., 2021), EPZ011989 (Sardoiwala et al., 2022)
Psoriasis	Keratinocytes and T helper cells (e.g., Th17, Th1)	GSK126 (Zhang et al., 2020c), EPZ-6438 (Muller et al., 2020)
Sjögren's syndrome	B cells, T cells (e.g., CD4$^+$ T cells, CD8$^+$ T cells)	GSK126 (He et al., 2022), GSK343 (Zhu et al., 2022)
Alzheimer's disease (AD)	Neurons, microglia and astrocytes	
Depression		EPZ-6438 (Sun et al., 2024)
Parkinson's disease (PD)	Dopaminergic neurons	GSK126 (Cai et al., 2020), GSK343 (Mannino et al., 2023), EPZ-6438 (Alsharif et al., 2021), EPZ011989 (Sardoiwala et al., 2020)
Diabetes	Pancreatic β cells	GSK126 (Al-Hasani et al., 2022), EPZ-6438 (Al-Hasani et al., 2024)
Obesity	Adipocytes	GSK126 (Wu et al., 2018)
Atherosclerosis	Vascular smooth muscle cells (VSMCs) and macrophages	GSK126 (Wei et al., 2021)
Osteoarthritis (OA)	Chondrocytes	GSK126 (Suo et al., 2023), EPZ-6438 (Allas et al., 2020), UNC1999 (Lian et al., 2018), GSK343 (Du et al., 2020), EPZ005687 (Chen et al., 2016)
Asthma	Airway epithelial cells and T helper cells (e.g., Th2)	3-DZNep (Li et al., 2021b), GSK343 (Du et al., 2022)

(Jiang et al., 2019). EZH2 influences macrophage polarization to a profibrotic M2 phenotype, exacerbating renal injury and fibrosis. EZH2 inhibition not only prevents this transition but also promotes the expression of protective factors like PTEN, which counteract profibrotic signaling cascades (Zhou et al., 2016, 2018, 2023).

The therapeutic potential of EZH2 inhibitors in renal fibrosis is demonstrated by the fact that compounds like 3-DZNeP and GSK126 blocked key fibrotic processes in animal models of kidney injury. These inhibitors have been shown to reduce collagen deposition, improve renal function, and attenuate the activation of fibrosis-related signaling pathways (Yan et al., 2024; Zhou et al., 2016). Additionally, natural compounds like Salvianolic acid B exhibit anti-fibrotic properties by targeting EZH2, further confirming the importance of EZH2 as a therapeutic target. By inhibiting EZH2, these treatments restore balance in pathways like PTEN/AKT and TGF-β, reduce histone methylation at key fibrotic gene loci, and ultimately improve kidney outcomes in models of renal fibrosis, making EZH2 inhibition a promising strategy for CKD treatment (Lin et al., 2023).

Pulmonary fibrosis

Pulmonary fibrosis is a chronic lung disease characterized by interstitial pneumonia with ECM proteins and fibroblast foci, which influence gas exchange and breathlessness (Koudstaal et al., 2023). In idiopathic pulmonary fibrosis (IPF), EZH2 represses antifibrotic genes, such as TSC2 and COX-2, and facilitates fibroblasts-to-myofibroblast transition (FMT). EZH2 also enhances the expression of profibrotic markers like α-SMA and fibronectin. Studies have shown that inhibition of EZH2 reverses the epigenetic silencing of key antifibrotic genes, thereby offering a potential target for therapeutic intervention in pulmonary fibrosis. Moreover, inhibition of EZH2 by compounds such as DZNeP or specific small interfering RNAs has been shown to prevent fibroblast differentiation, reduce macrophage polarization, and block EMT, all of which are key contributors to fibrotic tissue formation (Li et al., 2023a; Wu et al., 2023; Zhang et al., 2022).

Cardiac fibrosis

In cardiac fibrosis, the cardiac interstitium is deposited with extracellular matrix proteins, which are secreted by activated fibroblasts and myofibroblasts (Frangogiannis, 2021). EZH2 has also been identified as a key epigenetic regulator in the setting of cardiac fibrosis, a pathological state marked by fibroblast activation and ECM deposition. Through H3K27me3, EZH2 silences key anti-fibrotic genes, facilitating the excessive EMT, which is essential for the synthesis of collagen and the advancement of fibrosis. Many cardiovascular diseases, including heart failure, myocardial infarction, and atrial fibrillation, are caused by this process, in which the heart tissue stiffens and cardiac function is compromised due to increased ECM deposition (Ibarrola et al., 2024; Lee and Moon, 2024; Song et al., 2019).

