

Roles of ubiquitin-specific peptidase 22 in cellular fate: From embryonic survival to tissue repair, inflammation and metabolism (Review)

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Abstract. Ubiquitin-specific peptidase 22 (USP22), a key member of the deubiquitinase family, serves pivotal roles in tumorigenesis by driving tumor proliferation, metastasis and drug resistance. In addition to its role in oncology, its versatile functions in diverse physiological and pathological contexts have been revealed. These include ensuring embryonic viability through developmental signaling regulation, promoting tissue repair and contributing to ischemia-reperfusion injury, inflammatory responses and immune activation via cytokine and immune cell regulation. USP22 is also involved in fibrosis, metabolic homeostasis and tissue remodeling in patients with conditions such as asthma and pneumoconiosis. These multifaceted actions are mediated primarily through the deubiquitination of target proteins such as silent mating-type information regulation 2 homologue 1 and through epigenetic mechanisms, including histone modification. The present review summarized recent advances in USP22-mediated cell fate regulation and evaluates its therapeutic potential across diseases, underscoring promising prospects for clinical translation.

Contents

1. Introduction
2. Development and regeneration
3. Damage and repair
4. Inflammatory response and immune regulation
5. Fibrosis, steatosis and tissue remodeling
6. Discussion
7. Future directions and clinical prospects

1. Introduction

The Spt-Ada-Gcn5-acetyltransferase (SAGA) complex, a highly conserved 19-subunit machinery, spans evolutionary lineages from yeast to mammals (1,2). It harbors a tetrameric deubiquitinase module (DUBm) composed of ubiquitin-specific peptidase 22 (USP22), Ataxin 7/SAGA-associated factor 73 (ATXN7/Sgf73), Ataxin 7-like protein 3 (ATXN7L3/Sgf11) and ENY2 transcription/export complex subunit, which together form a tightly associated tetrameric DUBm (3,4). The DUBm is an independently folding subcomplex that connects to the rest of the SAGA via the C-terminal portion of Sgf73 (3). As a core component of SAGA, USP22 belongs to the ubiquitin-specific processing proteases (USPs); they make up the largest deubiquitinase subfamily and are known in yeast as UBPs (5). Structurally, USP22 features an N-terminal zinc finger domain and a C-terminal catalytic domain, which enable its enzymatic activity (6).

USP22 exerts robust protumorigenic effects across various malignancies by orchestrating key cellular processes (5,7). In patients with non-small cell lung cancer, USP22 promotes cell proliferation, invasion and stemness via murine double minute X/p53 pathway (8) inducing epithelial-mesenchymal transition (EMT) (9) and stabilizing murine double minute 2 to suppress ferroptosis (10). Ferroptosis is an iron dependent, nonapoptotic form of cell death driven by membrane lipid peroxidation (11). In patients with hepatocellular carcinoma, it facilitates tumor progression and drug resistance by stabilizing E2F transcription factor 6 (E2F6) to activate RAC-alpha serine/threonine-protein kinase (AKT) signaling (12),

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maintaining peroxisome proliferator-activated receptor γ (PPAR γ)-mediated lipid anabolism (13), and engaging the silent mating-type information regulation 2 homologue 1 (SIRT1)/AKT/multidrug resistance-associated protein 1 (MRP1) axis (14). In patients with prostate cancer, USP22 functions as an oncogenic driver by modulating cell proliferation and DNA damage repair (15). In patients with breast cancer, it enhances human epidermal growth factor receptor 2-driven invasive phenotypes by inhibiting the unfolded protein response (16). Additionally, in patients with colorectal cancer, USP22 promotes programmed death-ligand 1 (PD-L1) stability through deubiquitination (17), whereas in those with osteosarcoma, its upregulation is associated with tumor progression (18). Mechanistically, it also regulates necroptosis by modulating receptor-interacting protein kinase 3 stability (19).

Notably, while substantial research has focused on the role of USP22 in cancer stemness (20), emerging evidence has revealed its critical functions in nontumor pathologies. However, investigations into physiologic and pathogenic processes across various cell types, tissues and organ systems, remain fragmented, necessitating a comprehensive synthesis of its involvement in disease a etiology, functional roles and regulatory networks. Therefore, the present study reviewed the roles and regulatory mechanisms of USP22 across diverse biological processes and pathological conditions, including embryonic survival, skin wound healing, cellular and tissue damage and repair following ischemia-reperfusion, inflammatory and immune regulation, fibrosis and tissue remodeling. The detailed substrates of USP22 involved therein and their functions are summarized in Tables I-IV.

2. Development and regeneration

Embryonic survival. The SAGA complex harbors two enzymatic activities: the general control nonderepressible 5 (Gcn5) histone acetyltransferase and the USP22 deubiquitinase (21). Previous studies have shown that loss of GCN5 affects early embryogenesis, neural stem cell differentiation, retinoic acid signaling and fibroblast growth factor signaling (22,23). Additionally, USP22 is critical for regulating the differentiation of embryonic stem cells (24,25). Studies have shown that mice carrying a hypomorphic allele of *Usp22* exhibit reduced body size (26) whereas *Usp22* deletion leads to embryonic lethality in mice (27). This is mainly because USP22 exerts a deubiquitinating effect to stabilize the SIRT1 protein in embryonic cells, thereby inhibiting p53 acetylation-induced apoptosis and maintaining embryonic cell survival (27). Placental blood vessels also play a crucial role in embryonic development; abnormal placental vascular development and vascular dysfunction may result in uteroplacental perfusion disorders, intrauterine malnutrition and fetal growth restriction (28,29). Fetal growth restriction (FGR) refers to the failure of a fetus to achieve its growth potential in the uterus and is a common obstetric complication that can lead to various adverse outcomes (30,31). USP22 is essential for placental angiogenesis and embryonic survival because it regulates the functions of endothelial cells and pericytes. USP22 expression is downregulated in the placental tissues of patients with FGR, leading to inhibited

proliferation, increased apoptosis and impaired angiogenesis in human umbilical vein endothelial cells and its mechanism may involve downregulation of the PI3K/AKT signaling pathway (28). Another study indicated that *Usp22* deletion causes placental vascular development defects and subsequent early embryonic mortality, which is associated with impaired TGF- β receptor and RTK signaling pathways (32). The aforementioned mechanisms involving USP22 collectively contribute to poor embryonic development or even mortality, revealing the multiple protective roles of USP22 in embryonic development.

In contrast to that in FGR, upregulated USP22 in placental trophoblasts from patients with preeclampsia (PE) deubiquitinates and stabilizes a disintegrin and metalloprotease 9 (ADAM9), thereby inhibiting the activity of the Wnt/ β -catenin pathway. This suppresses the proliferation, migration, invasion and EMT of trophoblast cells and induces their apoptosis. This process may cause shallow trophoblast invasion and spiral artery rupture, leading to PE (33) (Table I; Fig. 1).

Although existing studies have revealed the multiple roles and related pathways of USP22 in embryonic survival, placental angiogenesis and pregnancy complications (FGR, PE), significant research gaps remain. The expression patterns and functional outcomes of USP22 differ between FGR and PE and further investigation is needed to clarify the regulatory mechanisms underlying these divergent phenotypes in different cell types, as well as their potential associations. The mouse models and single-cell lines used in recent studies cannot fully replicate the complexity of human placental development; additionally, mechanistic research has not effectively linked clinical diagnostic biomarkers and targeted intervention strategies and the crosstalk between various regulatory pathways remains to be further elucidated. These issues provide key directions for future research.

Cell fate. USP22 sustains neural progenitor/stem cell (NSC) pluripotency by prolonging the half-life of the hairy and enhancer of split 1 (Hes1), after which USP22 expression knockdown alters the abundance of cells but not the shape of the small intestine, indicating that USP22 not only preserves the number of stem cells but also modulates cell differentiation.

