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Dual-specific phosphatases-8: a new target for clinical disease intervention

Tingping Cao[1,2], Quanling Zhou[1,2], Fujun Li[1,2], Mingyue Wang[1,2], Ming Zhang[2], Xiaohui Li[2], Hailong Zhao[1] and Ya Zhou[1,2,3*]

Abstract
Dual-specific phosphatase-8 (DUSP8), identified as the first gene in a genome-wide association study (GWAS), is implicated in cellular oxidative stress, proliferation, apoptosis, and drug resistance through its negative regulation of the dephosphorylation activities of JNK, ERK, and p38 within the MAPK pathway. Recent studies have shown that DUSP8 plays a pivotal role in the progression of several human diseases, notably colorectal cancer, diabetic kidney disease, and breast cancer. This suggests that DUSP8 may represent a novel target for clinical intervention in these diseases. This review first introduces the biological structure and function of DUSP8, with a focus on its relationship with a series of diseases and the regulatory mechanisms involved. Furthermore, we concentrate on unresolved scientific questions in the current research, aiming to establish a new theoretical foundation for the diagnosis and treatment of related diseases.

Keywords DUSP8, MAPK, Colorectal cancer, Diabetic kidney disease, Regulatory mechanism

Introduction

Protein phosphorylation is crucial in eukaryotes implicating a multitude of human diseases. Specifically, the reversible phosphorylation of tyrosine in proteins is pivotal for regulating a myriad of biological processes in eukaryotes. It is integral to the development of various diseases by modulating cell proliferation, differentiation, energy metabolism, gene transcription, synaptic transmission, and insulin sensitivity. The process of protein phosphorylation is co-regulated by protein tyrosine kinases and protein tyrosine phosphatases, which, when expressed or functioning abnormally, can lead to serious human diseases such as cancer, diabetes, and cardiovascular diseases [1–3]. Based on their structural and substrate specificities, protein phosphatases are classified into serine/threonine phosphatases (Ser/Thr phosphatases), tyrosine phosphatases (Tyr phosphatases), and dual-specificity phosphatases (DUSPs). As a significant member of the protein tyrosine phosphatase (PTP) family, DUSPs play a crucial role in dephosphorylation [4, 5].

DUSPs can dephosphorylate both phosphoserine/threonine and phosphotyrosine residues on mitogen-activated protein kinases (MAPK), thereby inactivating their target kinases. Consequently, they are also referred to as MAPK phosphatases (MKPs). MKPs are involved in regulating cell proliferation and differentiation by negatively modulating the activities of c-Jun N-terminal kinase (JNK), Extracellular regulated kinase (ERK), and p38 within the MAPK pathway [6, 7]. They are intimately associated with the development of various human diseases, including cancer, inflammation, diabetes, and

*Correspondence:
Ya Zhou
zhouyazmc@163.com
[1]Department of Pathophysiology, Zunyi Medical University, Zunyi, Guizhou 563000, China
[2]Department of Physics, Zunyi Medical University, Zunyi, Guizhou 563000, China
[3]Key Laboratory of Cancer Prevention and Treatment of Guizhou Province, Zunyi, Guizhou 563000, China

neurodegenerative disorders [8–10]. For instance, Sun et al. [11] discovered that resveratrol (RES) enhances the expression of miR-512-3p. Overexpression of miR-512-3p targets DUSP1 and suppresses its expression, thereby inhibiting proliferation and inducing apoptosis of choroidal melanoma cells. Cho et al. [12] reported that overexpression of DUSP12 targets p38 and JNK for inhibition, significantly reducing the secretion of pro-inflammatory cytokine interleukin-6 (IL-6) and chemokines tumor necrosis factor-alpha (TNF-α), thus modulating the immune response of macrophages to microbial infections. He et al. [13] found that overexpression of miR-544 targets and suppresses DUSP13 expression, thereby inhibiting glioma cell proliferation, arresting the cell cycle, and promoting apoptosis. Asharaf et al. [14] found that elevated expression of DUSP7 was closely linked to poor prognosis and chemotherapy resistance in gastric cancer. Collectively, these findings suggest that DUSPs may be potential targets for therapeutic intervention in various diseases.

Meanwhile, several studies have demonstrated that dual-specificity phosphatase inhibitors (DUSPi) significantly inhibit cell proliferation and induce apoptosis. For instance, Sanders et al. [15] observed that DUSP1 is overexpressed in high-grade serous ovarian cancer (HGSOC) and is strongly correlated with poorer progression-free survival (PFS) and overall survival (OS) in patients with newly diagnosed HGSOC. Furthermore, they discovered that DUSPi inhibits cell proliferation and promotes apoptosis in a newly acquired HGSOC-resistant cell model. In a patient-derived xenograft HGSOC model, DUSPi also markedly suppressed tumor progression, suggesting that targeting DUSPs could be an effective therapeutic strategy for HGSOC. These findings suggest that research into DUSPs and DUSPi may offer promising new avenues for the treatment of a range of human diseases. Consequently, in-depth investigation of DUSPs and the development of novel targeted therapies are emerging as focal points in contemporary research.

Studies have revealed that Dual-specific phosphatase-8(DUSP8), a key member of the DUSPs family, exhibits significantly aberrant expression across a range of human diseases. It plays a crucial role in regulating cellular processes such as proliferation, metastasis, invasion, apoptosis, and drug resistance by negatively modulating the activation of the JNK, ERK, and p38 signaling pathways within the MAPK pathway. For example, DUSP8 can alleviate the inflammatory response in acute lung injury(ALI)by inhibiting the JNK/p38 MAPK signaling pathway [16]. And in patients with lung adenocarcinoma (LUAD), DUSP8 is silenced by miR-147b, leading to reduced expression levels, which is associated with poorer overall survival [17]. Additionally, study has found that the expression level of DUSP8 in breast cancer(BC) tissues is significantly higher than that in non-tumor tissues. Inhibiting DUSP8 expression in trastuzumab-resistant cells can suppress cell migration and proliferation, and reduce drug resistance by activating the MAPK signaling pathway in these cells [18]. And research indicates that DUSP8 expression is reduced in the kidney tissues of patients with diabetic nephropathy and in Diabetic kidney disease (DKD) mice, as well as in podocytes induced by high glucose. Moreover, DUSP8 can regulate the occurrence of high glucose-induced podocyte injury and mitochondrial dysfunction, thereby playing a role in the development of DKD [19]. The results of the above studies indicate that DUSP8 plays a significant role in various diseases, including ALI, LUAD, BC and DKD. This suggests that therapeutic strategies targeting DUSP8 may have applications in a range of clinical conditions, providing patients with a broader range of treatment options. Moreover, the expression level of DUSP8 is closely related to the progression and prognosis of multiple diseases, indicating that DUSP8 can also serve as a biomarker for assessing disease status, treatment effectiveness, and drug resistance. By detecting the expression levels of DUSP8, doctors can better understand the patient's disease condition, provide a basis for individualized treatment, optimize treatment plans, and improve the success rate of treatment.

In summary, DUSP8 as a therapeutic target has broad application prospects and significant clinical importance in the treatment of various diseases, may offering new hope for patients.

The structure and functions of DUSP8

Molecular structure

DUSP8 is a member of the DUSPs family, known for its ability to dephosphorylate both serine/threonine and tyrosine residues. The human *DUSP8* gene is mapped to the short arm of chromosome 11 at the 11p15.5 locus, and an intronless pseudogene is present on the long arm of chromosome 10 at 10q11.2 [20]. The gene spans a total length of 18,798 base pairs. The mouse *DUSP8* gene, also known as M3/6, is situated at the distal end of chromosome 7. Its sequence has homologs in the corresponding regions of human chromosomes, specifically at 11p and 10q11.2 and 10q22 [21]. Interestingly, a poxvirus H1 phosphatase gene (HVH-5), was identified as a DUSP8 homolog, contributing to the nomenclature of DUSP8. A sequence with 88% similarity to the HVH-5 transcript has been detected in human peripheral tissues and 11 BC cell lines. This sequence, believed to be a potential processed pseudogene due to the absence of introns, has been localized to chromosome 10q22.2 [22](Fig. 1A). Furthermore, the human DUSP8 protein is composed of 625 amino acids and has a molecular weight of approximately 65,827 Da. Its molecular structure is composed of several key

