Research progress on BTG2 in non-tumor diseases (Review)

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Abstract. The B-cell translocation gene 2 (BTG2), originally identified as a tumor suppressor, has been extensively studied in oncology research. However, its multifaceted functions in non-tumor diseases are still being recognized but not entirely understood. This review systematically synthesizes advances in the pivotal, context-dependent roles of BTG2 in non-tumor pathologies, including fibrotic, neurological, cardiovascular, inflammatory, metabolic and other systemic diseases. BTG2 is not merely a binary regulator but a context-sensitive molecular hub. Specific disease microenvironments, cell types and pathological stages contribute to its biological impact, whether protective or pathogenic. For instance, BTG2 promotes protective microglial activation in Alzheimer's disease while exacerbating neuronal death in acute spinal cord injury. Mechanistically, BTG2 influences cell fate decisions involving apoptosis, senescence, inflammation and metabolism by integrating signals from various pathways at the intersection of major regulatory networks, such as the neuro-immune-epigenetic axis and the metabolic-epigenetic-fibrosis network. It has emerged as a promising dual-purpose biomarker for disease diagnosis and prognosis, as well as a potential therapeutic target, owing to its dose-sensitive expression and regulatory position. However, because of its functional duality, therapeutic targeting necessitates precise, context-specific strategies. This review offers a novel, integrative perspective on BTG2 in non-tumor biology, underscoring its implication as a key regulatory node with extensive translational potential.

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Contents

1. Introduction

The B-cell translocation gene (BTG)/transducer of ERBB2 (TOB) protein family is a highly conserved group of regulatory proteins that consists of BTG1, BTG2/PC3/BTG anti-proliferation factor 2 (Tis21), BTG3/ANA, BTG4/PC3B, TOB1/TOB and TOB2 (1). The BTG domain, which consists of two distinctive subregions, Box A and Box B, is a highly conserved functional module shared by all members (2). These subregions mediate interactions with different transcriptional regulators and proteins involved in mRNA metabolism (3). The highly dynamic expression profile and precise molecular regulatory processes as an immediate early response gene make BTG2 distinctive within the BTG family. This establishes BTG2 as an essential quantitative threshold sensor for cellular stress responses and fate determination. Compared with other family members, BTG2 responds rapidly to DNA damage events, oncogene activation or growth signaling, facilitating quick intervention in cellular processes. At the molecular level, BTG2 only uses its conserved Box A and Box B domains to exert its non-catalytic adapter function. Based on upstream signal intensities, it competes stoichiometrically with the carbon catabolite repression 4-negative on TATA-less C-C motif chemokine receptor 4 (CCR4-NOT) deadenylation complex and protein arginine methyltransferase 1 (PRMT1) methyltransferase to mediate the quantitative redistribution of downstream mRNA stability and protein modification state. Because of its molecular design, BTG2 can coordinate binary destiny decisions between irreversible apoptosis and reversible cell cycle arrest by integrating stress magnitude and environmental cues in a manner comparable to an environmentally dependent resistor. BTG2 differs from other members of the family owing to its distinctive spatiotemporal sensitivity, signal

integration capacity and plasticity. Within this family, BTG2 is one of the most extensively studied and functionally diverse core members because of its impact on stress response, DNA damage repair, signaling pathways and cell cycle regulation. Its mechanisms of action and pathophysiological relevance extend beyond the scope of tumor suppression (4-8).

BTG2 belongs to the BTG/TOB antiproliferative protein family. The BTG2 gene is found on human chromosome 1q32 and encodes a protein containing 158 amino acids and a relative molecular mass of ~20 kDa (8). Its conserved BTG domain (9), which confers dual regulatory functions, is central to its basic molecular activity. First, by selectively attaching to the deadenylase CCR4-NOT transcription complex subunit 7 (CNOT7, also known as CAF1), a key linker protein in the mRNA degradation complex, it drives the deadenylation and degradation of target Mrna (10) and accelerates post-transcriptional regulation. Second, it accurately modifies the transcriptional activity of downstream genes as a transcriptional co-regulator by interacting with critical signaling molecules, such as p53 and Smad (11,12).