NSCs residing in the adult mammalian brain contribute to neurodevelopment and repair via proliferative and differentiation functions (34,35), with the dynamic Hes1 gene expression playing a pivotal role in normal developmental timing and fate determination (36,37). USP22 interacts with the transcription factor Hes1 to prolong its half-life and inhibit neuronal differentiation while maintaining cell stemness by sustaining the periodic oscillation of Hes1 (38). In patients with traumatic brain injury (TBI), overexpression of USP22 promotes the proliferation of NSCs in the hippocampal dentate gyrus region and inhibits their differentiation into mature neurons, thereby improving hippocampus-dependent cognitive impairment. USP22 is expected to be a potential therapeutic target for post-TBI treatment (39). Proper regulation of gene expression patterns serves a vital role in determining cell fate and regulating cell differentiation (40-42). *Usp22* is widely expressed in most embryonic tissues at embryonic Day 15.5 (E15.5). Systemic knockdown of *Usp22* expression does not

Table I. USP22 in development and regeneration.

Functional category	Substrate	Cell/tissue	Reported function/outcome	Ubiquitination mechanism
Development and cell fate	SIRT1	Embryonic stem cells	Maintains embryonic cell survival by inhibiting the p53 apoptotic pathway	Deubiquitination and stabilization
	/	Placental endothelial and pericyte cells	Promotes placental angiogenesis and embryonic survival	/
	HES1	Neural stem cells	Maintains stem cell pluripotency and inhibits neuronal differentiation	Stabilization (prolongs protein half-life)
	ADAM9	Trophoblast cells	Inhibits proliferation, migration and EMT in preeclampsia	Stabilization, leading to inhibition of Wnt/ β -catenin pathway
Tissue repair and regeneration	HIF-1 α	Vascular endothelial cells (from ADSCs)	Promotes angiogenesis and collagen synthesis for skin wound healing	Stabilization and promotion of nuclear translocation
	/	Intestinal epithelium	Enhances intestinal cell proliferation and tissue regeneration after I/R injury	/ (affects cell cycle progression)

USP22, ubiquitin-specific peptidase 22; SIRT1, silent mating-type information regulation 2 homologue 1; HES1, hairy and enhancer of split 1; ADAM9, a disintegrin and metalloprotease 9; HIF-1 α , hypoxia inducible factor 1 subunit alpha.

Table II. USP22 in damage and repair.

Functional category	Substrate	Cell/tissue	Reported function/outcome	Ubiquitination mechanism
Cell survival and apoptosis	HMGB1	Podocytes	Promotes apoptosis and inflammation in hypertensive nephropathy	Deubiquitination, preventing proteasomal degradation
	SIRT1	Pancreatic β -cells	Protects against apoptosis and ferroptosis; its degradation is induced in T2DM	Deubiquitination (its loss leads to SIRT1 degradation)
	β -catenin	Neurons (cerebral tissue)	Promotes neuronal survival by activating anti-apoptotic gene expression	Stabilization in the nucleus
	KDM3A	Cardiomyocytes	Alleviates cardiomyocyte apoptosis following I/R injury	Stabilization, leading to increased YAP1 transcription
Ferroptosis regulation	SIRT1	Cardiomyocytes	Inhibits ferroptosis by reducing p53-mediated repression of SLC7A11	Deubiquitination and stabilization
Autophagy and oxidative stress	PTEN	Neurons (cerebral tissue)	Promotes excessive autophagy and oxidative stress during cerebral I/R injury	Deubiquitination and stabilization

HMGB1, high mobility group box 1; SIRT1, silent mating-type information regulation 2 homologue 1; KDM3A, lysine-specific demethylase 3A; PTEN, phosphatase and tensin homolog; T2DM, type 2 diabetes mellitus; I/R, ischemia/reperfusion; SLC7A11, solute carrier family 7 member 11; YAP1, Yes-associated protein 1.

affect the overall morphology of the mouse small intestine or the number of Olfactomedin4-positive (Olfm4⁺) stem cells but rather causes changes in the abundance of specific differentiated cell populations (goblet cells and Paneth cells) (26). These findings indicate that USP22 primarily affects the differentiation stage rather than the size of the stem cell pool and that these changes are independent of H2B monoubiquitination (Table I; Fig. 1).

Currently, research on the regulation of stem cell function by USP22 remains notably inadequate. Hes1 is a key gene related to intestinal epithelial cell proliferation and differentiation and is highly expressed in stem cells and progenitor cells (43). However, the finding that USP22 expression knockdown does not affect the number of intestinal stem cells contradicts their regulatory relationship in NSCs. This discrepancy may be associated with differences in the basal

Table III. USP22 in inflammatory response and immune regulation.

Functional category	Substrate	Cell/tissue	Reported function/outcome	Ubiquitination mechanism
Inflammation and immune regulation	TRAF6	Corneal cells	Promotes pro-inflammatory cytokine expression in bacterial keratitis	Deubiquitination, inhibiting its proteasomal degradation to activate the NF- κ B pathway
	BRD4	Hepatocytes	Promotes inflammatory cytokine expression in alcohol-related liver disease	Deubiquitination and stabilization, exacerbating hepatic inflammation
	ATG5	Macrophages	Inhibits NLRP3 inflammasome activation by promoting autophagy	Deubiquitination and stabilization
	PU.1	Microglia	Suppresses M1 polarization and neuroinflammation by inhibiting the NLRP3 inflammasome pathway	Deubiquitination and stabilization
Antiviral immunity	KPNA2	Various (immune system)	Enhances antiviral defense by promoting IRF3 nuclear translocation	Deubiquitination and stabilization
	NP (SARS-CoV-2)	Various (immune system)	Promotes viral replication	Deubiquitination of viral nucleocapsid protein
Immune cell regulation	H2Bub1 (histone mark)	Hematopoietic system	Regulates systemic emergency hematopoiesis; its loss enhances innate immunity	Deubiquitination of histone H2B
	NFATc2	Jurkat T-cells	Augments IL-2 transcription	Deubiquitination and stabilization
	FOXP3	Regulatory T-cells (Tregs)	Maintains Treg stability and immune homeostasis	Deubiquitination and stabilization
	H2Aub1 (histone mark)	iNKT cells	Promotes iNKT cell development and maturation	Deubiquitination of histone H2A
	PD-L1	Various	Inhibits excessive CD8+ T-cell activation and immunopathology	Deubiquitination and stabilization

TRAF6, tumor necrosis factor receptor-associated factor 6; BRD4, bromodomain-containing protein 4; ATG5, autophagy-related 5; PU.1, proto-oncogene; KPNA2, karyopherin subunit alpha 2; NP, nucleocapsid protein; H2Bub1, Histone H2B monoubiquitination; NFATc2, nuclear factor of activated T cells 2; Foxp3, forkhead box P3; H2Aub1, Histone H2A monoubiquitination; PD-L1, programmed death-ligand 1; NLRP3, NLR family pyrin domain containing 3; IRF3, interferon regulatory factor 3; iNKT, innate invariant natural killer T.

expression of USP22 or Hes1 in different cell types; the underlying tissue-specific regulatory network crosstalk still requires further elucidation.

Skin wound healing. Cutaneous wounds secondary to traumatic injuries, thermal burns, surgical procedures and diabetic complications constitute common clinical entities (44). Mesenchymal stem cells derived from adipose tissue are referred to as adipose-derived stem cells (ADSCs) (45). Under hypoxic conditions, USP22 in ADSCs and their exosomes is transferred to vascular endothelial cells, where it directly interacts with and stabilizes hypoxia inducible factor 1 subunit alpha (HIF-1 α) protein, promoting its nuclear translocation to activate the downstream vascular endothelial growth factor A (VEGF-A)/vascular endothelial growth factor receptor 2 (VEGFR2) pathway (Fig. 1), thereby enhancing angiogenesis and collagen synthesis (46). This mechanism reveals a novel strategy targeting the USP22/HIF-1 α /VEGF axis for trauma

repair (47). Notably, investigating the relationship between the homeostatic maintenance of this process and scarring represents an intriguing research direction (Table I; Fig. 1).

3. Damage and repair

Cell death. The regulatory role of USP22 in cell death differs across organs: In renal podocytes, upregulated USP22 expression exacerbates apoptosis and inflammatory responses by interacting with SIRT1 or stabilizing high mobility group box 1 (HMGB1); whereas in pancreatic β -cells, downregulated USP22 expression triggers ubiquitin-mediated degradation of SIRT1, activating mitochondrial apoptosis and ferroptosis pathways.