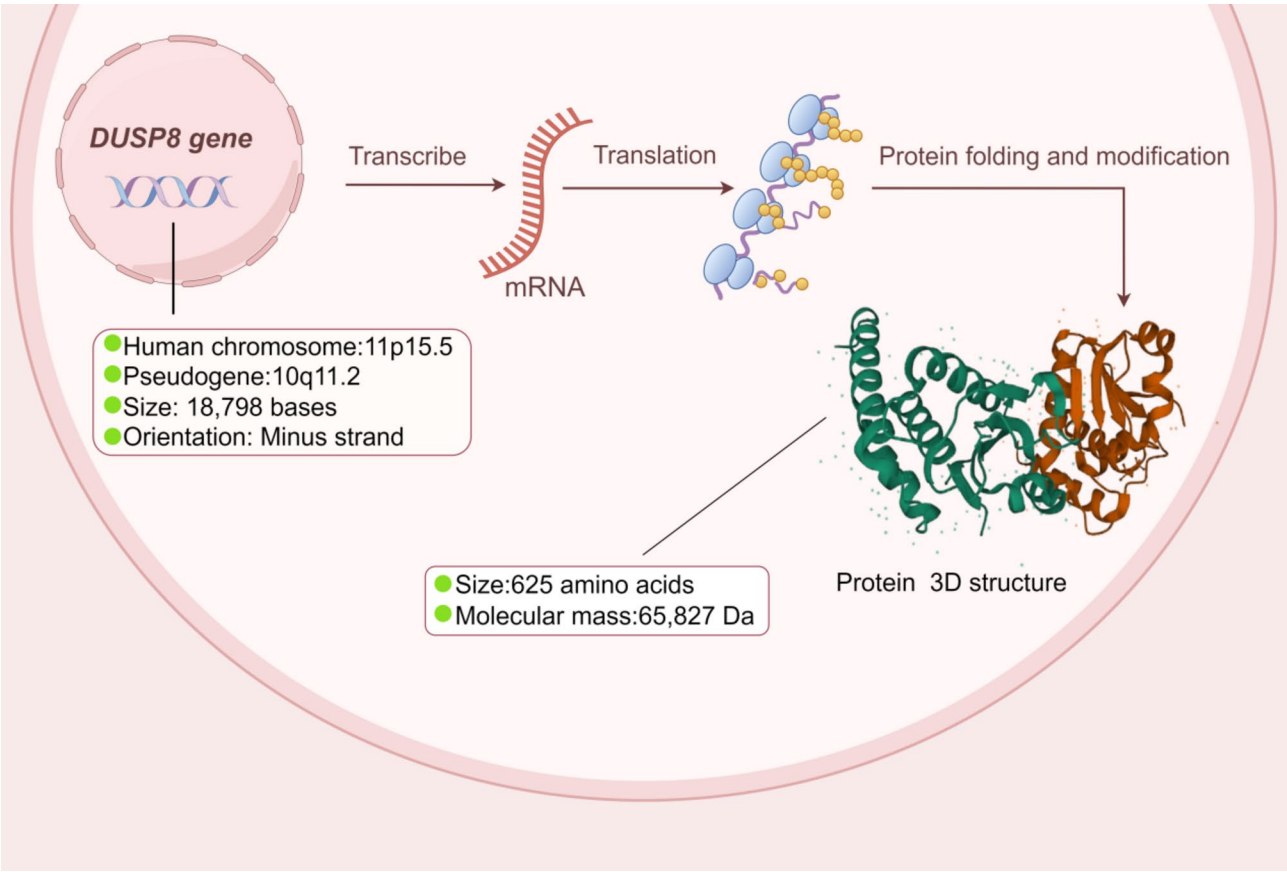

Fig. 1 A The structure of DUSP8. (By Figdraw.)

functional domains, which are crucial for its function in dephosphorylation and regulation of signaling pathways. The protein chain N23-138 C and N162-430 C form the Rhodanese domain, which contains the kinase interaction motif (KIM: KLVKRRLQQG, N5362C). It also encodes the tyrosine-protein phosphatase domain, including the active site (AS: HCLAGISR, N245-252 C). Additionally, it has a Pro-rich region (N310-550 C) at the C-terminal region. The Rhodanese domain primarily interacts with the CD docking domain of MAPK through its D-site on the surface. This interaction forms the basis of DUSP8's efficient dephosphorylation of MAPK. The Tyrosine-protein phosphatase domain contains the catalytic site (Cys-246, which is replaced by Ser-246 in PDB database.) and its surrounding key residues (such as His-245, Leu-247, Ala-248, Gly-249, Ile-250, Ser-251 etc.), which together form a "pocket-like" structure. This pocket structure specifically recognizes and binds to the T-X-Y activation loop of the substrate, allowing Cys-246 to dephosphorylate the phosphorylated T and Y residues, thereby regulating the activity of MAPK. This enables DUSP8 to achieve specific binding and regulation through dephosphorylation of MAPK [7](Fig. 1B). It is primarily localized to the cytoplasm and is predominantly expressed in adult brain, heart, and skeletal muscle. Its expression can be induced by factors such as nerve growth factor and insulin [23].

Biological functions

DUSP8, a dual-specificity phosphatase, possesses phosphatase activity that is crucial for the regulation of its substrates. It inactivates target kinases by negatively regulating MAPK activity, specifically dephosphorylating phosphoserine/threonine and phosphotyrosine residues. This action leads to negative regulation of JNK, ERK, and p38 within the MAPK family, which are integral to cellular processes such as oxidative stress, proliferation, and differentiation. For instance, research indicates that the expression of DUSP8 is upregulated in ureteric tip cells, and reduced p38MAPK phosphorylation is observed in integrin-linked kinase (ILK)-deficient renal tissues. The overexpression of DUSP8 reduces ureteric branching and inhibits p38MAPK activation, suggesting that ILK may suppress renal branching morphogenesis via the DUSP8-p38MAPK pathway [24]. Furthermore, DUSP8 is highly expressed in limbic regions, including the hippocampus. Baumann et al. [25] reported that DUSP8 knockout (DUSP8-KO) mice exhibited reduced hippocampal

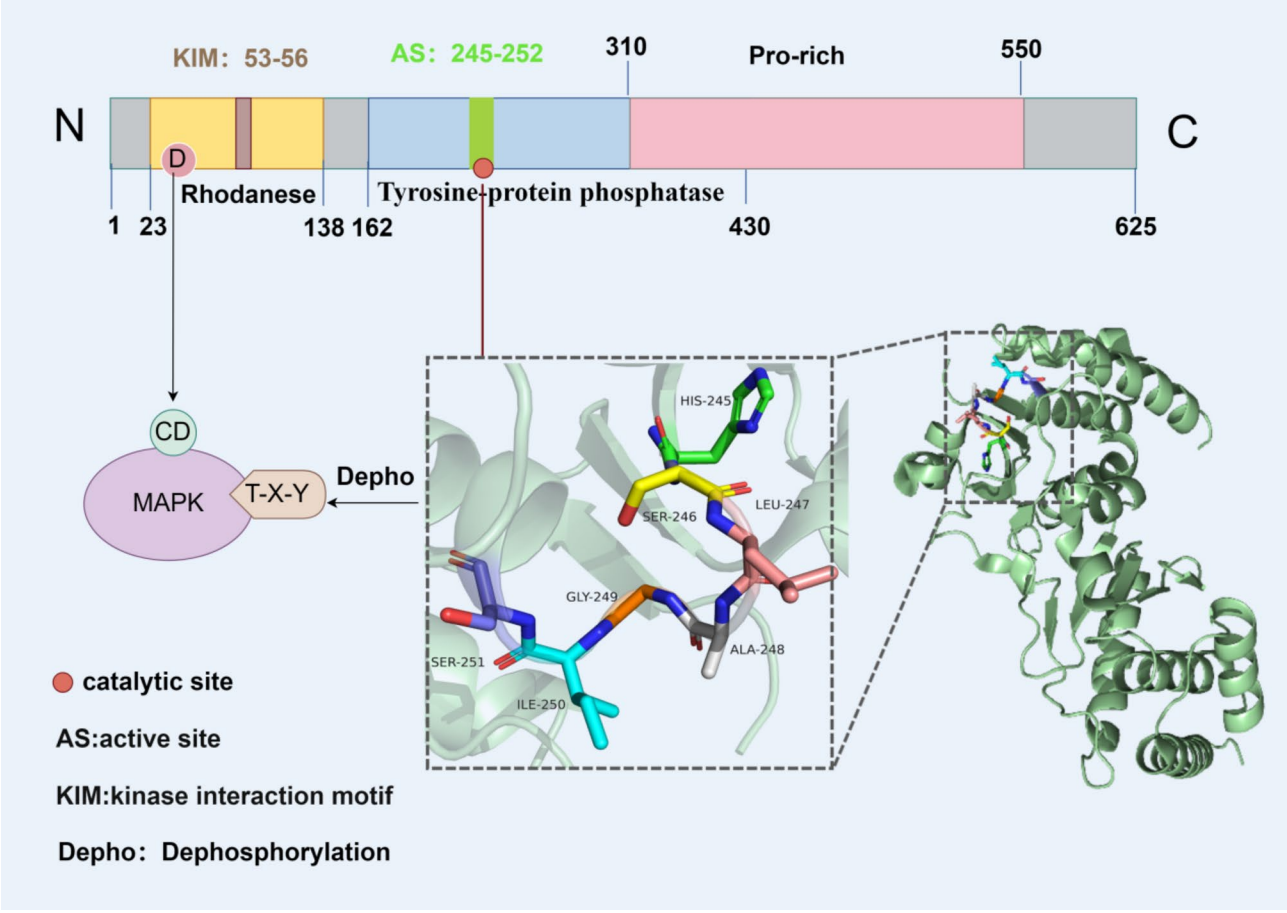

Fig. 1B Schematic diagram of DUSP8 protein structural domains. (By Figdraw.) Note: T and Y represent phosphorylated threonine and tyrosine residues, respectively, while X is any amino acid