The core biological functions of BTG2 are primarily reflected as the braking and directing of cell fate through these processes. It triggers the cell cycle to enter G1 phase arrest (5,13), which compels cells to stop proliferating while initiating differentiation-related processes (14). Consequently, BTG2 is essential for suppressing aberrant proliferation, promoting cell differentiation and maintaining tissue homeostasis. These characteristics position BTG2 as a pivotal molecular hub that regulates development, stress responses and the advancement of non-neoplastic diseases while establishing it as a crucial tumor suppressor.

Research on BTG2 has traditionally focused on tumor biology (15-18) because of its central role in cell cycle arrest, cellular stress (19) and the DNA damage response (5,20,21), as well as BTG2 downregulation in various cancers and its evident tumor suppressor activity (22-25). However, the understanding of BTG2 is expanding. Research perspectives have steadily expanded from cancer to non-neoplastic disorders owing to advancements in genomics and the development of disease models. This former cell cycle gatekeeper has demonstrated surprising adaptability: BTG2 is expressed in organs, such as the spleen, thymus, lungs, stomach, large intestine and kidneys (26-28). Building upon our own previous research, BTG2 promotes podocyte injury in focal segmental glomerulosclerosis (FSGS) through a Smad3-dependent mechanism, including epithelial-mesenchymal transition (EMT) and fibrosis. The relationship between BTG2 and renal fibrosis is the subject of further investigation by the group. Furthermore, BTG2 is central to conditions such as fibrotic diseases (29), neurological diseases and cardiovascular disorders (30). Building on this, the present review extends its scope to explore the association between BTG2 and other fibrotic diseases. Non-oncological disorders are being investigated considering the earlier focus on oncology contexts. These results compel a reevaluation of the biological relevance of BTG2, suggesting that it may serve as a cellular homeostasis regulator implicated in pathophysiological events.

This review aimed to systematically summarize the research progress on BTG2 in non-neoplastic diseases, emphasizing its molecular mechanisms and pathophysiological importance in fibrotic diseases, neurological disorders and cardiovascular diseases. This systematic literature review further intended to explore the translational medical impact and potential therapeutic strategies targeting the BTG2 signaling network to offer comprehensive theoretical references and novel insights into related research fields.

2. BTG2 and fibrosis

By controlling the cell cycle, apoptosis and pathways such as TGF-β/Smad3 and phosphoinositide-3 kinase (PI3K)/protein kinase B (AKT), BTG2 contributes to organ fibrosis, particularly in the heart, kidneys and liver (31,32). Additionally, it influences the pathological progression of fibrosis by regulating fibroblast proliferation and extracellular matrix deposition (33).

Renal fibrosis. The impact of BTG2 in renal fibrosis depends on the cell type and specific mechanisms. Through a Smad3-dependent mechanism, BTG2 causes podocyte damage in FSGS, including EMT and fibrosis. Selective BTG2 knockout in podocytes significantly inhibits the expression of EMT markers (such as α-smooth muscle actin and vimentin) and restores the epithelial marker E-cadherin, preventing podocyte injury (34). Furthermore, single-cell sequencing has shown that EMT and fibrosis are strongly related to elevated BTG2 expression in proximal tubular cells in diabetic nephropathy (DN) models. By preventing differentiation into this phenotype, sodium glucose cotransporter 2 inhibitors (SGLT2i) can reduce the number of fibrogenic subpopulations and the proportion of BTG2-high-expressing cells, thereby suppressing EMT and fibrosis advancement. Thus, SGLT2i may improve tubular fibrosis by downregulating BTG2 and suppressing Smad3-dependent pathways, indicating that BTG2 may serve as both a pathogenic factor and an intervention target for renal fibrosis in DN (33). However, under high-glucose conditions, decreased BTG2 expression has been strongly related to enhanced EMT, aggravated renal fibrosis and increased podocyte apoptosis. Conversely, BTG2 overexpression can attenuate renal fibrosis by inhibiting mTOR complex 1 (mTORC1) signaling, increasing autophagy and suppressing EMT (35). Together, BTG2 is central to the occurrence and regulation of renal fibrosis, which necessitates further investigation into potential interventions. Renal fibrosis is the best example of this context-dependent functionality, which challenges any straightforward binary classification of BTG2 as either entirely protective or entirely pathogenic.