Glomerular podocytes are indispensable for maintaining the structural and functional integrity of the glomerular filtration barrier (48). In high-glucose environments, Usp22 expression is spontaneously upregulated in podocytes, promoting podocyte

Table IV. USP22 in fibrosis, steatosis and tissue remodeling.

Functional category	Substrate	Cell/tissue	Reported function/outcome	Ubiquitination mechanism
Fibrosis and tissue remodeling	SIRT1	Glomerular Mesangial cells	Reduces ECM deposition and suppresses FN/TGF- β 1 production	Removes K48-linked ubiquitin chains to prevent proteasomal degradation
	Snail1	Renal tubular Epithelial cells	Promotes EMT and tubulointerstitial fibrosis	Deubiquitination and stabilization
	BRD4	Airway smooth Muscle cells	Drives ASMC proliferation and airway collagen deposition in asthma	Stabilization, leading to Hedgehog pathway activation
	HIF-1 α	Cardiomyocytes	Promotes cardiac hypertrophy and fibrosis	Deubiquitination and stabilization
	FoxM1	Endometrial Stromal cells	Promotes endometrial stromal cell decidualization	Deubiquitination and stabilization
Metabolic homeostasis	SIRT1	Hepatocytes	Maintains hepatic lipid metabolic homeostasis by activating fatty acid oxidation	Deubiquitination and stabilization
	SIRT1	Macrophages	Suppresses atherosclerosis progression by repressing foam cell formation	Deubiquitination (as part of the USP22/SIRT1 axis)

USP22, ubiquitin-specific peptidase 22; SIRT1, silent mating-type information regulation 2 homologue 1; Snail1, Snail Homolog 1; BRD4, bromodomain-containing protein 4; HIF-1 α , hypoxia inducible factor 1 subunit alpha; FoxM1, forkhead box protein M1; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; ASMC, airway smooth muscle cell.

depletion, whereas Usp22 expression knockdown protects podocytes from high-glucose induced injury (49). Resveratrol mitigates the progression of diabetic nephropathy by inhibiting USP22 expression, which may be associated with increased SIRT1 expression (27,50). Findings from another study (51) may help elucidate the underlying cause of this phenomenon: Under high-glucose conditions, embryonic lethal abnormal vision-like 1 (ELAVL1) binds to and stabilizes USP22 mRNA, thereby upregulating USP22 protein expression. USP22 subsequently inhibits the proteasomal degradation of acyl-CoA synthetase long-chain family member 4 (ACSL4) through deubiquitination. Excessive ACSL4 expression promotes intracellular lipid peroxidation in podocytes, ultimately triggering ferroptosis (51). HMGB1, a damage-associated molecular pattern, is sensed by Toll-like receptors (TLRs) (52). In patients with hypertensive nephropathy (HN), USP22 is significantly upregulated in podocytes, leading to HMGB1 deubiquitination, thereby inhibiting its proteasomal degradation. The accumulation of HMGB1 promotes apoptosis and inflammatory factor release and activates inflammatory pathways in renal tubular epithelial cells via the paracrine effect of podocytes, further inducing renal injury (53).

A previous study (53) clarified the pro-pathological role of USP22 in podocyte injury associated with high glucose-induced nephropathy and HN. However, USP22 exhibits substrate specificity in various renal injury models, making the subsequent targeted development of specific USP22 inhibitors feasible. These findings provide key directions for the precise targeting of USP22 in the prevention and treatment of podocyte injury-related nephropathy.

In the pancreas of patients with type 2 diabetes mellitus, inflammatory, senescent and oxidative stress processes may coexist (54). Given the weak antioxidant defense of pancreatic islet β -cells, chronic hyperglycemic exposure triggers oxidative stress-mediated β -cell dysfunction (55,56). Hyperglycemia-induced p38 mitogen-activated protein kinase (p38MAPK) hyperactivation in β -cells downregulates USP22 expression, promoting mitochondrial superoxide accumulation via the SIRT1/SIRT3/peroxiredoxin 3 (PRDX3) axis to elicit β cell apoptosis through NADPH oxidase (NOX)/c-Jun N-terminal kinase (JNK)/66 kDa src homology and collagen domain-containing protein (p66Shc) signalosome activation. The dipeptidyl peptidase-4 (DPP-4) inhibitor teneligliptin protects pancreatic islet β -cells by suppressing p38MAPK to upregulate USP22 expression (57). Additionally, lipid peroxidation induces ferroptosis (58) via miR-144-3p: This miRNA upregulates and targets the USP22 3' UTR, promoting SIRT1 proteasomal degradation to activate the ferroptotic pathway (59). Therefore, USP22/SIRT1 clearly serves a crucial roles in the functional maintenance and cell survival of pancreatic islet β -cells (Table II; Fig. 2).

These bidirectional effects in podocytes and β -cells, mediated by tissue-specific stress signals and USP22-mediated differential regulation of core targets, collectively highlight USP22's tissue-dependent function and the essential role of SIRT1 deubiquitination in cell survival.

Ischemia-reperfusion (I/R) injury. I/R injury constitutes an inevitable form of damage incurred during revascularization and is commonly encountered in clinical scenarios such