volume and behavioral changes, such as mildly impaired spatial learning, increased motor activity, and heightened anxiety. In vitro studies have shown higher levels of ERK phosphorylation in the hippocampus of KO mice. Similarly, human hippocampi with the DUSP8 allele variant SNP rs2334499:C > T have been found to have reduced hippocampal volume, indicating that DUSP8 may influence hippocampal size and behavior in both humans and mice. Moreover, aberrant expression of DUSP8 is closely associated with the development of various clinical diseases (Table 1). What is more, It serves as the direct target molecule of some miRNAs, which are implicated in the pathogenesis of several conditions. For instance, in colorectal cancer (CRC), downregulation of DUSP8 expression significantly diminishes the inhibitory effect of Antisense Oligonucleotides (ASOs) against miR-21 on the proliferation and migration of CRC cells, with alterations in the p-AKT and p-ERK signaling pathways [26]. In atherosclerosis (AS), deficiency of miR-21 promotes DUSP8 expression, and DUSP8 overexpression inhibits phosphorylation of p38 and JNK, thereby reducing AS formation and macrophage infiltration [27]. In Diabetic kidney disease (DKD), overexpression of DUSP8 counteracts miR-93-5p overexpression and promotes the secretion of inflammatory factors and apoptosis in HPC [28] (Fig. 2).

Relationship between DUSP8 and diseases

DUSP8 and inflammatory diseases

Inflammation is a fundamental pathological process that the body initiates in response to stimuli such as trauma or infection, serving as a defense mechanism. Extensive research has established the significant role of various members of the DUSP family in the regulation of inflammatory processes. For instance, Cho et al. [27] demonstrated that overexpression of DUSP12 in a stable cell line could effectively inhibit the P38 and JNK pathways, leading to a significant reduction in the secretion of pro-inflammatory cytokines like IL-6 and TNF-α. Additionally, Liu et al. [29] reported that Short-chain fatty acids (SCFA) can upregulate miR-145 by inhibiting the expression of CEBPB (CCAAT enhancer-binding protein β), thereby suppressing the expression of dual-specificity phosphatase 6 (DUSP6). This mechanism further

Table 1 Relationship between DUSP8 and some human diseases and regulatory mechanisms

Type of disease	DUSP8 expression profiles	Regulatory mechanisms	Effects	bibliography
Inflammations	Low expression	Overexpression of DUSP8 dephosphorylates JNK and p38MAPK.	Alleviates inflammatory response	[29]
Acute Lung Injury (ALI)	Low expression	Overexpression led to a significant decrease in the secretion of pro-inflammatory cytokines	Ameliorates ALI	[30]
Breast Cancer (BC)	High Expression	Down-regulation of DUSP8 expression by activating ERK and p38 dephosphorylation in the MAPK pathway	Inhibits apoptosis and promotes their drug resistance	[18]
Triple negative breast cancer (TNBC)	High Expression	Modulates the p38MAPK signaling pathway	Inhibits apoptosis of MDA-MB-231 in TNBC cells	[31]
Epstein-Barr virus infection (EBV)	Low expression	LMP1 inhibits the expression of DUSP8 by activating the ERK and p38 signaling pathways.	Inhibits apoptosis in EBV-infected cells	[32]
Type 2 Diabetes Mellitus (T2DM)	High Expression	Hyperactivation of hypothalamic JNK signaling in DUSP8 loss-of-function mice exposed to HFD	Impaires systemic glucose and insulin sensitivity	[33]
Cerebral Hemorrhage (ICH)	Low expression	Inhibits ERK1/2 phosphorylation levels	Leads to a reduction in hemorrhagic injury and promotes hematoma resorption	[34]
Cerebral ischemia	Low expression	Up-regulation of DUSP8 expression inhibits ischemia-induced JNK dephosphorylation activity	Protects neurons from cerebral ischemic damage	[35]
Ventricular remodeling (VR)	Low expression	Activates the ERK1/2 Signaling Pathway	Mild hypercontraction of cardiomyocytes and formation of a cardiac phenotype similar to ventricular remodeling.	[36]

attenuates the development of intestinal inflammation. Similarly, Liu et al. [30] discovered that downregulation of DUSP1 expression significantly inhibits the activation of the MAPK/NF-κB signaling pathway and apoptosis in THP-1 macrophages. This also lessens the inflammatory response induced by attenuated Mycobacterium bovis bacillus Calmette-Guérin (BCG), among other effects. These findings underscore the close association of DUSP family members with the development of inflammatory processes and suggest their potential as targets for anti-inflammatory therapies.

In recent years, research has highlighted the significant regulatory role of DUSP8 in inflammatory responses. For instance, Wang et al. [31] have been observed DUSP8 expression has been markedly decreased in Bone marrow derived macrophage (BMDM). They have found that overexpression of DUSP8 can significantly mitigate the inflammatory response in macrophages induced by lipopolysaccharide (LPS). This effect has been attributed to the inhibition of JNK and p38MAPK signaling pathways, leading to a substantial reduction in the expression and phagocytic capacity of the macrophage surface molecules CD80 and CD86. Additionally, Xu [32] has reported that DUSP8 expression has been significantly downregulated in mice with LPS-induced ALI. Overexpression of DUSP8 has been shown to reduce the production of inflammatory cytokines such as IL-6 and TNF-α in LPS-stimulated BMDM, which has significantly ameliorated LPS-induced ALI. Furthermore, Ferguson et al. [33] have demonstrated that the knockdown of *DUSP1*, *DUSP8*, and *DUSP16* genes using RNAi technology has significantly enhanced the signaling intensity and duration of ERK, JNK, and p38 in the MAPK pathway. This has resulted in a pronounced increase in the expression of MAPK-dependent inflammatory genes in adipocytes.

Additionally, a large number of previous research results have indicated that miR-21 plays an important role in the development of coronary atherosclerosis by regulating the inflammatory response, promoting the proliferation of vascular smooth muscle cells, and inhibiting their apoptosis [34, 35]. For example, Gao et al. [27] have found that miR-21 expression has been significantly elevated in coronary artery disease and atherosclerotic plaques in mice. However, miR-21 defects can directly inhibit the expression of its target molecule, DUSP8, and thus inhibit AS formation and macrophage infiltration. Furthermore, Chuang et al. [36] have reported high levels of DUSP8 expression in T cells from patients with asthma and atopic dermatitis. Through the use of T-cell specific DUSP8 conditional knockout (T-DUSP8 cKO) mice, mass spectrometry, ChIP-Seq, and immunoassay, they have discovered an interaction between DUSP8 and the transcriptional deterrent protein Pur-α. Specifically, DUSP8 has been found to dephosphorylate Pur-α, modulating TGF-β signaling. This leads to the nuclear export of Pur-α, thereby promoting the transcription of IL-9 and the differentiation of Th9 cells.

To sum up, the above research results indicate that DUSP8 plays a significant role in inhibiting inflammatory signaling pathways and regulating immune cell