Recent studies have revealed that EZH2 mediates EMT by interacting with pathways such as the TGF-β/Smad signaling cascade (Song et al., 2019). Inhibition of EZH2 using selective inhibitors like GSK126 has been shown to significantly reduce the expression of fibrotic markers, such as collagen I, collagen III, TGF-β1, and α-SMA, thereby mitigating fibrosis and improving cardiac function (Aziz et al., 2023). Additionally, EZH2 interacts with lncRNAs, such as NEAT1 and MALAT1, which recruit EZH2 to pro-fibrotic gene promoters, further exacerbating fibrosis through enhanced signaling and ECM deposition (Ge et al., 2022). By downregulating fibrogenic pathways and reactivating anti-fibrotic genes, EZH2 inhibitors present a viable approach for managing conditions like heart failure and atrial fibrillation, providing new avenues for therapeutic intervention in cardiovascular disease.

EZH2 contributes significantly to fibrotic disorders by encouraging fibroblast activation and ECM deposition via epigenetic changes such as H3K27me3, which inhibit anti-fibrotic genes. In various organs, EZH2 enhances fibrosis via pathways such as TGF-β/Smad and PTEN/AKT, and through interactions with lncRNAs, leading to abnormal FMT and tissue stiffening (Fig. 2A). EZH2 inhibitors (e.g., EPZ-6438, 3-DZNeP, GSK126) have shown efficacy in preclinical models by reversing fibrotic markers, preventing fibroblast activation and improving organ function (Table 1).

However, the timing of EZH2 inhibitor administration is crucial in the treatment of fibrotic diseases. For liver and renal fibrosis, EZH2 inhibition might be most effective during the progressive stage of fibrosis to prevent ECM deposition and fibroblast activation. Nevertheless, in pulmonary and cardiac fibrosis, the ideal window may be during the early stages of FMT to prevent permanent tissue damage. Moreover, combination therapies, such as the use of EZH2 inhibitors with anti-fibrotic agents or vitamin D analogs, could enhance efficacy and broaden the therapeutic window by targeting multiple fibrotic pathways simultaneously.

EZH2 in metabolic diseases

Metabolic disorders, such as obesity and diabetes, are global health problems in the modern society. These diseases lead to multisystemic complications like cardiovascular disease, hyperglycemia, and many types of cancer. To date, EZH2 has been found to regulate adipocyte differentiation and β-cell regeneration, contributing to insulin resistance, whereas its inhibition helps reduce fat accumulation and mitigates oxidative stress, highlighting its potential as a therapeutic target (Wang, 2022).

Obesity

Obesity is featured by excessive accumulation of adiposity and is strongly linked to an increased risk of metabolic disorders and cancer (Reinisch et al., 2024). Recent studies have showed that the intrinsic risk of obesity arises not only through genetic variants but also through epigenetic predisposition (Hinte et al., 2024), and the regulation of brown and beige adipose differentiation is a promising therapeutic target for obesity (Liu et al., 2017). Accumulating data reveal that EZH2 influences obesity and insulin resistance by regulating adipocyte differentiation and metabolic functions (Wang, 2022). EZH2 knockout mice exhibit reduced white fat mass, smaller adipocytes, and increased beige and brown fat, making them more resistant to diet-induced obesity and insulin resistance (Wu et al., 2021b). This effect is partly due to the enhanced fatty acid β-oxidation and the downregulation of adipogenic markers like PPARγ and adiponectin (Shoucri et al., 2017; Yiew et al., 2019). Furthermore, EZH2 promotes white adipocyte differentiation via its methylation activity, which can be inhibited by the EZH2 inhibitor GSK126, significantly reducing lipid accumulation and downregulating pro-adipogenic factors (Wu et al., 2018). These findings suggest that inhibiting EZH2 could be a therapeutic approach for combating obesity and improving metabolic health.