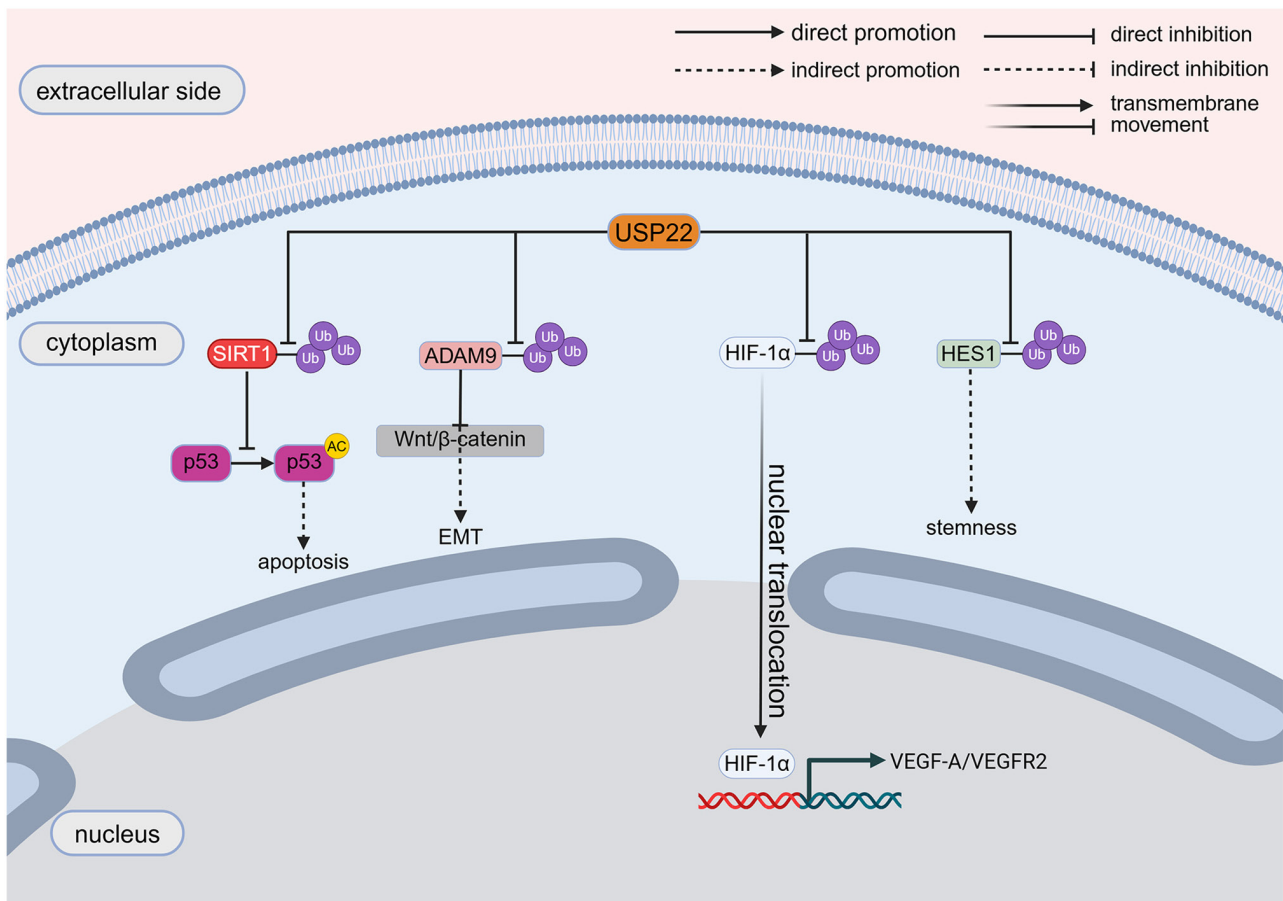


Figure 1. USP22-related signaling pathways in development and regeneration. USP22 stabilizes SIRT1, HIF-1 α , ADAM9 and HES1 through deubiquitination. SIRT1 inhibits p53 acetylation, thereby suppressing cell apoptosis; increased nuclear translocation of HIF-1 α promotes the transcription of VEGF-A/VEGFR2; ADAM9 inhibits the Wnt/ β -catenin pathway, thereby suppressing EMT; and HES1 maintains cell stemness. USP22, ubiquitin-specific peptidase 22; SIRT1, silent mating-type information regulation 2 homologue 1; HIF-1 α , hypoxia inducible factor 1 subunit alpha; ADAM9, a disintegrin and metalloprotease 9; HES1, hairy and enhancer of split 1; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; EMT, epithelial-mesenchymal transition.

as trauma, arterial thrombotic or embolic disorders, shock, major surgical procedures and organ transplantation (60-63). USP22 serves a pivotal regulatory role in I/R injury, mediating pathophysiology in cardiac, intestinal and cerebral tissues via distinct molecular mechanisms. Its dysregulated expression and function are intimately linked to cell death and cell cycle control, positioning it as a potential therapeutic target for ischemic diseases.

Myocardial I/R (MI/R) injury is a critical determinant of postinfarction complications (64), involving core mechanisms such as ferroptosis, oxidative stress and apoptosis (65-67). USP22 deubiquitinates and stabilizes SIRT1, reducing p53 protein expression and acetylation levels to relieve the transcriptional repression of solute carrier family 7 member 11 (SLC7A11), thereby decreasing iron-dependent lipid peroxidation and cardiomyocyte ferroptosis (68). Additionally, sevoflurane postconditioning upregulates USP22 expression to stabilize lysine-specific demethylase 3A (KDM3A), reducing H3K9me2 methylation at the Yes-associated protein 1 (YAP1) promoter to promote YAP1 transcription, thus mitigating cardiomyocyte apoptosis and improving cardiac function (69). These studies reveal that USP22 serves dual protective roles in MI/R injury by regulating the SIRT1/p53/SLC7A11 and KDM3A/YAP1 axes (70,71).

Intestinal I/R lesions are mechanisms that maintain a number of diseases and are early factors in systemic inflammatory response systems, in clinical practice dysfunction syndromes of various organs are associated with high mortality rates (72-74). During the 0-24 h post-I/R period, USP22 expression reaches a nadir at 6 h and is positively associated with the G₁-phase marker cyclin D1 and proliferation marker proliferating cell nuclear antigen (PCNA). USP22 deletion impairs post-I/R cell proliferation, induced G₁ arrest and blocked S-phase entry, whereas USP22 overexpression reverse these phenotypes (20).

Acute ischemic stroke is a major health hazard that causes physical disability, cognitive impairment and even mortality and affects millions of individuals worldwide each year (75,76). However, the available treatment strategies for stroke are limited (77). Therefore, identifying potential brain protectors or initiating endogenous neuroprotective mechanisms against acute cerebral ischemia is highly important. The long non-coding (lnc)RNA KLF3-AS1 carried by bone marrow mesenchymal stem cell-derived exosomes (BMSC-exos) sponges microRNA (miR)-206 to upregulate USP22 mRNA expression. It subsequently stabilizes the SIRT1 protein via its deubiquitinating activity, alleviates cerebral I/R injury through the anti-inflammatory and antioxidant effects of