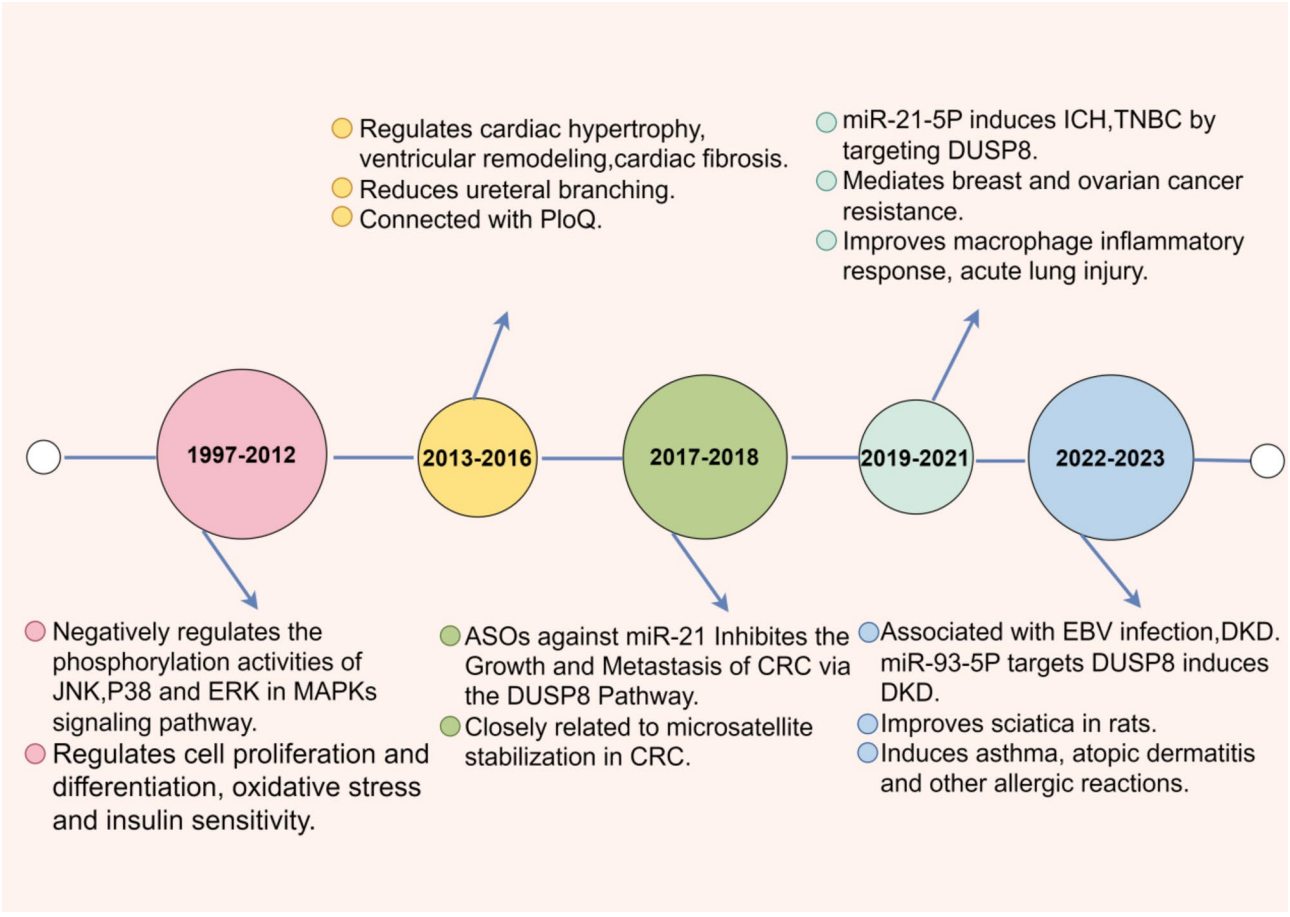

Fig. 2 Timeline of the research progression of DUSP8. (By Figdraw.)

functions, suggesting its potential as a therapeutic target for inflammatory diseases. By upregulating the expression of DUSP8 or enhancing its activity, the production of inflammatory factors can be suppressed, thereby alleviating the symptoms of inflammatory diseases. Additionally, the expression level of DUSP8 may serve as a biomarker for inflammatory diseases. For example, in certain inflammatory diseases, the expression level of DUSP8 may undergo significant changes, and its expression could be detected to provide a reference for the diagnosis of inflammatory diseases. Therefore, further investigation into the role of DUSP8 in inflammatory diseases and its potential applications can offer more theoretical basis and practical guidance for the diagnosis and treatment of inflammatory diseases.

DUSP8 and cancer

Recent advancements in medical research have illuminated the close association between DUSP8 and the development of a diverse range of clinical tumors. This dual-specificity phosphatase has emerged as a significant factor in the pathology of colorectal, breast, and ovarian cancers. Its influence extends to critical aspects of tumor biology, including promoting tumor cell growth, facilitating invasive behaviors, enhancing metastatic potential, regulating apoptosis, and modulating drug resistance. These multifaceted roles of DUSP8 suggest its potential as a biomarker for cancer progression and a target for therapeutic intervention strategies.

miR-21, a significant member of the miRNA family, has been implicated in the regulation of CRC cell proliferation, migration, and apoptosis. For instance, Schetter et al. [37] have discovered a correlation between elevated miR-21 expression and poor patient survival rates, as well as unfavorable therapeutic outcomes. They also demonstrated that the overexpression of miR-21 can enhance the proliferative, invasive, and metastatic capabilities of CRC cells. Building on this, Ding et al. [26] have identified a direct targeting interaction between DUSP8 and miR-21 in CRC. They revealed that DUSP8 is a novel target gene for miR-21. Overexpression of DUSP8 has been found to significantly suppress the proliferation and migration of CRC cells in both in vivo and in vitro models. The downregulation of DUSP8 expression diminished the inhibitory effects of ASOs against miR-21 on CRC cell proliferation and migration. This was accompanied

by alterations in the p-AKT and p-ERK signaling pathways. Subsequent studies have revealed a close association between DUSP8 expression and microsatellite (MS) stability in CRC. The interaction of DUSP8 with dephosphorylated substrates varies between CRC cells with high microsatellite instability (MSI-H) and those with microsatellite stability (MSS). This differential binding pattern influences the cellular response to DUSP8 overexpression. Specifically, in MSI-H CRC cells, DUSP8 overexpression has been shown to promote both in vivo and in vitro growth and to inhibit apoptosis. In contrast, in MSS CRC cells, the overexpression of DUSP8 inhibits growth and enhances apoptosis [38]. The study results indicate that DUSP8 exerts a dual regulatory role in CRC and the expression level of DUSP8 is closely related to the MS status in CRC, which providing a basis for the selection of treatment plans for patients.

Breast cancer (BC) is the most prevalent malignant tumor among women, with a mortality rate that exceeds that of lung and gastric cancers. The incidence of BC is increasing among younger individuals, posing a significant threat to women's health. Statistical analysis projects that by 2040, the cancer burden of BC could reach 3 million new cases and 1 million deaths annually [39]. Recent research by Zhang et al. [18] has shed light on the role of DUSP8 in BC. They found that DUSP8 was highly expressed in BC cells and was significantly upregulated in trastuzumab-naïve patients, and down-regulation of DUSP8 expression can inhibit the proliferation and migration of BC lineage cells through the activation of ERK and the dephosphorylation of p38, which also contributes to a reduction in trastuzumab resistance in BT474/TR and SKBR3/TR cells.

Triple-negative breast cancer (TNBC) is recognized as an aggressive subtype of BC with a particularly poor prognosis, posing a significant threat to women's health. Through analysis of the Cancer Public Database, key miRNAs involved in the regulation of TNBC were identified, with miR-21-5p emerging as a significant player. Moreover, Tan et al. [40], through analysis of the Cancer Genome Atlas (TCGA) and the Gene Expression Database (GED), discovered that the expression level of plasma miR-21-5p was significantly elevated in TNBC cell lines. Meanwhile, they observed a significant decrease in miR-21-5p expression levels in TNBC patients following chemotherapy. These findings suggest that miR-21-5p may serve as a pivotal biomarker for predicting TNBC prognosis. Further investigation by Tan et al. [41] revealed that DUSP8 is a direct target gene of miR-21-5p and exhibits an antagonistic relationship with it in TNBC. Bioinformatics analysis indicated that treatment of TNBC cells, such as MDA-MB-231, with doxorubicin led to a significant suppression of miR-21-5p expression, accompanied by the activation of DUSP8. Importantly, DUSP8 has been found to induce apoptosis in TNBC cells through the p38MAPK signaling pathway. These insights highlight the complex interplay between miR-21-5p and DUSP8 in TNBC and underscore the potential of DUSP8 as a therapeutic target and prognostic indicator in the management of this aggressive cancer subtype.

Additionally, study has found that high methylation of the DUSP8 promoter is relatively common in advanced epithelial ovarian cancer and is closely related to patients' clinical prognosis. Specifically, in ovarian cancer, methylation of the DUSP8 promoter leads to downregulation of its expression, which may weaken its negative regulatory effect on the MAPK signaling pathway, thereby promoting the proliferation and survival of tumor cells. Moreover, DUSP8 methylation is a favorable predictive factor for progression-free survival (PFS) and overall survival (OS). Therefore, the methylation status of the DUSP8 promoter can serve as a potential biomarker for ovarian cancer prognosis. Its methylation status can not only predict patients' PFS and OS but also potentially guide clinical treatment [42].

Turkowski et al. [17]found that DUSP8 was silenced by its transcriptional regulator miR-147b in patients with lung adenocarcinoma (LUAD), and down-regulation of DUSP8 expression was significantly associated with low overall survival, suggesting that DUSP8 could serve as an important indicator for assessing the prognosis of patients with LUAD. Whereas increased DUSP8 expression inhibited cancer growth in mouse models, therefore, modulating the expression of DUSP8 could serve as a potential therapeutic strategy.

Lin et al. [43] were the first to describe the interaction between DUSP8 and the Epstein-Barr virus (EBV). They discovered that overexpression of the *DUSP6* and *DUSP8* genes reduce the aggregation ability of EBV-immortalized lymphoblastoid cell lines (LCLs). Importantly, following EBV infection, the viral oncogene Latent Membrane Protein 1 (LMP1) was found to inhibit the expression of *DUSP6* and *DUSP8* genes by activating the ERK or p38 signaling pathways, which in turn suppressed apoptosis in EBV-infected cells.