In addition to its role in adipogenesis, EZH2 involves in several molecular pathways that influence the fate of mesenchymal stem cells (MSCs) (Zhu et al., 2016b). EZH2 represses the expression of HOPX, a key factor that inhibits MSC differentiation into adipocytes while promoting osteogenesis. This regulation underscores EZH2's ability to steer MSC differentiation toward the adipogenic pathway. Moreover, the circular RNA SAMD4A, which is increased in obese individuals, stabilizes EZH2 via the miR-138-5p/EZH2 pathway to promote adipogenesis (Liu et al., 2020). The modulation of EZH2 activity not only influences adipocyte differentiation but also preserves MSC multipotency, which is essential for maintaining a balance between adipogenic and osteogenic lineage commitment. Thus, targeting EZH2 could offer a dual approach to obesity treatment by reducing fat accumulation while preserving stem cell pluripotency.

Diabetes

Diabetes arises from the destruction of functional insulin-producing β-cells in the islets of Langerhans in the pancreas, leading to impaired regulation of blood glucose levels and the onset of insulin-dependent diabetes (Brusko et al., 2021). The H3K27me3 modification function of EZH2 contributes to impaired β-cell regeneration and promotes tissue fibrosis. EZH2 inhibitors like GSK126 and EPZ-6438 have shown potential in stimulating the conversion of pancreatic ductal progenitor cells into β-like cells, which enhances insulin production and secretion, crucial for managing type 1 diabetes (T1D) (Al-Hasani et al., 2024). Additionally, these inhibitors can mitigate diabetic complications by reducing repressive H3K27me3 marks, which are implicated in conditions like diabetic retinopathy and nephropathy (Naina Marikar et al., 2023).

The role of EZH2 extends beyond β-cell regeneration to impact diabetic complications through mechanisms involving ferroptosis, inflammation, and fibrosis. For instance, its interaction with ferroptosis-related pathways has been linked to diabetic nephropathy and testicular damage, highlighting its potential as a therapeutic target (Wang et al., 2024a; Yan et al., 2024). In cardiovascular and renal complications of diabetes, targeting EZH2 has demonstrated the ability to counteract oxidative stress, inflammation, and fibrosis by modulating key signaling pathways such as AMPK/EZH2/PPAR-γ (Li et al., 2024b; Xiao et al., 2024).

Atherosclerosis

Atherogenesis is marked by the accumulation of excessive lipids in the intimal layer of arterial beds, forming plaques. The rupture of these plaques may trigger myocardial infarction and stroke (Lin et al., 2024). In atherosclerosis, EZH2 involves in inflammation, endothelial dysfunction, and vascular smooth muscle cell (VSMC) proliferation—key contributors to plaque formation and vascular stiffening in atherosclerosis. Elevated EZH2 expression drives endothelial-to-mesenchymal transition (EndMT) and promotes fibrogenic pathways, such as collagen synthesis, through the repression of microRNAs like miR-29c, leading to ECM deposition and arterial obstruction (Fledderus et al., 2024).

Pharmacological inhibitors, such as GSK126, have been demonstrated to mitigate VSMC proliferation and ECM deposition, thereby alleviating vascular remodeling and plaque formation (Wei et al., 2021). Furthermore, EZH2 modulates miRNA pathways, particularly its interaction with miR-214-3p, which downregulates EZH2 and reduces collagen synthesis and fibrosis, offering an additional mechanism for limiting atherosclerotic damage (Zhu et al., 2016a). Additionally, EZH2's suppression of anti-inflammatory genes exacerbates endothelial dysfunction and inflammation, processes that are crucial to the development of atherosclerotic plaques (Meng et al., 2020; Yin et al., 2024). Targeting EZH2 with specific inhibitors has been shown to reduce vascular stiffness, inflammation, and plaque burden.

In aforementioned metabolic diseases, EZH2 influences adipogenesis and insulin production. It promotes the accumulation of white fat while inhibiting beige and brown fat formation, contributing to obesity and insulin resistance. EZH2 also impacts β-cell regeneration, tissue fibrosis, and diabetic complications (Fig. 2B). Inhibition of EZH2 has shown promise in reducing fat accumulation, enhancing insulin production, and alleviating complications related to oxidative stress, inflammation, and fibrosis (Table 1).

Given the metabolic and immunological interplay in diseases like diabetes and obesity, the optimal therapeutic window for EZH2 inhibitors likely occurs during the early to mid-stages of disease progression (Fig. 3). Early intervention could prevent excessive fat accumulation, preserve β-cell function, and reduce the development of diabetic complications by modulating both metabolic and inflammatory pathways. The dual role of EZH2 in regulating both metabolism and immune responses underscores its potential as a therapeutic target, where combining EZH2 inhibitors with other metabolic or anti-inflammatory agents could improve therapeutic outcomes and provide broader disease control.