Myocardial fibrosis. Based on the condition, BTG2 plays varied roles in myocardial fibrosis. BTG2 exacerbates myocardial injury and fibrosis by triggering cardiomyocyte apoptosis and counteracting the protective effects of microRNA (miR)-21 under ischemic and hypoxic conditions (36). Furthermore, miR-25-5p promotes cardiac fibroblast activation and fibrosis by suppressing BTG2 and reducing superoxide dismutase 2 levels, thereby enhancing the expression of fibrosis-related genes (30). Collectively, BTG2 exhibits diverse biological roles depending on the pathological context. BTG2 often functions as a protective factor with anti-proliferative and antioxidant properties during chronic fibrosis or oxidative stress. By

contrast, BTG2 may exert pathogenic effects by promoting apoptosis and aggravating myocardial damage under acute ischemic and hypoxic conditions.

Furthermore, in myocardial fibrosis, non-coding RNAs, such as miR-21 and miR-125b-5p, exert anti-apoptotic and anti-fibrotic effects by directly targeting and inhibiting BTG2 (36,37). BTG2 contributes both to fibroblast activation and to the indirect regulation of tissue repair and fibrosis through the modulation of the immune microenvironment (e.g., macrophage polarization) or through metabolic homeostasis (38).

Oral submucous fibrosis. The transcription factor PU.1 directly targets BTG2, and PU.1 directly regulates its expression during oral submucous fibrosis (OSF) pathogenesis. Mechanistically, arecoline-induced metabolic reprogramming leads to lactylation of the transcription factor YY1 at the K183 residue. Lactylated YY1 enhances the expression and transcriptional activity of PU.1, promotes its binding to the BTG2 promoter and drives BTG2 upregulation. Increased BTG2 expression accelerates fibrosis by mediating fibroblast senescence and collagen accumulation. Specifically, BTG2 overexpression induces fibroblasts to exhibit a senescent phenotype (e.g., senescence-associated β-gal positivity), which is linked to cellular dysfunction and fibrosis. Additionally, BTG2 activation enhances collagen synthesis and deposition, which is a key contributor to the aberrant tissue structure that characterizes fibrosis. Notably, BTG2 expression is upregulated in the early stages of OSF, potentially serving as a defense mechanism to prevent excessive fibroblast activation. However, BTG2 expression becomes dysregulated under persistent metabolic stress and epigenetic alterations in the late stages, eventually exacerbating uncontrolled fibrosis (29).

Other fibrotic diseases. Besides the kidneys, heart and oral cavity, BTG2 may contribute to fibrotic diseases of other organs. BTG2 is a molecular marker for the advancement of liver fibrosis and has been positively correlated with disease severity (39,40). Additionally, it can be used to monitor the therapeutic response to agents, such as *Graptopetalum paraguayense*, in liver fibrosis (39).

No studies on pulmonary fibrosis have reported a direct correlation between BTG2 expression and disease occurrence or severity. The absence of functional validation studies likely reflects inadequate research rather than a definitive lack of biological relevance. Future studies using lung-specific genetic models and clinical cohort analyses are warranted to determine the functional implication of BTG2 in pulmonary fibrotic pathology.

In summary, BTG2 serves as a bidirectional regulatory factor that either promotes or inhibits fibrosis in different organs, cell types and stages of the illness. Its effect is based on upstream miRNA and transcription factor networks, as well as the metabolic and hypoxic microenvironment (Fig. 1). To achieve the optimal anti-fibrotic intervention effects while avoiding potential adverse effects, therapeutic strategies targeting BTG2 must consider the particular organs, cell types and disease stages. Additionally, they must implement a refined, temporally specific regulation of BTG2.

3. Neurological diseases

BTG2 has multifaceted functions in neurological diseases, and its functional consequences substantially depend on the cell type, pathological stimulus and disease stages.

Neurodegenerative diseases. In neurodegenerative diseases, BTG2 has major regulatory roles (41) and potential neuroprotective effects. BTG2 appears to contribute to microglia-mediated amyloid clearance in Alzheimer's disease (AD). Results from a study involving beta-secretase 1 (BACE1) deletion in 5xFAD mice suggested that BACE1 loss leads to the upregulation of several transient transcription factors, including BTG2, which is associated with microglial transition toward a phagocytic disease-associated microglia stage (DAM1) phenotype. The conditional deletion of Bace1 in microglia reduced the expression of DAM2 marker genes and decreased amyloid plaque burden, supporting the idea that BTG2 upregulation promotes protective microglial responses. Notably, both homeostatic microglia and DAM2 show low BTG2 levels; however, BTG2 is markedly upregulated during the homeostatic-to-DAM1 transition, corroborating its role as a transitional activation marker related to reduced amyloid pathology (42). Furthermore, the miR-16-5p/BTG2 axis influences hippocampal neuronal function, autophagy and apoptosis (37). Thus, BTG2 may serve as a favorable marker for the activated status of protective microglia in AD. However, further mechanistic studies and validation in human samples are warranted before establishing it as a reliable diagnostic or therapeutic target. Likewise, BTG2 has been identified as a key neuroprotective gene in Huntington's disease and its genetic variant may affect the disease process through the same transcriptional regulatory mechanism (43).