In summary, the expression levels of DUSP8 in various types of cancer are significantly different from those in normal tissues, indicating that it can serve as a potential tumor biomarker for the diagnosis and screening of cancer. Additionally, DUSP8 plays a role in tumor cell proliferation, migration, and apoptosis by inhibiting the activation of signaling pathways such as JNK and p38MAPK, suggesting that it can be a potential target for cancer therapy. Furthermore, the expression level of DUSP8 is associated with the survival of cancer patients, indicating that the expression level of DUSP8 can serve as one of the indicators for assessing cancer prognosis. So,

through continuous in-depth research and exploration, DUSP8 is expected to play a greater role in the diagnosis, treatment, and prognosis assessment of cancer, bringing more hope and help to cancer patients.

DUSP8 and metabolic disorders

Diabetes mellitus (DM) is a prevalent and significant metabolic disorder that poses a substantial health risk. It is primarily categorized into two types: Type 1 diabetes mellitus (T1DM), characterized by insufficient insulin production by the pancreas, and Type 2 diabetes mellitus (T2DM), which involves the body's inability to utilize insulin effectively. T2DM represents over 90% of diabetes cases and with its incidence increasing, highlighting the urgent need for novel and effective therapeutic targets. Recent large-scale genome-wide association studies and metabolic microarray analyses have identified a correlation between the minor allele of the DUSP8 single nucleotide polymorphism (SNP) rs2334499 and an increased risk of T2DM, particularly in males [44]. This association has led to the classification of DUSP8 SNP rs2334499 as a T2DM risk gene, offering new avenues for targeted diabetes treatment and prevention strategies. For example, Schriever et al. [45] discovered that the brain, particularly the hypothalamus, has high levels of DUSP8. In their study, it was observed that in mice, DUSP8 levels in the hypothalamus were upregulated in response to obesity induced by a high-fat diet (HFD). Male mice deficient in DUSP8 and exposed to HFD exhibited impaired feedback of the hypothalamic-pituitary-adrenal axis and hyperactivation of hypothalamic JNK signaling. This led to compromised systemic glucose tolerance and insulin sensitivity. These impairments could be reversed by overexpressing DUSP8, which inhibits JNK signaling, or by inducing chemoadrenalectomy with methylpyrrolidone, thereby restoring glucose homeostasis in DUSP8 loss-of-function mice. Furthermore, the sex-specific role of DUSP8 in regulating hypothalamic JNK signaling, glucose tolerance, and insulin sensitivity was found to align with observations in human males. Comparative functional MRI data from human volunteers indicated that the diabetes risk allele of the DUSP8 SNP rs2334499 is associated with hypothalamic insulin resistance in males. Additionally, increased DUSP8 expression was observed in the hypothalamic funicular nucleus of human patients with T2DM, suggesting a potential link between DUSP8, insulin resistance, and diabetes risk. In summary, DUSP8 has emerged as a significant hypothalamic factor associated with T2DM, demonstrating a crucial role in the regulation of glucose homeostasis in both mice and humans. The work of Baumann et al. [46] further implicates DUSP8 in dietary behaviors, with carriers of the DUSP8 SNP rs2334499 diabetes risk allele exhibiting a preference for sweet, high-calorie foods. This suggests that DUSP8, beyond its metabolic functions, may also influence food choice and foraging behavior in humans and mice, underscoring its multifaceted impact on T2DM risk.

Diabetic kidney disease (DKD) is a prevalent complication of T2DM, and its management presents significant challenges. Chen et al. [47] have systematically explored the current treatment landscape for DKD, emphasizing the need for improved diagnostic tools, predictive markers, and therapeutic strategies to enhance patient care. Previous researches have established that the MAPK signaling pathway, comprising ERK1/2 and p38, play a crucial role in the progression of DKD [48, 49]. These signaling components are linked to cellular processes such as proliferation, differentiation, and oxidative stress. In the context of renal disease, angiotensin II can be activated by oxidative stress products, like hyperglycemia, contributing to the development of DKD's pathological processes. Understanding the intricate relationship between the MAPK pathway and DKD may reveal novel therapeutic targets and predictive biomarkers, potentially leading to more effective treatments and better patient outcomes [50]. Recent research has implicated DUSP8, in conjunction with the JNK and p38 signaling pathways within the MAPK family, in the pathogenesis of DKD. For instance, Liu et al. [19] observed that in both DKD patients and mouse models, DUSP8 expression was significantly diminished in renal tissues and HPC under high glucose conditions, whereas JNK phosphorylation levels were markedly elevated. They also demonstrated that overexpression of DUSP8 could mitigate high glucose-induced damage to HPC injury and mitochondrial dysfunction by inhibiting JNK phosphorylation activity.

Furthermore, Study has found that in the HepG2 cell line model induced by high glucose, the expression level of miR-93-5p is significantly increased. Overexpression of miR-93-5p can inhibit cell viability and glucose consumption. Conversely, inhibition of miR-93-5p can significantly enhance cell survival and glucose consumption. This suggests that miR-93-5p may influence cell behavior under high-glucose conditions by regulating cell metabolism and proliferation capacity [51]. Bioinformatics analysis suggested that miR-93-5p binds to the 3' untranslated region (UTR) of DUSP8, indicating a potential reciprocal targeting relationship. This finding is particularly noteworthy since previous studies have implicated miR-93-5p in the high glucose-induced processes of proliferation, metastasis, and invasion in mouse thylakoid cell. These insights highlight the complex interplay between DUSP8, miRNAs, and the MAPK pathways in DKD and could have significant implications for the development of therapeutic strategies targeting these pathways. However, the precise role of miR-93-5p in the development of DKD and its relationship with DUSP8 expression is not yet fully understood, and the exact regulatory

mechanisms warrant further study. While Liu et al. [19] reported a decrease in DUSP8 expression with high glucose conditions, Gu et al. [28] found the opposite: high glucose induced a significant increase in DUSP8 mRNA and protein levels in HPC and a corresponding decrease in miR-93-5p expression. And they demonstrated that overexpression of miR-93-5p significantly reduced the secretion of inflammatory cytokines IL-6 and TNF-α and the promotion of apoptosis in HPC under high glucose conditions. This suggests that miR-93-5p may play a protective role against HPC injury in DKD. Conversely, silencing DUSP8 expression mimics the effects of miR-93-5p overexpression, whereas DUSP8 overexpression appears to counteract the protective effects of miR-93-5p, potentially contributing to the secretion of inflammatory factors and apoptosis in HPC, which could promote the development of DKD. These findings indicate a complex interplay between miR-93-5p and DUSP8 in the context of DKD, and further research is needed to clarify their regulatory relationships and potential as therapeutic targets. Moreover, Liu et al. [52] discovered that miR-21 expression is significantly up-regulated in diabetic cardiomyopathy. They found that miR-21 inhibits its direct target molecule, DUSP8, by binding to the 3' untranslated region (UTR) of its mRNA. This inhibition leads to the activation of the JNK/SAPK and p38 signaling pathways, which in turn promotes the proliferation of cardiac fibroblast cells and collagen synthesis, contributing to the development of cardiac fibrosis. Additionally, recent studies have found that the expression levels of miR-21 and YKL-40 in serum are significantly elevated in patients with DKD. These biomarkers are closely associated with the progression of DKD, offering new avenues for the clinical diagnosis and treatment of diabetic nephropathy [53]. This finding raises the question of whether DUSP8 also serves as a functional target molecule in DKD, a possibility that warrants further investigation.

Atherosclerosis (AS) is a prevalent metabolic disease that poses a significant threat to human health. Studies have found that miRNA regulate gene expression by inducing mRNA degradation or inhibiting its translation, and are involved in a variety of physiological and pathological processes, including inflammation, lipid metabolism, and platelet activation [54–58]. Among these, miR-21 has been identified to be highly expressed in AS [59]. Overexpression of miR-21 in coronary artery disease correlates positively with disease severity and negatively with plaque stability [60]. Jin et al. [61] experimentally demonstrated that miR-21 knockout mice exhibit increased macrophage infiltration and foam cell formation in the vascular wall, suggesting that miR-21 has a key regulatory role in AS development. Additionally, Gao et al. [27] found that miR-21 expression is significantly elevated in atherosclerotic plaques in both coronary artery disease patients and mice. They also discovered that miR-21 deficiency directly inhibits the expression of its target molecule DUSP8, thereby reducing AS formation and macrophage infiltration. These findings indicate that miR-21 and its target DUSP8 are integral to the pathogenesis of AS, offering potential avenues for therapeutic intervention and providing new insights into the molecular mechanisms underlying this disease.

In summary, DUSP8 exerts significant regulatory influence over the pathogenesis and progression of metabolic diseases, including T2DM, DKD, and AS. These findings not only underscore the multifaceted role of DUSP8 but also highlight its potential as a novel biomarker and therapeutic target. The exploration of DUSP8's role in metabolic diseases opens new avenues for diagnosis and targeted treatment strategies, offering hope for the development of more effective clinical interventions in the future.