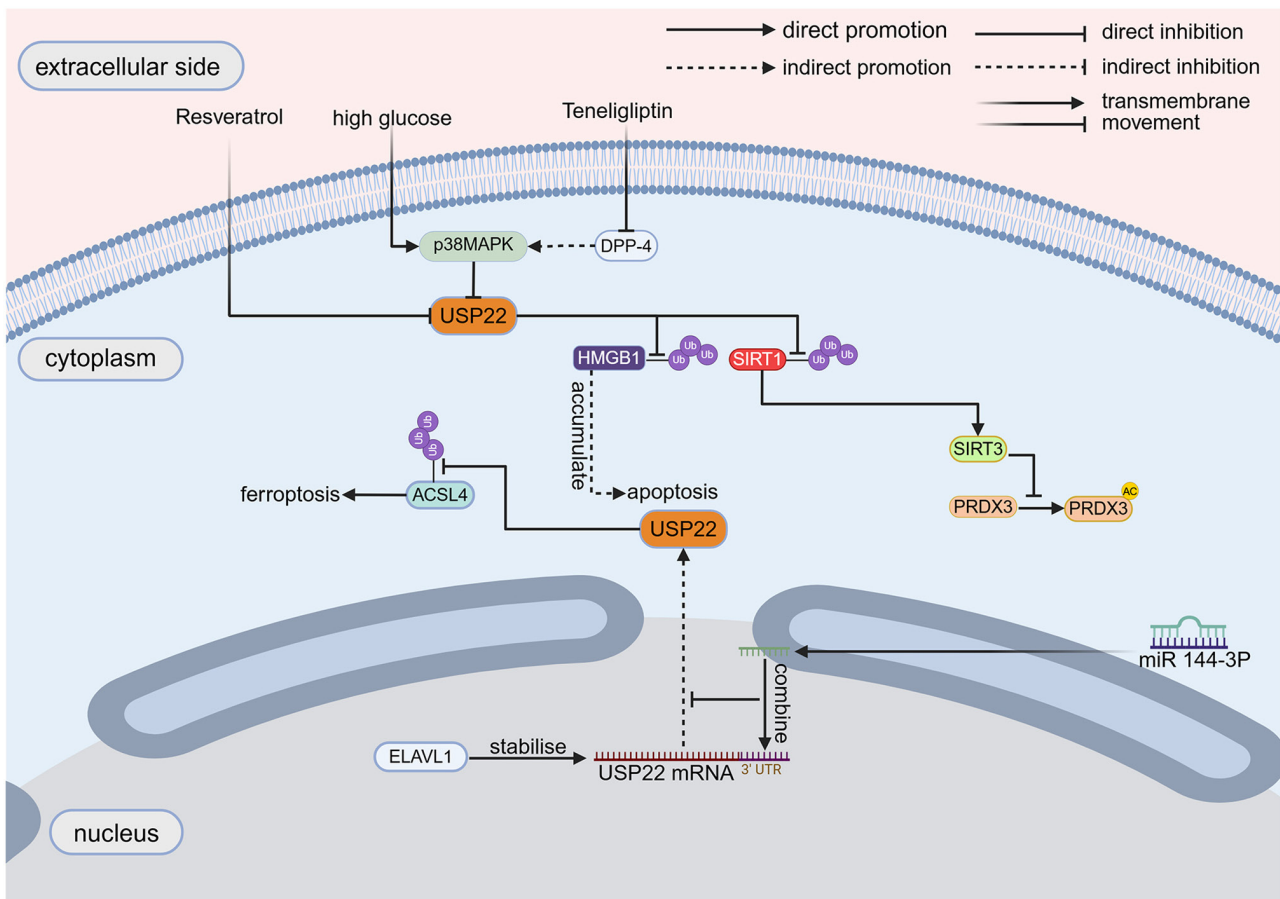


Figure 2. USP22 can deubiquitinate HMGB1 and SIRT1 proteins. Specifically, HMGB1 promotes cellular apoptosis. Under high-glucose conditions, p38MAPK can inhibit USP22 and induce cellular apoptosis via the SIRT1/SIRT3/PRDX3 pathway, while the DPP-4 inhibitor Teneligliptin can indirectly inhibit the activity of p38MAPK. miR-144-3p can target and bind to the 3' UTR of the USP22 gene, inhibiting USP22 protein expression and leading to the degradation of SIRT1 protein. Resveratrol can directly inhibit USP22 protein expression. ELAVL1 can promote USP22 protein expression by stabilizing USP22 mRNA and facilitate cellular ferroptosis by deubiquitinating ACSL4. USP22, ubiquitin-specific peptidase 22; HMGB1, high mobility group box 1; SIRT1, silent mating-type information regulation 2 homologue 1; p38MAPK, p38 mitogen-activated protein kinase; PRDX3, peroxiredoxin 3; DPP-4, dipeptidyl peptidase-4; miR, microRNA; ELAVL1, embryonic lethal abnormal vision-like 1; ACSL4, Acyl-CoA synthetase long chain family member 4.

SIRT1 and promotes neurological function recovery (78). In contrast to the aforementioned neuroprotective role of USP22 after I/R, USP22 is highly expressed in cerebral I/R injury. It stabilizes the phosphatase and tensin homolog (PTEN) protein through direct interaction and deubiquitination, inhibits the mTOR/TFEB pathway and promotes excessive autophagy and oxidative stress (79). The contradictory role of USP22 in cerebral I/R injury essentially reflects multidimensional-dependent functional heterogeneity; its function is not inherently determined but is jointly regulated by substrate specificity, cell type, ischemic time window, microenvironmental signals, expression level and subcellular localization (80). Briefly, during cerebral I/R injury, USP22 has distinct effects on microglia and neurons. This contradiction also suggests that USP22 is not merely a 'protective factor' or 'damaging factor' but rather a 'hub molecule in the signaling network' in cerebral I/R injury whose functional orientation depends on the dynamic needs of the pathological microenvironment.

Hypoxic postconditioning (HPC) is an endogenous neuroprotective strategy (81). It can stabilize nuclear β -catenin protein expression through two pathways: Reducing the nuclear localization of SKP1 and CUL1 (components of the SCF^{ndm2A} E3 ligase complex) and upregulating nuclear USP22

expression. Furthermore, it activates Wnt signaling pathway, promotes the expression of antiapoptotic genes such as Survivin and enhances neuronal survival (82) (Table II; Fig. 3).

4. Inflammatory response and immune regulation

Antiviral immunity. USP22 exerts paradoxical regulatory effects during viral infections, whose function depends on the specific viral type and the host cellular microenvironment. USP22 can regulate both type I IFNs and type III interferon (IFN- λ) expression, indicating that USP22 is a broad-spectrum antiviral regulator across interferon types (Fig. 3).

In antiviral immunity, USP22 stabilizes karyopherin subunit alpha 2 (KPNA2) to promote interferon regulatory factor 3 (IRF3) nuclear translocation, activating IFN- β and interferon-stimulated genes for antiviral defense (83). Conversely, in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, USP22 deubiquitinates nucleocapsid protein (NP) to increase viral replication. Sulbactam inhibits infection by downregulating USP22 expression and promoting ubiquitination-mediated degradation of NP (84). USP22 expression knockout in epithelial cells increases IFN- λ secretion and suppressing viral replication (85). Thus, USP22 may

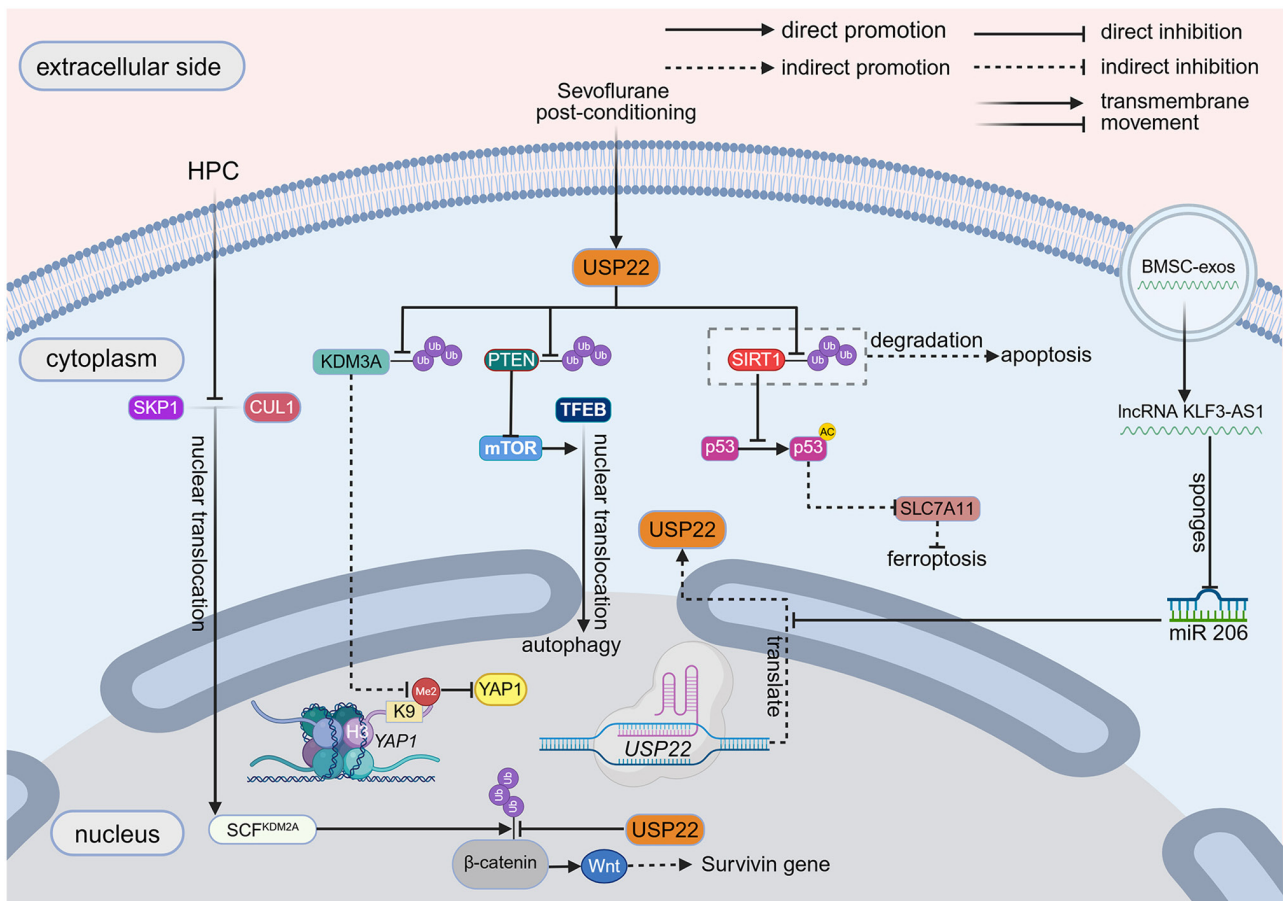


Figure 3. USP22 can deubiquitinate PTEN, SIRT1 and KDM3A proteins. Specifically, PTEN inhibits the mTOR/TFEB pathway; SIRT1 reduces the acetylation level of p53 protein and promotes SLC7A11 expression, thereby decreasing the occurrence of ferroptosis; KDM3A downregulates the level of H3K9me2 and promotes YAP1 transcription. Under high-glucose conditions, the lncRNA KLF3-AS1 carried by BMSC-exos upregulates USP22 expression at the transcriptional level by sponging miR-206. HPC can reduce the nuclear localization levels of SKP1 and CUL1, thereby decreasing the formation of the SCF^{KDM2A} E3 ubiquitin ligase complex; meanwhile, nuclear USP22 deubiquitinates β -catenin, activates the Wnt signaling pathway and promotes the expression of genes such as Survivin. USP22, ubiquitin-specific peptidase 22; PTEN, phosphatase and tensin homolog; SIRT1, silent mating-type information regulation 2 homologue 1; KDM3A, lysine-specific demethylase 3A; TFEB, transcription factor EB.

contribute to the replication of certain viruses and serve as a key node in the regulation of mucosal immunity regulation (Table III; Fig. 4).