EZH2 in neurological disorders

Neuroinflammation, neuronal survival, and cognitive functions are key markers of neurological disorders. Overexpression of EZH2 promotes the above pathological progression in conditions like AD, PD, or depression. Through pharmacological agents or targeted delivery systems, EZH2 inhibitors have shown promise in reducing neuroinflammation, enhancing neuronal resilience, and rebalancing gene expression linked to neuroprotection.

Alzheimer's disease

Alzheimer's disease (AD) is a progressive and debilitating neurological disorder. Histopathologically, AD is defined as the profusion of Aβ plaques and neurofibrillary (Tau) tangles in the brain, which is the main cause of dementia (Jucker and Walker, 2023; Scheltens et al., 2021). In AD, EZH2 has been found to affect neuronal function and neuroinflammation through its interactions with biomarkers associated with AD, such as the lncRNA XIST, which contributes to neuroinflammation and Amyloid-β (Aβ) accumulation by epigenetically repressing the Aβ-degrading enzyme neprilysin (NEP). This repression

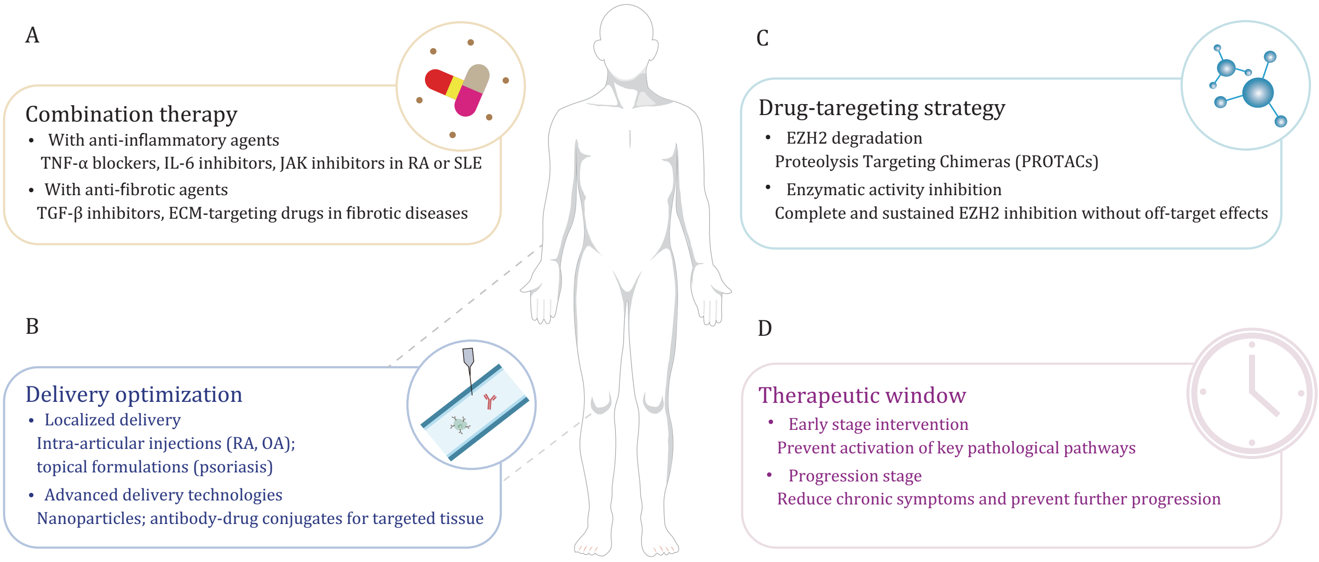

Figure 3. Future outlook for the CDE3 model: combination, delivery, and EZH2 targeting strategy. The CDE3 model presents integrating combination therapy, delivery strategies, EZH2 targeting degradation, EZH2 Enzymatic inhibition and Early intervention for improved treatment strategies: (A) Combination therapies with anti-autoimmune and anti-fibrotic agents are proposed. (B) Delivery strategies focus on localized methods and advanced technologies for targeted efficacy. (C) Drug optimization against EZH2, achieving precise inhibition via EZH2 direct degradation and sustained enzymatic inhibition while minimizing off-target effects. (D) Therapeutic window emphasizes early intervention to prevent disease progression and mitigate chronic damage. The CDE3 model provides a comprehensive approach to optimizing future therapies in autoimmune and fibrotic diseases. This figure was adapted from online open materials, and redrawn by the authors using Adobe Illustrator.

leads to the exacerbation of neurodegenerative processes in AD (Yan et al., 2022).