DUSP8 with other diseases

Intracerebral haemorrhage (ICH) is hemorrhage caused by rupture of blood vessels in the brain parenchyma, characterized by a sudden onset and high early mortality rate. Survivors often suffer from various sequelae. Inflammation plays a significant role in ICH progression and represents a potential therapeutic target. Ouyang et al. [62] discovered that miR-21-5p levels were significantly elevated in the plasma of ICH patients. Through microarray analysis, they identified miR-21-5p as highly responsive to the regulation of heme oxygenase-1 (HO-1) in ICH-afflicted rats. DUSP8, a direct target of miR-21-5p, was found to have its expression significantly increased by the downregulation of miR-21-5p. This upregulation of DUSP8 promotes HO-1 production through the activation of the p-ERK/HO-1 signaling pathway. This mechanism contributes to the reduction of hemorrhagic injury within 24 h post-ICH and aids in the resorption of the hematoma after 10 days of ICH. These findings suggest that the miR-21-5p/DUSP8/HO-1 axis may play a crucial role in the inflammatory response following ICH, offering a promising direction for the development of targeted therapies to mitigate ICH-induced brain injury.

Previous studies have demonstrated that rosiglitazone, a peroxisome proliferator-activated receptor (PPAR)-γ agonist, exhibits protective effects against cerebral ischemia in animal models [63–65]. However, the underlying mechanisms remain unclear. Okami et al. [66] reported that treatment with rosiglitazone led to an increase in DUSP8 expression in tissues affected by cerebral ischemia. This upregulation of DUSP8 has been found to suppress the phosphorylation activity of JNK and p38, thereby reducing cell apoptosis and inflammatory responses and protecting neurons potentially from the damage caused by ischemia. This study indicates that

DUSP8, by activating the p-ERK/HO-1 pathway, inhibits the pro-inflammatory effects of miR-21-5p, thereby providing a novel mechanism and potential therapeutic target for the treatment of ICH.

In ventricular remodeling(VR), it has been found that MAPK signaling is involved in the growth regulation of adult cardiomyocytes, and DUSP8 can modulate the basal tone, amplitude, and duration of MAPK signaling by dephosphorylating MAPK and thereby regulating MAPK signaling. For example, Liu [67] found that knockdown of DUSP8 prevents non-alcoholic fatty liver disease-related cardiac toxicity (NAFT) Signaling-Induced Cardiomyopathy by increasing JNK phosphorylation for cardioprotection, which suggests that DUSP8 has an important role in regulating cardiac hypertrophy in vivo and in vitro. Furthermore, Liu et al. [68] observed that adult cardiomyocytes from mice deficient in the *DUSP8* gene exhibited morphological changes, being thicker and shorter. They found that extracellular signaling in the heart activated the ERK 1/2 pathway both at baseline and in response to acute pathological stress. This activation led to a mild over-contraction of the cardiomyocytes, resulting in a cardiac phenotype similar to VR.

Liao et al. [69] discovered that in rats subjected to spinal nerve ligation (SNL) surgery, DUSP8 expression was significantly diminished in the ipsilateral spinal cord (ISC) tissues. Additionally, they observed that exposure to LPS, a known activator of the immune response, reduced DUSP8 expression in mouse microglia. Notably, adenoviral-mediated overexpression of DUSP8 substantially alleviated SNL-induced neuropathic pain in these rats. The mechanism is that DUSP8 can directly bind to Transforming growth factor-beta activated kinase-1 (TAK1) in microglia. TAK1 is a key kinase in the TAK1/p38/JNK signaling pathway. Both SNL and LPS can activate the TAK1/p38/JNK1/2 signaling pathway. However, overexpression of DUSP8 can strongly inhibit the activation of this signaling pathway. Blocking TAK1 can significantly reduce LPS-induced inflammation and neuronal death, thereby helping to protect neurons and alleviate neuropathic pain.

Polyglutamine (polyQ) diseases are a class of inherited neurodegenerative disorders arising from the misfolding and aggregation of polyQ proteins due to an expansion of polyQ repeat sequences. Transcriptional dysfunction and oxidative damage are recognized as primary mechanisms in the pathogenesis of polyQ diseases. Misfolded polyQ proteins typically accumulate in intranuclear inclusion bodies, leading to increased production of reactive oxygen species (ROS) and activation of stress signaling pathways. DUSP8 can dephosphorylate JNK and p38MAPK, thereby inhibiting their activity. This helps to alleviate cellular stress responses, reduce the aggregation of polyQ proteins, prevent the formation of inclusion bodies, and maintain protein homeostasis within the cell. The interplay between polyQ proteins, DUSP8, and the MAPK pathway underscores the complexity of polyQ disease pathology and highlights potential therapeutic targets for intervention [70].

In addition, Liu et al. [71] found that DUSP6/8 double-deficient mice exhibited elevated ERK1/2 phosphorylation in several tissues, with no change observed in p38 and JNK phosphorylation levels. Moreover, these mice had significantly lower serum triglycerides and lipid content in the liver and visceral adipose tissue. Interestingly, their glucose tolerance was greatly improved. These findings indicate that DUSP6/8 double-deficient mice have enhanced ERK1/2 activity, which may confer increased resistance to diet-induced obesity.

In summary, DUSP8 stands out as an essential member of the DUSPs, exerting a pivotal role in the pathogenesis of a multitude of diseases through the modulation of its expression levels. The profound influence of DUSP8 on disease processes underscores the importance of in-depth research into this phosphatase. Such studies are anticipated to pave the way for novel diagnostic approaches and therapeutic strategies, offering fresh insights into the management of a spectrum of clinical conditions (Fig. 3).

Summary and prospects

DUSP8, a crucial member of the DUSPs family, has been implicated in the pathogenesis of numerous human diseases. It exerts its functional role by negatively regulating the phosphorylation activities of the MAPK, including JNK, ERK, and p38. This regulation is pivotal for controlling oxidative stress in macrophages and for driving key processes in tumor cells, such as proliferation, metastasis, invasion, apoptosis, and drug resistance. Especially noteworthy is DUSP8's role as a direct target molecule in a variety of clinically relevant diseases. This places DUSP8 at the forefront as an emerging target for targeted therapies, offering promising avenues for the development of novel treatment strategies. While existing research has shed light on the regulatory mechanisms of DUSP8 expression in certain diseases, there remain numerous challenges and questions to be addressed. Further investigation is necessary to unravel the full spectrum of DUSP8's biological functions and its potential as a therapeutic target (Fig. 4).

Firstly, the precise mechanisms governing DUSP8 expression in various diseases are not yet fully understood and require further elucidation. Key questions include the differences in the promoter regions and associated transcription factors across various tissues and cell types, as well as potential epigenetic regulatory mechanisms. Current researches predominantly indicate that DUSP8 mRNA levels are subject to tight regulation by