Bacterial infection. In various disease models such as sepsis-induced myocardial dysfunction, sepsis and keratitis, USP22 performs dual regulatory functions and promotes inflammatory responses under specific pathological conditions. Its specific role depends on various factors including the cellular microenvironment, substrate protein interactions and pathogen types.

Sepsis-induced myocardial dysfunction (SIMD) is intimately linked to inflammation, oxidative stress and other pathological processes (86). During SIMD, the expression of the cardiac lncRNA, metastasis-associated lung adenocarcinoma transcript 1 increases significantly, promoting H3K27me3 methylation at the USP22 promoter via enhancer of zeste 2 polycomb repressive complex 2 subunit binding to repress USP22 expression. This exacerbates myocardial oxidative stress, increases proinflammatory cytokines expression, promotes apoptosis, reduces anti-inflammatory factors and worsens cardiac function (87). In sepsis models, USP22 deubiquitinates and stabilizes autophagy-related 5

(ATG5) to promote autophagosome formation, inhibit NLR family pyrin domain containing 3 (NLRP3) inflammasome activation and lead to lysosomal degradation, thereby regulating various inflammatory diseases (88). Notably, USP22 modulates NLRP3 expression via alternative mechanisms, such as indirectly regulating NLRP3 expression in microglia by inhibiting Spi-1 proto-oncogene during neuroinflammation (88-90). This discovery enables novel therapeutic strategies for NLRP3-associated diseases including gout, atherosclerosis, type 2 diabetes and Alzheimer's disease (88,91-93). USP22 suppresses inflammation not only by reducing inflammasome activation but also by inhibiting the stimulator of interferon response cGAMP interactor 1 (STING) pathway to decrease inflammatory cytokine expression (94). In intestinal epithelial cells, USP22 negatively regulates the STING pathway to suppress excessive IFN- λ activation and maintain epithelial immune homeostasis (85). Additionally, USP22 recruits ubiquitin-specific protease 13 (USP13) to remove K27-linked ubiquitin chains from STING, further inhibiting aberrant type I interferon activation and preventing excessive immunopathological damage (90,95). Collectively, these findings demonstrate the anti-inflammatory role of USP22.

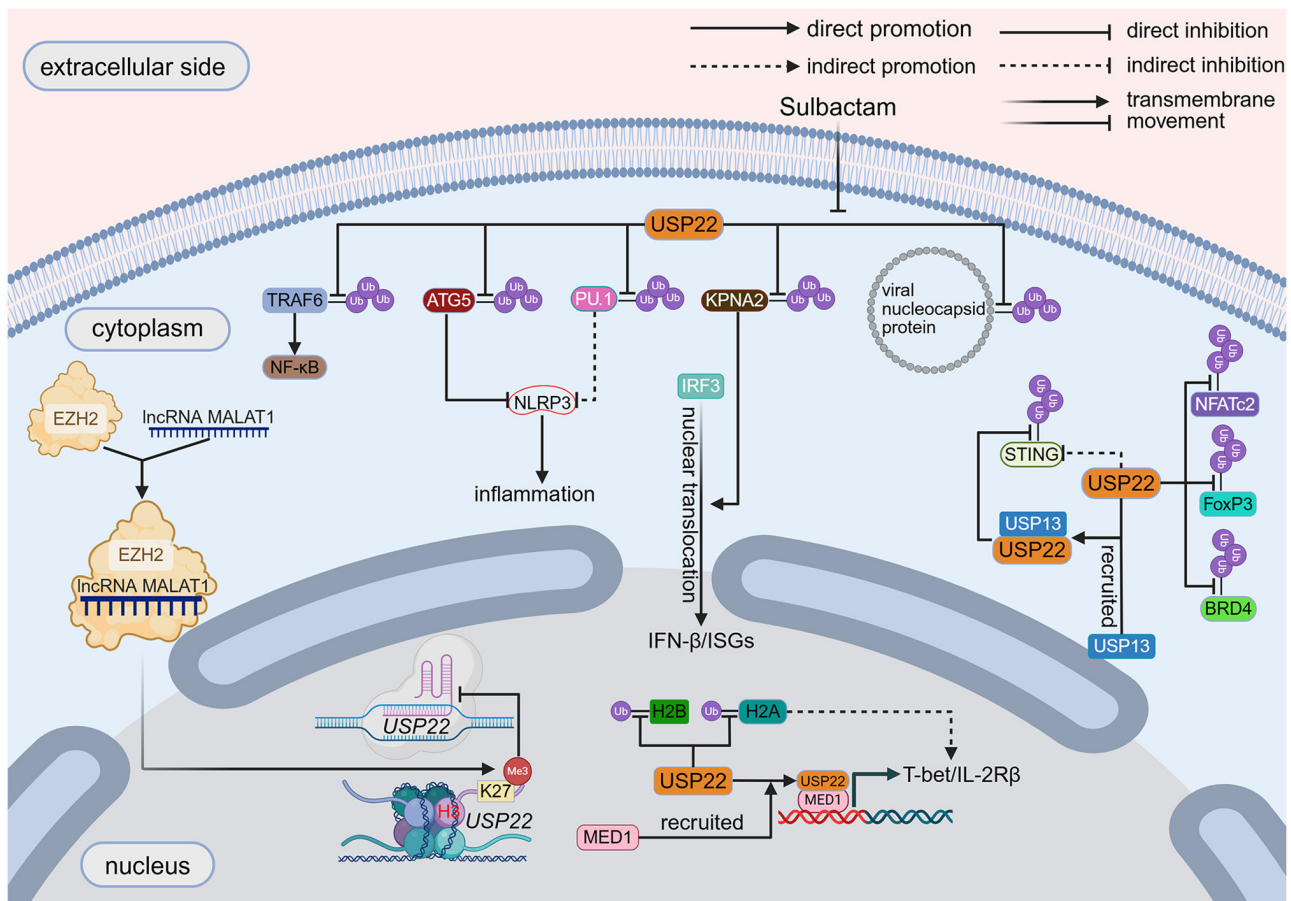


Figure 4. USP22-relevant signaling pathways in inflammatory response and immune regulation. USP22 deubiquitinates and stabilizes KPNA2, viral nucleocapsid protein (NP), ATG5, PU.1 and TRAF6. KPNA2 promotes the nuclear translocation of the transcription factor IRF3; the NP promotes viral replication, while the antibiotic sulbactam can downregulate USP22; ATG5 and PU.1 inhibit the activation of the NLRP3 inflammasome; TRAF6 activates the NF- κ B pathway. LncRNA MALAT1 binds to EZH2 to promote H3K27me3 modification in the USP22 promoter region, thereby inhibiting USP22 expression. USP22 negatively regulates the STING pathway and recruits USP13 to further remove the ubiquitin chain of STING. USP22 can promote the transcription of T-bet and IL-2R β either by removing the monoubiquitination modification of histone H2A or by binding to MED1. USP22 stabilizes BRD4, H2B, NFATc2 and FOXP3 through deubiquitination. USP22, ubiquitin-specific peptidase 22; KPNA2, karyopherin subunit alpha 2; NP, nucleocapsid protein; ATG5, autophagy-related 5; PU.1, proto-oncogene; TRAF6, tumor necrosis factor receptor-associated factor 6; IRF3, interferon regulatory factor 3; NLRP3, NLR family pyrin domain containing 3; NF- κ B, nuclear factor kappa B subunit 1; LncRNA, long non-coding RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; H3K27me3, trimethylation of histone H3 lysine 27; STING, stimulator of interferon response cGAMP interactor 1; IL-, interleukin; H2A, Histone H2A; MED1, mediator complex subunit 1; BRD4, bromodomain containing 4; NFATc2, nuclear factor of activated T cells 2; Foxp3, forkhead box P3.