Inhibitors of EZH2 have shown potential in preclinical models by modulating pathways involved in neuroprotection and reducing neuronal apoptosis (Table 1). For instance, targeting the STAT3/EZH2 axis has been found to alleviate neuronal apoptosis by regulating astrocyte activation and neurotrophic factor secretion (Zhou and Xu, 2024). Additionally, the use of Proteolysis Targeting Chimeras (PROTACs) to degrade EZH2 specifically offers a novel approach to tackle AD by selectively targeting and removing the protein involved in pathological processes (Scheepstra et al., 2019). Overall, the development of EZH2 inhibitors and degraders represents a significant advancement in the search for effective therapies for AD.

Parkinson's disease

Parkinson's disease (PD), a fast-growing neurodegenerative condition, is characterized by the deposition of misfolded alpha-synuclein (α-Syn) into neuropathological inclusions in neurons (Bloem et al., 2021; Carceles-Cordon et al., 2023). PD is a chronic neurodegenerative infirmity marked by the degeneration of dopaminergic neurons, though the exact causes remain unclear. Epigenetic regulation is a promising mechanism to explore PD regulation, and EZH2 has been revealed linked to several pathogenic mechanisms in PD, including neuroinflammation, oxidative stress and the aggregation of α-Syn, a hallmark of the disease. EZH2 contributes to disease progression by interacting with lncRNAs like SOX21-AS1 and MALAT1, which modulate inflammatory responses and neuronal damage through epigenetic silencing of protective genes such as SOCS3 and NRF2 (Cai et al., 2020; Feng et al., 2024).

The application of EZH2 inhibitors in PD indicates encouraging prospects for the creation of new treatments. Methyltransferase activity inhibitor GSK-343 have demonstrated neuroprotective effects in animal models by mitigating neuroinflammation and reducing dopaminergic neuronal loss (Mannino et al., 2023) (Table 1). Additionally, strategies involving nanoparticles to deliver EZH2 inhibitors or activators of associated pathways, like FTY720, have been explored to enhance bioavailability and therapeutic efficacy (Sardoiwala et al., 2021). In order to enhance neuronal survival and function, these strategies seek to alter EZH2 activity, underscoring the significance of tailored epigenetic treatments in treating the intricate pathophysiology of PD.

Depression

Depression is a psychiatric disorder characterized by persistently depressed mood, disturbed attention and memory, tiredness, and lack of energy, which impair the patients' well-being and quality of life (Dillon and Pizzagalli, 2018). Recent work suggests that depression is caused by abnormalities of functional connectivity in different brain networks (Chai et al., 2023). EZH2 epigenetically silences genes involved in neuronal plasticity, inflammation, and cognitive function—central processes linked to depressive-like behaviors (Li et al., 2024a; Sun et al., 2024). Chronic stress and neuroinflammation, key contributors to depression, have been shown to increase EZH2 expression, particularly in critical brain regions such as the hippocampus and prefrontal cortex, thereby exacerbating depressive symptoms (Palomer et al., 2016; Sun et al., 2024).

A key factor in the pathophysiology of neurodegenerative illnesses including PD and AD is microglia overaction. Evidence showed that EZH2 modulates microglial activation, which in turn triggers the release of pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α. These cytokines further intensify neuroinflammation and lead to the progression of depression (Wang et al., 2020a; Wu et al., 2021a). EZH2 also downregulates miRNAs, including miR-29b-3p and miR-15a-5p, resulting in increased expression of inflammatory mediators such as CXCL10 and driving neuroinflammatory processes linked to depressive-like behaviors (Huang et al., 2022). Inhibition of EZH2, either through pharmacological agents like EPZ-6438 or genetic knockdown, has been shown to alleviate depressive symptoms by reducing neuroinflammation, enhancing neuronal survival, and shifting microglial polarization to an anti-inflammatory state (Wang et al., 2020a) (Table 1).

Additionally, EZH2 interacts with other histone-modifying enzymes such as KDM6 (JMJD3) to regulate gene expression involved in mood regulation (Palomer et al., 2016; Wu et al., 2021a). In the context of ketamine's sustained anti-depressant effects, EZH2 is involved in promoting long-lasting behavioral changes by increasing H3K27me3 levels in key brain regions like the anterior paraventricular nucleus of the thalamus (aPVT). This highlights EZH2's broader role in epigenetic regulation, influencing not only inflammation but also neuronal plasticity, making it a promising target for novel therapeutic interventions in depression (Kawatake-Kuno et al., 2024).