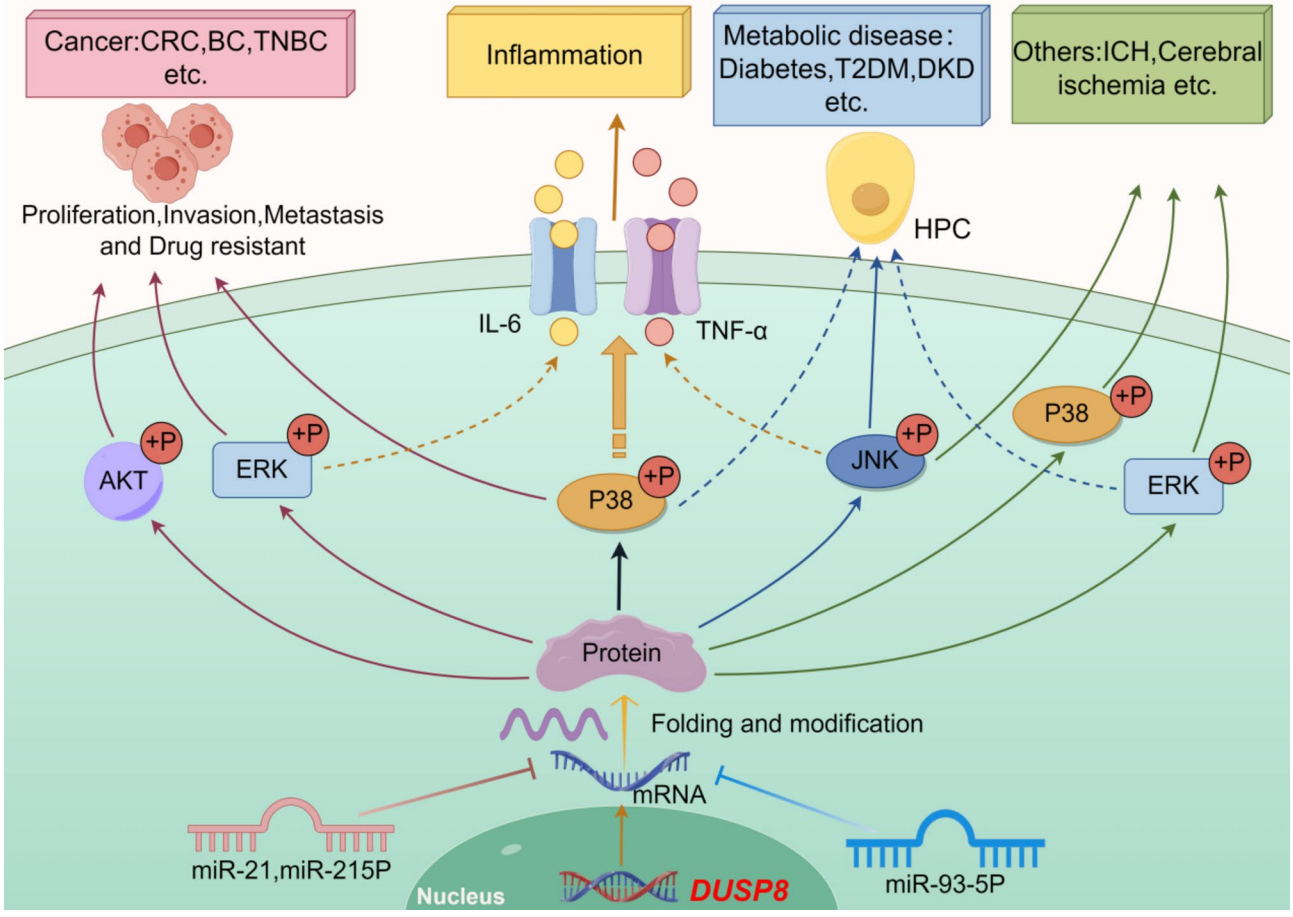

Fig. 3 Mechanistic overview of DUSP8's Role in regulating multiple human diseases. (By Figdraw.)

a range of non-coding RNAs, including miR-21, miR-147b, miR-21-5p, and miR-93-5p. These miRNAs regulate the expression of DUSP8 by targeting its 3'UTR in various tumors, thereby affecting tumor progression and treatment response. For example, in LUAD, miR-147b inhibits the expression of DUSP8 by targeting its 3'UTR, thereby promoting the proliferation, migration, and epithelial-mesenchymal transition (EMT) of tumor cells [17]. In CRC, miR-21 inhibits the expression of DUSP8 by targeting its 3'UTR, thereby promoting the proliferation and migration of tumor cells [26]. We speculate that the differences in the regulatory mechanisms of DUSP8 expression in different cells are closely related to the inherent differences between these cells, as well as the levels of related regulatory molecules and DUSP8 itself. Similarly, in our other studies, we found that the expression of miR-7 in $CD4^+$ T cells is mainly regulated by the transcription factor C/EBPa [72], while in lung cancer cells, the expression of miR-7 is mainly regulated by the transcription factor NF-1 [73]. Although the regulatory mechanisms of DUSP8 in different cells still need to be clarified, these interesting phenomena suggest that when developing therapeutic strategies targeting DUSP8, it is necessary to carefully consider the differences in the regulation of DUSP8 expression in different disease states within cells, so as to achieve precision treatment and better intervention effects.

Secondly, the regulatory interactions between DUSP8 and intracellular signaling pathways are not well-defined. Evidence indicates that DUSP8 plays a dual role in the signaling regulation of different tumor cells. On the one hand, DUSP8 regulates the MAPK signaling pathway through dephosphorylation and may function as a tumor suppressor. For example, In patients with LUAD, overexpression of DUSP8 exhibits tumor-suppressive phenotypes in both in vitro and in vivo experimental models by regulating the activity of the JNK signaling pathway [17]. Conversely, DUSP8 downregulation can inhibit the proliferation and migration of BC cells by activating the ERK signaling pathway and dephosphorylating the p38 signaling pathway, which helps to reduce the resistance of BT474/TR and SKBR3/TR cells to trastuzumab [18]. And in CRC, the role of DUSP8 is also paradoxical. For example, overexpression of DUSP8 promotes the in vivo and in vitro growth and inhibits apoptosis of MSI-H CRC cells, while it inhibits the growth and promotes apoptosis

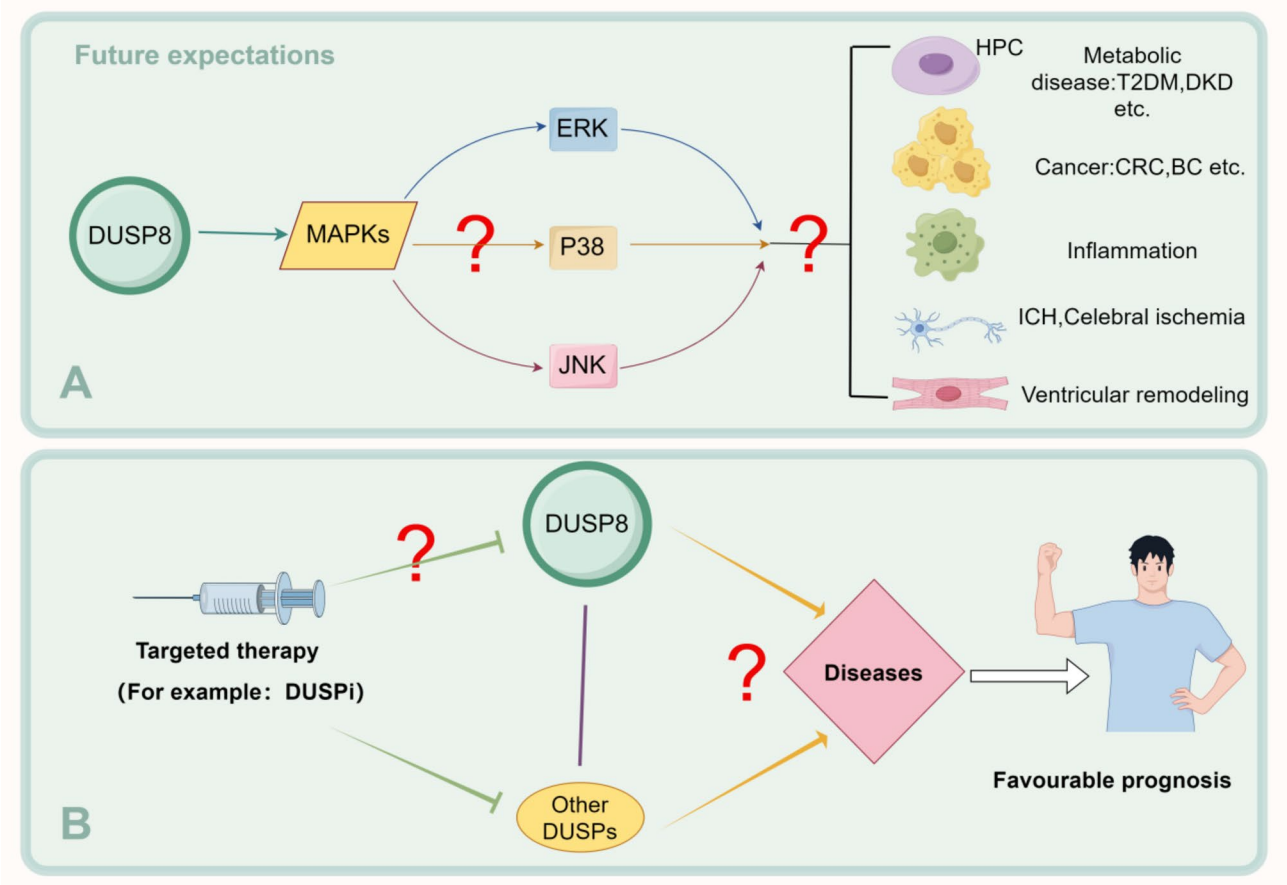

Fig. 4 Prospects for future research works on DUSP8. (By Figdraw.)

of MSS-CRC cells, the contradiction is related to the differential dephosphorylation of substrates p-JNK1/2, p-ERK1/2, and p-p38 in different types of cells [38]. We speculate that this interesting phenomenon may be related to the following two factors. First, DUSP8 mainly exerts its effects by regulating its target molecules, such as JNK and ERK. It is now known that the expression levels of these substrate molecules vary among different tumor cells. Therefore, the effects of DUSP8 on these substrates will differ. Second, the functions of DUSP8 substrates may also differ in specific cells. Furthermore, the relationships between the various signaling pathways and how they intersect with DUSP8's regulatory functions also need to be explored. In summary, unraveling the intricate regulatory network of DUSP8, from its transcriptional control by non-coding RNAs to its modulation of intracellular signaling pathways, is essential. This knowledge will not only deepen our understanding of the pathophysiological processes in which DUSP8 is implicated but also inform the development of targeted therapies for a variety of diseases. In addition, emerging research has highlighted the close association between metabolomic alterations encompassing shifts in the metabolism of sugars, fats, and amino acids and the development of various diseases. These alterations may reflect the underlying metabolic reprogramming that occurs in response to disease states. A pertinent question arises: could the downstream regulatory effects of DUSP8 lead to relevant metabolomic changes that, in turn, influence disease processes? If so, understanding these changes could provide insights into the metabolic pathways influenced by DUSP8 and their contribution to disease pathogenesis.