In *Pseudomonas aeruginosa*-induced keratitis, USP22 deubiquitinates tumor necrosis factor receptor-associated factor 6 (TRAF6), inhibiting its proteasomal degradation to activate the nuclear factor kappa B subunit 1 pathway and promote the expression of proinflammatory cytokines (96). Alcohol-related liver disease (ALD), a common chronic liver disorder, is associated with alcohol intoxication as a major global cause of premature mortality (97,98). Elevated USP22 expression in liver tissues from patients with ALD deubiquitinates and stabilizes bromodomain containing 4 (BRD4), promoting inflammatory cytokine expression/secretion to exacerbate hepatic injury and inflammation (99). These findings demonstrate that USP22 also exerts proinflammatory effects in specific contexts (Table III; Fig. 4).

Existing studies have mentioned only influencing factors such as the cellular microenvironment and pathogen type, but none of these studies have clarified how upstream signals alter functional bias. Across various inflammatory models, it remains unknown why USP22 selects ATG5, STING,

TRAF6, or BRD4 as substrates as well as the nature of the underlying substrate competition mechanism and molecular switches.

Regulation of immune cells. USP22 serves multidimensional roles in immune cell regulation, dynamically modulating emergency hematopoiesis (100), microglial polarization (89), T cell function (110-117) and macrophage lipid metabolism (118-120) via epigenetic modification, signaling pathway activation and transcription factor stabilization. Its functional diversity, closely linked to cell-type-specific substrate interactions, offers potential therapeutic targets for immune-related diseases such as autoimmunity and atherosclerosis.

Emergency hematopoiesis, a crisis state of the immune system, serves two primary functions: i) Increasing blood cell production to compensate for massive losses during inflammation and infection (100) and ii) 'preactivating' immunity to facilitate faster clearance of infectious agents (101).

Pan-hematopoietic-specific knockout of *Usp22* expression increases H2Bub1 levels and activates the expression of inflammation-related genes, myeloid-associated transcription factors and mitochondrial respiratory genes to drive progenitor proliferation and differentiation. This manifests as systemic emergency hematopoiesis, significantly enhancing the innate immune capacity against *Listeria* infection (102).

Alzheimer's disease (AD) represents the foremost cause of neurodegenerative dementia on a global scale (103). Major depressive disorder is a primary cause of physical and mental disability globally and affects hundreds of millions of individuals (104). The two diseases are intricately linked to microglia, which, as the first line of immune defense in the central nervous system, elicit inflammation that is associated with neurodegenerative diseases and depressive-like behaviors (105). USP22 acts as a deubiquitinase for PU.1, positively regulating PU.1 stability (106) to promote microglial polarization towards the M2 phenotype (89), a process involved in AD-associated inflammatory responses (107,108). Similarly, USP22 can stabilize its downstream substrate KAT2A through K48-linked deubiquitination, thereby promoting microglial mitochondrial damage and oxidative stress and exacerbating central inflammation and depressive-like behaviors. A study identified the material basis underlying mental disorders, providing a supplementary theoretical foundation for the pharmacotherapy of mental illnesses (109).

USP22 exerts multifaceted functions in T cell regulation, with these activities only beginning to be characterized (110-114). In Jurkat T cells, USP22 directly associates with nuclear factor of activated T cells 2 (NFATc2) to sustain the protein, thereby augmenting the transcription of interleukin-2 (IL-2) (110). In regulatory T cells (Tregs), USP22 preserves immune homeostasis by maintaining forkhead box P3 (Foxp3) expression; Treg-specific USP22 knockout elicits autoimmune predisposition, whereas *Usp22* ablation alleviates Treg-mediated suppression of antitumor immunity (102,115). In innate invariant natural killer T (iNKT) cells, USP22 drives T-bet/IL-2R β expression and iNKT maturation through H2A deubiquitination or interaction with coactivator mediator complex subunit 1 (116). Furthermore, USP22 sustains PD-L1 expression to curb excessive CD8 $^{+}$ T cell activation; and USP22 deficiency exacerbates T cell-mediated immunopathological injury (117).

Macrophage internalization of oxidized low-density lipoprotein to form foam cells constitutes a pathophysiological signature of atherosclerosis (118). In macrophages, the C1q/TNF-related protein 9-mediated USP22/SIRT1 axis hinders atherosclerotic advancement by increasing autophagic flux, decreasing lipid deposition and repressing foam cell formation-related gene expression (119). USP22 is expressed at low levels in macrophages in atherosclerotic lesions. Its overexpression can deubiquitinate and stabilize PPAR γ protein and upregulate the expression of efferocytosis-related molecules, thereby inhibiting foam cell formation and improving plaque stability. Conversely, the application of USP22 inhibitors exacerbates the progression of atherosclerosis (120). These findings collectively suggest that USP22 may serve as a potential therapeutic target for the treatment of atherosclerosis (Table III; Fig. 4).

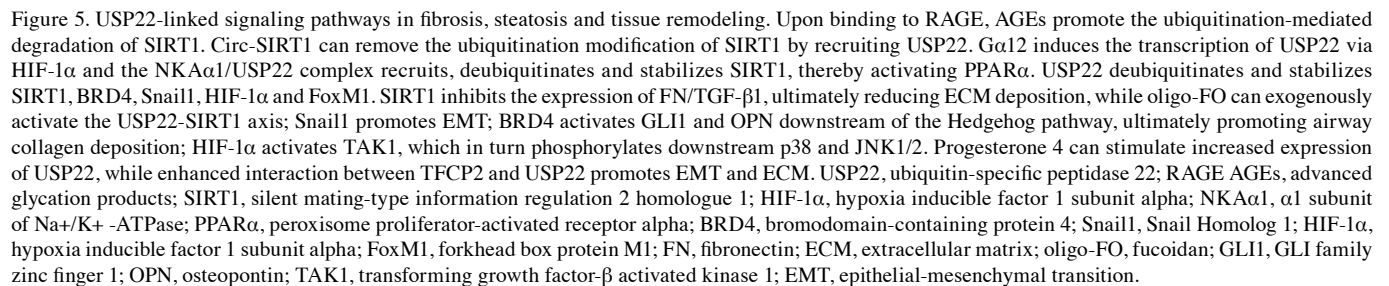
5. Fibrosis, steatosis and tissue remodeling

Fibrosis. USP22 serves pivotal regulatory roles in various fibrotic disorders. In patients with diabetic kidney disease (DKD) and HN, it contributes to renal fibrogenesis via distinct mechanisms, including the inhibition of glomerular mesangial fibrosis (121,122) and the promotion of tubulointerstitial fibrosis (123) and podocyte apoptosis (53,106). In patients with pneumoconiosis, USP22 facilitates EMT and extracellular matrix (ECM) deposition (Fig. 4). These insights offer potential therapeutic targets for treating fibrotic diseases (124).

DKD, a major microvascular complication of diabetes, is a leading cause of end-stage renal disease (125). In glomerular mesangial cells, advanced glycation products (AGEs) promote SIRT1 degradation via the ubiquitin-proteasome pathway, whereas USP22 specifically removes K48-linked ubiquitin chains from SIRT1 to stabilize its expression, suppress fibronectin (FN)/TGF- β 1 production and reduce ECM deposition (50,121,122). Similarly, low-molecular-weight fucoidan blocks AGE/RAGE pathway-induced ECM accumulation by activating the USP22/SIRT1 axis, significantly ameliorating renal fibrosis in diabetic conditions (121,126,127).