Other non-cancerous diseases

Osteoarthritis

Around the world, osteoarthritis (OA) is the most common rheumatic disease. OA impacts the whole joint and is characterized by cartilage breakdown, joint dysfunction, pain, and stiffness. The pathophysiology of OA is associated with a number of variables, including age, gender, weight, genetics, behavior and environment (Glyn-Jones et al., 2015; Martel-Pelletier et al., 2016). The progression of the illness is also significantly influenced by epigenetic control (Grandi and Bhutani, 2020). During the onset of OA, the chondrocytes are activated by IL1β and TNFa, and secrete proteases to degrade ECM, leading to cartilage erosion (Rai, 2024). Chondrocytes in healthy cartilage remain stable, non-proliferative, whereas in OA, they multiply and undergo aberrant differentiation. LncRNAs and miRNAs are involved in this process by binding to EZH2. For example, lncRNA CIR binds to EZH2 to downregulate ATOH8, inhibiting chondrogenic differentiation, while lncRNA MEG3 interacts with EZH2 to block the differentiation of mesenchymal stem cells into chondrocytes by inhibiting TRIB2 (Liu et al., 2021b). Additionally, the overexpression of Syndecan 1, which contributes to cartilage degradation, is associated with reduced miR-138 levels due to EZH2-mediated histone methylation of the miR-138 promoter (Wang et al., 2021).

EZH2 also promotes cartilage damage in OA and is regulated by miR-17-5p and miR-19b-3p, which leads to chondrocyte apoptosis and ECM degradation (Li et al., 2020b). Inhibition of EZH2 can cause spontaneous articular cartilage damage by suppressing Atg12 signaling, which lowers chondrocyte survival and cartilage formation (Lian et al., 2018). In OA mice models, intra-articular injection of EZH2 inhibitors, such as EPZ-6438 and DZNep, slows cartilage deterioration and improves joint function. By inhibiting the expression of collagen X, Hedgehog, MMP-13, ADAMT-4, and ADAMT-5, the inflammation and cartilage hypertrophy was reduced (Allas et al., 2020; Aury-Landas et al., 2017) (Table 1). Notably, EZH2 gene deficiency has been linked to increased MMP-13 and collagen X expression. EZH2 deletion also downregulates wound healing-related genes like TNFSF13B and leads to cartilage hypertrophy. In addition, chondrocyte maturation and endochondral ossification are encouraged by EZH2 depletion (Du et al., 2020). Overall, while EZH2 may support cartilage remodeling by regulating cell proliferation and differentiation, its overactivity in OA could promote cartilage degradation and inflammation. Future research is needed to explore the specific roles of EZH2 under different conditions and identify its potential as a target for OA treatment.

Asthma

Asthma, a prevalent chronic airway illness marked by immunological dysregulation that results in an excess of type 2 cytokines such as IL-4, IL-5, and IL-13, is an urgent public health concern (Gans and Gavrilova, 2020). In response to inhaled allergen, IL-2 and IL-10 cause the formation of TH2 cells in the lung and drive allergic asthma (He et al., 2024). Recent studies have shown that EZH2 contributes to asthma by regulating the differentiation of $CD4^+$ T helper cells and invariant NK T cells, both of which are pivotal in the development of allergic airway inflammation. EZH2 controls the balance between Th1 and Th2 cells by influencing the production of cytokines such as IL-4 and IL-13, which exacerbate airway hyperreactivity and mucus overproduction (Tumes et al., 2013). Additionally, EZH2 inhibitors, such as DZNep, or focusing on the EZH2/NF-κB pathway, might lessen inflammation and alleviate asthma symptoms in murine models (Li et al., 2021b) (Table 1).

Furthermore, EZH2 has been found to suppress the expression of miR-34b by inhibiting the tumor suppressor gene FOXO3 in bronchial epithelial cells, promoting asthma progression through the dysregulation of inflammatory factors (Liu et al., 2021a). Overall, these findings highlight EZH2 as a potential therapeutic target in asthma, with ongoing research focusing on the development of EZH2 inhibitors to modulate immune responses and reduce airway inflammation.