Neurodevelopment and neural stem cell homeostasis. BTG2 is an important regulator of neurodevelopment and neural stem cell homeostasis. BTG2 precisely regulates the production of neuronal populations and the construction of neural circuits in the early phases of neurodevelopment by preventing neural stem cells from proliferating and promoting their differentiation into neurons (44). This function is mechanistically similar to the role of BTG2 in B-cell development, where it suppresses the expression of non-lineage genes and maintains lineage commitment (7). Thus, BTG2 may serve as a universal cell fate regulator with conserved functions across tissue development. The BTG2 gene is likely involved in regulating the typical and pathological development of neural stem cells and progenitor cells. Changes in BTG2 gene expression were observed in multiple brain regions associated with neuronal differentiation and projection after puberty in a study on valproic acid exposure (45).

Apart from regulating the proliferation and differentiation of neural stem cells, BTG2 influences the refining neuronal migration, synapse formation and synaptic function. For instance, BTG2 expression changes in zebrafish models have been associated with rhodamine B-induced neurodevelopmental abnormalities (46,47). Further mechanistic investigations suggest that BTG2 interacts with YTH N6-methyladenosine RNA binding protein F3 and regulates the mRNA stability of synapse-related genes (such as

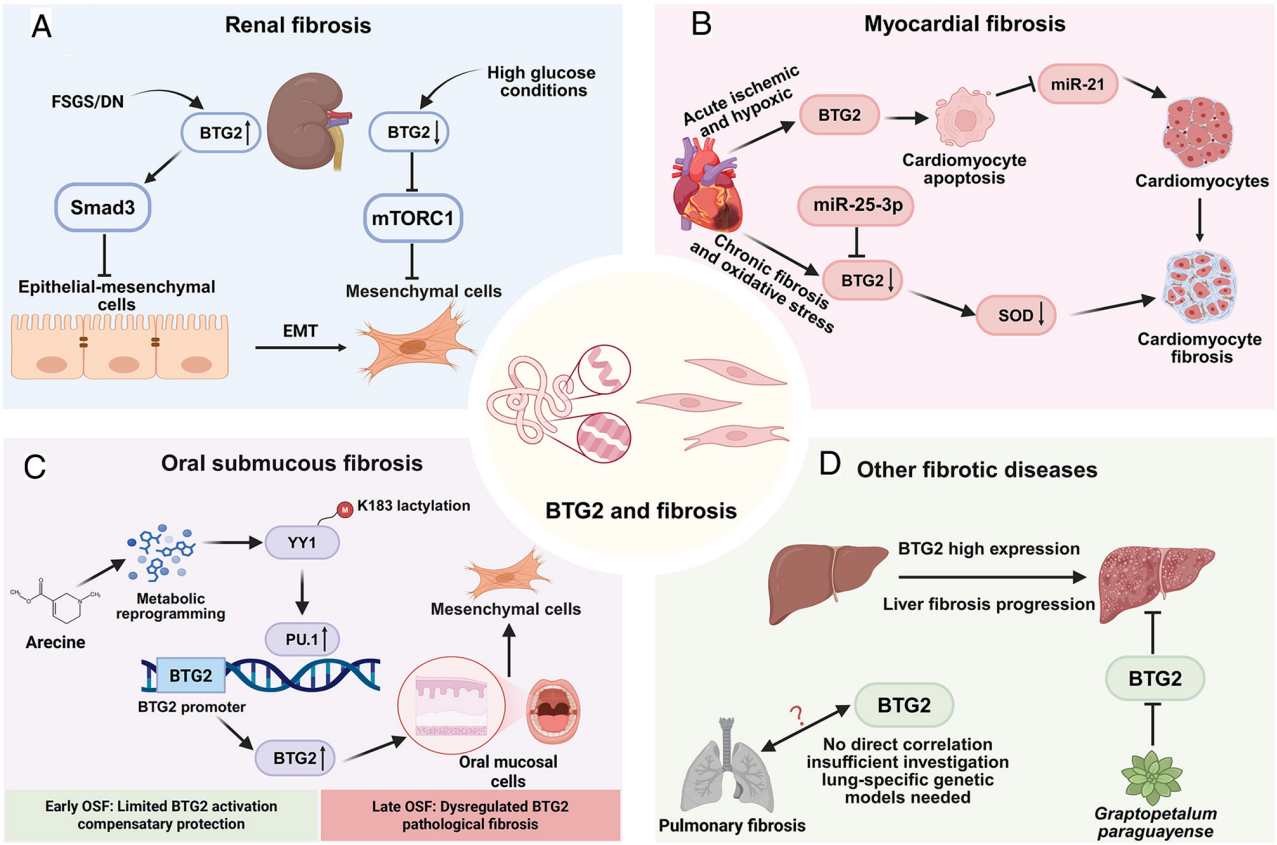

Figure 1. Regulatory mechanisms by which BTG2 influences various fibrotic diseases. This figure illustrates the mechanisms of action of BTG2 in four types of fibrotic diseases: (A) Renal fibrosis: BTG2 expression is upregulated in FSGS and DN. It activates the Smad3 pathway, promoting EMT and exacerbating renal fibrosis. However, BTG2 expression is downregulated under hyperglycemic conditions, which increases mTORC1 activity and similarly drives mesenchymal transition and the fibrotic process. (B) Myocardial fibrosis: BTG2 is upregulated during acute ischemic-hypoxic conditions and inhibits miR-21, inducing cardiomyocyte apoptosis. MiR-25-3p targets and suppresses BTG2 expression under chronic fibrosis and oxidative stress, thereby decreasing SOD activity and exacerbating oxidative damage. Finally, it triggers cardiomyocyte fibrosis. (C) OSF: Through metabolic reprogramming, arecine