Thirdly, how to develop new methods of clinical intervention and treatment by regulating DUSP8 targets. For example, Zandi et al. [74] have concluded that DUSPs proteins, integral to the regulation of cell proliferation, survival, and apoptosis, play a pivotal role in tumorigenesis, malignant progression, and therapeutic resistance. Their influence on the MAPK signaling pathway suggests that targeting DUSPs proteins and their downstream molecular targets could lead to the development of more effective cancer therapies. Additionally, Ríos et al. [75] have argued for a comprehensive approach to studying the molecular and functional aspects of DUSPs proteins. This includes the development of DUSPi with enhanced specificity and efficacy. The use of such inhibitors could be instrumental in both the prevention and mitigation

of various human diseases. These studies underscore the potential of DUSPs-targeted therapies in medicine, highlighting the need for continued research and development in this area.

Additionally, how to understand the individual roles of DUSPs molecules, elucidating the relationships between different DUSPs, especially in the context of specific diseases, is crucial. For instance, Vriendt Veerle de et al. [76] found that DUSP4 expression could serve as a marker for heterogeneous signaling transmission in CRC patients. And Ichimanda et al. [77] have discovered that the downregulation of DUSP4 expression can lead to the inverse activation of the ERK signaling pathway. Which in turn can promote the proliferation and invasion of CRC lineage cells; Yan et al. [78] have identified that DUSP5 is expressed at lower levels in CRC and is significantly associated with key clinical parameters, including tumor differentiation, TNM stage, lymph node metastasis, and distant metastasis. Patients with higher expression levels of DUSP5 exhibited more favorable CRC-specific disease-free survival compared to those with lower DUSP5 expression. Moreover, advanced-stage CRC patients with high DUSP5 expression responded better to FOLFOX chemotherapy, suggesting that DUSP5 could serve as a novel prognostic indicator for patients with advanced CRC; and Qiu et al. [79] discovered that DUSP9 expression is significantly downregulated in CRC tissues, which correlates closely with the depth of tumor infiltration, TNM staging, and patient survival rates. Notably, DUSP9 has been shown to exert inhibitory effects on the proliferation, invasion, metastasis, and overall tumor growth of CRC cells in both in vivo and in vitro studies. Additionally, overexpression of DUSP10 was found to promote the growth of CRC cell lines and mouse xenografts, while silencing of DUSP10 expression yielded the opposite effect [80]. Interestingly, Ding et al. [26] reported that DUSP8 is expressed in CRC, and its overexpression has been shown to significantly inhibit the proliferation and migration of CRC cells both in vivo and in vitro. This inhibition is associated with alterations in the p-AKT and p-ERK signaling pathways. Additionally, it has been observed that the effects of DUSP8 overexpression can vary depending on the molecular subtype of CRC. In MSI-H CRC cells, DUSP8 overexpression promotes growth and inhibits apoptosis, while in MSS CRC cells, it has the opposite effect, inhibiting growth and promoting apoptosis [38]. These studies suggest that different DUSPs molecules have similar or opposite roles in the same type of disease or cell. Therefore, how to choose the optimal intervention program, which is important for the subsequent development of therapeutic strategies for gene intervention targeting DUSP8.

Finally, although DUSP8 shows promise as a potential therapeutic target in cancer treatment, its roles in metabolic disorders and inflammatory diseases suggest that targeting DUSP8 in clinical applications may still pose significant risks and challenges. For instance, DUSP8 plays a crucial role in metabolic processes, particularly in the regulation of glucose metabolism in the hypothalamus. Studies have shown that DUSP8 regulates the activity of the HPA axis through signaling pathways such as JNK, thereby modulating systemic glucose tolerance [45]. Therefore, therapeutic strategies targeting DUSP8 may disrupt this metabolic regulatory mechanism, increasing the risk of metabolic disorders, especially in patients with obesity or diabetes. Additionally, SNPs in DUSP8 are associated with an increased risk of type 2 diabetes, particularly in males [44]. This implies that changes in the function or expression levels of DUSP8 could have profound effects on metabolic diseases. Thus, when considering DUSP8 as a therapeutic target, it is essential to carefully evaluate its potential impacts on the metabolic system, especially its potential interference with insulin sensitivity and glucose metabolism. Similarly, DUSP8 also plays an important role in inflammatory responses. Inflammatory responses commonly involve the activation of various intracellular signaling pathways, such as the MAPK signaling pathway (including ERK, JNK, and p38MAPK). Overactivation of these signaling pathways can lead to the production of pro-inflammatory cytokines (such as TNF-α, IL-6, and IL-1β) [81–84]. DUSP8, as a dual-specificity phosphatase, can dephosphorylate ERK, JNK, and p38MAPK, thereby inhibiting the activity of these kinases. In this manner, DUSP8 can reduce the overactivation of inflammatory signaling pathways, thereby decreasing the production of pro-inflammatory cytokines and exerting an anti-inflammatory effect. For example, studies have found that in LPS-induced macrophage inflammatory models, overexpression of DUSP8 significantly inhibited the phosphorylation levels of JNK and p38MAPK, reduced the secretion of TNF-a and IL-6, thereby alleviating macrophage inflammatory responses and significantly improving LPS-induced acute lung injury (ALI) [31, 32]. This suggests that changes in the expression levels or activity of DUSP8 can influence the body's inflammatory responses and pathological processes by modulating the activity of the MAPK signaling pathway. Therefore, given the complexity of the role of inflammatory responses in tissue damage and repair within the body, therapeutic strategies targeting DUSP8 need to take into account the dual nature of inflammatory responses and conduct a systematic assessment of the potential benefits and risks of treatment in order to achieve the best intervention effect.

In conclusion, the swift progress in molecular biology, spatial transcriptomics, metabolomics, and related technologies is poised to significantly enhance our understanding of the biological structure of DUSP8 and its

intricate regulatory mechanisms in the context of clinical diseases. This in-depth research will facilitate a more systematic and comprehensive appreciation of the roles played by the DUSPs family in biological processes and disease pathogenesis and lay a novel foundation for research focused on the prevention and diagnosis of diseases, with a particular emphasis on the regulatory mechanisms of DUSP8. The exploration of DUSP8's regulatory landscape will not only contribute to our fundamental knowledge of biology but also pave the way for more personalized and effective treatment strategies in medicine.

Abbreviations

DUSP8	Dual-specific phosphatase-8
GWAS	Genome-wide association study
Ser/Thrs–phosphatases	Serine/Threonine phosphatases
Tyr-phosphatases	Tyrosine phosphatases
DUSPs	Dual-specific phosphatases
PTP	Protein tyrosine phosphatases
MAPK	Mitogen-activated protein kinases
MKPs	MAPK phosphatases
JNK	C-JunN-terminal kinase
ERK	Extracellular regulated kinase
IPF	Idiopathic pulmonary fibrosis
HGSOC	High-grade serous ovarian cancer
PFS	Progression-free survival
OS	Overall survival
DUSPi	DUSP inhibitors
CRC	Colorectal cancer
ASOs	Antisense Oligonucleotides
BC	Breast cancer
DUSP8-KO	DUSP8 knockout
HVH-5	Poxvirus H1 phosphatase gene clone 5
BCG	Bacillus Calmette-Guérin
ILK	Integrin-linked kinase
AS	Atherosclerosis
miRNAs	MicroRNAs
miR-21	MicroRNA-21
DKD	Diabetic kidney disease
HPC	Human glomerular podocytes
SCFA	Short-chain fatty acids
CEBPB	CCAAT enhancer-binding proteinβ
LPS	Lipopolysaccharide
BMDM	Bone marrow derived macrophage
TNF-α	Tumor necrosis factor-α
ALI	Acute lung injury
DUSP8 conditional KO mice	T-DUSP8 cKO
MSI-H	Microsatellite Stability
TNBC	Triple-negative breast cancer
TCGA	The Cancer Genome Atlas
GED	Gene Expression Database
ILK	Integrin-linked kinase
LUAD	Lung adenocarcinoma
EBV	Epstein-Barr virus
LCL	Lymphoblastoid cell line
DM	Diabetes mellitus
T2DM	Type 2 diabetes mellitus
DUSP8 SNP rs2334499	DUSP8 single nucleotide polymorphism rs2334499
NAFT	Non-alcoholic fatty liver disease-related cardiac toxicity
TAK1	Transforming growth factor -activated kinase-1
PPAR	Peroxisome proliferator-activated receptor

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Declarations

Ethics approval and consent to participate
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Consent for publication
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