Strategy of drug delivery, timing, and combination approach

As mentioned above, the development of EZH2 inhibitors, originally aimed at cancer treatment, has shown promising potential in treating non-cancerous diseases as well. However, challenges remain in areas such as combination therapy, drug delivery strategies, and therapeutic window. To optimize the therapeutic application, we propose the CDE3 model, which integrates combination therapy, delivery strategies, EZH2 targeting degradation, EZH2 enzymatic inhibition, and early intervention (Fig. 3). The potential of combination therapy is an important consideration for improving the efficacy of EZH2 inhibitors. For autoimmune diseases like SLE or RA, combining EZH2 inhibitors with anti-inflammatory agents, such as TNF-α blockers, IL-6 inhibitors, or JAK inhibitors, could enhance disease control by targeting multiple inflammatory pathways simultaneously. This strategy would not only improve the management of inflammatory symptoms but also help preserve overall immune function, mitigating the risk of immunosuppression often associated with EZH2 inhibition (Fig. 3A). Similarly, in fibrotic diseases, the combination of EZH2 inhibitors with anti-fibrotic agents, such as TGF-β inhibitors, could target multiple fibrogenic pathways, reducing fibroblast activation and ECM deposition. Such an approach could prevent further fibrosis progression, especially in early to mid-stage fibrotic conditions, while also offering therapeutic benefits in the later stages by mitigating chronic symptoms (Fig. 3A).

Systemic administration can disrupt immune homeostasis and tissue function in non-cancerous conditions, leading to off-target effects, immune dysregulation, or impaired tissue repair (Dinarello, 2010; Moslehi et al., 2018; Soehnlein et al., 2017; Zhang et al., 2023c). To overcome these issues, localized delivery systems are emerging as a key focus. In diseases like RA and OA, intra-articular injections could directly target synovial inflammation while minimizing systemic exposure (Bustamante et al., 2018; Xu et al., 2024; Zhou et al., 2024). Similarly, topical formulations for conditions like psoriasis can address keratinocyte proliferation and inflammation with fewer side effects (Jain et al., 2016; Wang et al., 2024b). Advanced delivery methods, including nanoparticle-based systems and antibody-drug conjugates, may offer precision targeting of EZH2 in affected tissues, enhancing therapeutic efficacy and reducing risks to healthy tissues (Fig. 3B).

In addition to inhibitors targeting the enzymatic activity of EZH2, developing strategies for the direct degradation of the EZH2 protein itself is another critical approach worth considering. One promising method is the use of proteolysis targeting chimeras (PROTACs), which harness the ubiquitin-proteasome system to selectively degrade EZH2 in disease lesions where it is highly expressed (Fig. 3C) (Bekes et al., 2022). This approach offers several potential advantages, including the ability to achieve more complete and sustained EZH2 inhibition compared to traditional small-molecule inhibitors, as well as reducing potential off-target effects associated with enzyme inhibition alone (Scheepstra et al., 2019). Overall, further research is required to pinpoint the exact pathways by which EZH2 advances non-cancerous conditions. Such as which strategy may weigh out or trump the other between enzymatic activity inhibition and degrading the protein itself.

Due to its dual role in regulating immune function and metabolic reprogramming, timing of intervention plays a crucial role in maximizing the efficacy of EZH2 inhibitors. Early-stage treatment—before irreversible damage—provides the opportunity to prevent long-term tissue degradation, preserve organ function, and halt disease progression (Fig. 3D) (Brudno and Kochenderfer, 2016). For late-stage interventions, the goal may shift towards reducing chronic symptoms, stabilizing the condition, and preventing further complications rather than reversing the disease entirely (Fig. 3D).

Overall, while the role of EZH2 in cancer has been thoroughly explored, its participation in non-cancerous diseases is an emerging and fascinating field with a lot of therapeutic promise. The CDE3 model provides a structured approach to improving efficacy and minimizing off-target effects in EZH2-related non-cancer therapies. Further investigation into the various roles that EZH2 plays in various illnesses will lead to novel therapeutic approaches and the possibility of better control of a broad spectrum of ailments.

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Author contributions

All authors participated in the design and discussion of manuscript conception and outline, contributed to editing of the draft manuscript. All authors approved the final version of the manuscript.

Conflict of interest

All the authors of this paper declare that they have no conflicts of interest.

Consent to participate

The authors declare their agreement to participate.

Consent for publication

The authors declare their agreement to publish.

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