EMT serves a critical role in promoting pulmonary fibrosis in patients with pneumoconiosis and tubulointerstitial fibrosis related to DKD (123,124,128). Pneumoconiosis, which has been identified as a major global public health threat, is caused by prolonged inhalation of mineral dust leading to extensive pulmonary fibrosis (124,129). Integrated analysis of radiomics and transcriptomics revealed that high expression of transcription factor CP2 (TFCP2) is positively associated with pulmonary fibrosis severity. Following mineral dust inhalation, enhanced TFCP2/USP22 interaction in lung epithelial cells activates the PI3K/AKT signaling pathway, thereby promoting EMT and ECM deposition (124). As a key EMT transcription factor, Snail Homolog 1 (Snail1) is deubiquitinated and stabilized by USP22 in renal tubular epithelial cells, driving their transition to mesenchymal cells and the gradual replacement of normal tubules and/or the surrounding matrix by matrix proteins (123,130,131). Quercetin ameliorates the pathological process of tubulointerstitial fibrosis by reducing USP22-Snail1 binding and abolishing the deubiquitination-mediated stabilization of Snail1 (132). In patients with HN, the accumulation of paracrine HMGB1 in podocytes induces fibrotic marker expression in tubular epithelial cells, exacerbating renal interstitial inflammation and fibrosis (53) (Table IV; Fig. 5).

Hepatic steatosis. Nonalcoholic fatty liver disease (NAFLD), renamed metabolic fatty liver disease (MAFLD), has become the most common liver disease in the world (133,134). The activity of Na $^{+}$ /K $^{+}$ -ATPase (NKA), a classic ubiquitous ion pump (135), is significantly reduced and the expression of the NKA α 1 subunit is decreased in hepatocytes under hyperglycemic/hyperinsulinemia conditions (136,137). Decreased NKA activity in liver tissues of patients with NAFLD and HFD-fed mice diminishes the formation of membrane-associated NKA α 1/USP22 complexes, impairing the recruitment and deubiquitination-mediated stabilization of SIRT1 to disrupt fatty acid oxidation (FAO) (138). Ga12, a recently identified G12 family member of G protein α subunits, is widely expressed in the liver (139-141) and Ga12



Myocardial hypertrophy, a compensatory response of the heart to physiological or pathological pressure overload, can progress to heart failure (70,71,148). In the hypertrophic myocardium, Circ-SIRT1 expression is significantly downregulated. Overexpression of Circ-SIRT1 results in the recruitment of USP22 to remove ubiquitin modifications from SIRT1, stabilizing its protein level to promote autophagy and inhibit cardiomyocyte hypertrophy and cardiac remodeling (149). Paradoxically, USP22 protein expression is upregulated in myocardial hypertrophy. Upregulated USP22 stabilizes hypoxia-inducible factor 1 α , thereby activating transforming growth factor- β activated kinase 1 to phosphorylate downstream p38 and JNK1/2, promoting myocardial hypertrophy, fibrosis and dysfunction (150). These findings suggest that downregulated Circ-SIRT1 and upregulated USP22 expression may synergistically drive myocardial

hypertrophy, whereas Circ-SIRT1 overexpression counteracts USP22-mediated effects to inhibit hypertrophic phenotypes. Additional studies (151) have explained the upregulation of USP22 expression in cardiomyocytes following chronic heart failure: POZ/BTB and AT hook containing zinc finger 1 transcriptionally activate USP22 expression by binding to its promoter (151).

Human endometrial stromal cells (hESCs), which act as endometrial mesenchymal/stem cells, participate in monthly regeneration (152). Endometritis disrupts hESC function (153,154), leading to decidualization failure and an increased risk of early miscarriage (155). Decidualization, a prerequisite for blastocyst implantation and placental development (156,157), is regulated by ovarian hormones (158). USP22 influences the pathological progression of endometritis by modulating hESC inflammatory responses, ferroptosis and decidualization. Endometritis reduces USP22 expression in hESCs, whereas USP22 overexpression alleviates inflammation, suppresses ferroptosis and ameliorates decidualization failure (159). USP22 expression is significantly decreased in the endometrium of patients with recurrent implantation failure, accompanied by enhanced proteasomal degradation of forkhead box protein M1, leading to reduced endometrial receptivity (160). During early pregnancy and uterine decidualization, progesterone stimulates USP22 upregulation in mouse endometrial stromal cells, indicating that progesterone induces USP22 expression via the progesterone/progesterone receptor pathway to promote decidualization (161) (Table IV; Fig. 5).

6. Discussion

Molecular mechanisms of USP22 in disease regulation. As a core deubiquitinase in the SAGA complex, USP22 exerts pleiotropic regulatory effects through two major molecular mechanisms and serves as a key node in biological and pathological networks.

First, the USP22-SIRT1-centred regulatory axis has extensive pandisease relevance and acts as a core regulatory module across tissues and diseases. By deubiquitinating and stabilizing SIRT1, USP22 regulates diverse downstream signaling pathways in different physiological and pathological contexts to maintain cellular function and tissue homeostasis. In metabolism-related diseases, this axis regulates FAO and metabolic balance and functions as a common driver of metabolic syndrome-associated pathological processes. In patients with fibrotic diseases such as diabetic nephropathy, the USP22-SIRT1 axis inhibits the expression of fibrosis-related factors, reduces extracellular matrix deposition and exerts anti-fibrotic effects. In I/R injury of tissues such as the myocardium and brain, the axis protects cells through anti-inflammatory, antioxidative and antiapoptotic effects. Additionally, it is involved in physiological processes such as pancreatic β -cell survival and hepatic lipid metabolic homeostasis, with its dysfunction closely linked to the development and progression of various diseases. Systematic validation of the regulatory patterns of this axis in various disease cohorts is expected to establish it as a universal biomarker for metabolic disorders and oxidative stress-related diseases, laying the foundation for the development of cross-disease therapeutic agents.

Second, USP22 forms a microenvironment-specific regulatory network through dynamic interactions with diverse proteins and the core mechanism underlying its functional duality can be summarized as the crosstalk between substrate competition and its own posttranslational modifications. The functional tendency of USP22 is not fixed but is jointly shaped by its posttranslational modification status and the competitive binding of downstream substrates. This dynamic balance enables it to adapt to the signal requirements of different microenvironments, thereby exhibiting contrasting effects such as anti-inflammatory or proinflammatory effects and protective or damaging effects. Moreover, as a core component of the SAGA complex, the functions of USP22 are finely regulated by upstream signaling networks and its regulatory scope and precision are further expanded through crosstalk with key signaling pathways. Notably, USP22 can also target disease-specific substrates, which not only serve as key mediators of its functions but also act as molecular markers to distinguish different pathological states. This provides a basis for precise disease classification and addresses the lack of specific biomarkers for the clinical diagnosis of certain diseases.

7. Future directions and clinical prospects

The clinical translation of the functions of USP22 focuses on the precise expansion of drug development and the clinical implementation of diagnostic biomarkers and the exploration of more targeted translational pathways on the basis of existing research foundations. In terms of drug development, the combined application of drug repurposing has become a key direction: Combining DPP-4 inhibitors with inflammation-regulating inhibitors can synergistically regulate USP22-related axes in metabolic diseases, simultaneously improving metabolic disorders and inflammatory responses to enhance intervention efficacy. The optimization potential of natural products is worthy of exploration; enhancing the bioavailability of quercetin, oligofucoidan and other compounds through nanocarrier technology can provide new options for low-cost adjuvant therapy. To address the double-edged sword effect of USP22, a disease stage-subcellular localization dual-guided strategy can reduce off-target effects and combining this strategy with artificial intelligence-assisted design of substrate-specific inhibitors is expected to overcome the limitations of traditional drugs.

In the field of diagnostic biomarkers, USP22-substrate modules exhibit prominent clinical value: USP22-ADAM9 can distinguish preeclampsia from fetal growth restriction and USP22-Snail1 can assess the progression of renal fibrosis. Following validation in clinical cohorts, these modules are expected to be transformed into diagnostic or prognostic assessment tools. Single-cell spatial multiomics technology can further screen specific biomarker panels to improve diagnostic accuracy. Additionally, the potential value of USP22 in the intervention of aging-related diseases and the enhancement of stem cell transplantation efficacy has opened up new scenarios for its clinical application and future research should focus on exploring the translational feasibility of these directions.

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Availability of data and materials

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Authors' contributions

JNX and CYZ wrote the main manuscript text, YDZ consulted research materials and XX and SBL assisted with topic selection and guided writing. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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