induces K183 lactylation of the YY1 protein, thereby activating PU.1 and upregulating BTG2 promoter activity, which increases BTG2 expression. In the early stages of OSF, limited BTG2 activation exerts a compensatory protective effect; however, in the late stages, BTG2 dysregulation drives the transdifferentiation of oral mucosal cells into mesenchymal cells, causing pathological fibrosis. (D) Other fibrotic diseases: In liver fibrosis, high BTG2 expression has been positively correlated with disease progression; *Graptopetalum paraguayense* extracts can alleviate liver fibrosis by inhibiting BTG2 expression. In pulmonary fibrosis, no direct evidence has correlated BTG2 with disease onset and progression; further research based on lung-specific genetic models is warranted. FSGS, focal segmental glomerulosclerosis; DN, diabetic nephropathy; SOD, superoxide dismutase; OSF, oral submucous fibrosis; miR, microRNA; EMT, epithelial-mesenchymal transition; mTORC1, mTOR complex 1; BTG2, B-cell translocation gene 2; OSF, oral submucous fibrosis.

cerebellin 1 precursor), thereby influencing synaptic structure and cognitive function (48).

Therefore, BTG2 regulates neurodevelopment through cell-autonomous mechanisms while influencing the establishment and maintenance of neural function through post-transcriptional regulatory pathways. Thus, BTG2 may serve as a key integrative factor in neurodevelopment. Dysregulated BTG2 expression or function may be strongly associated with neurodevelopmental disorders and related pathological processes.

Demyelinating diseases. BTG2 functions as a protective marker in multiple sclerosis (MS). It has been defined as a marker gene associated with microglial homeostasis and anti-proliferation, and BTG2 expression depends on p38α signaling. In the male experimental autoimmune encephalomyelitis (EAE) model, p38α loss caused the widespread downregulation of homeostatic genes, such as BTG2. This makes microglia more susceptible to transitioning from a homeostatic state to an inflammatory and disease-associated microglia state, which is accompanied by a clinical exacerbation of EAE (49). Thus, BTG2 expression must be maintained to preserve microglial homeostasis and limit neuroinflammation, and downregulated BTG2 serves as a negative prognostic marker of the loss of endogenous neuroprotective mechanisms. Notably, this protective role has been primarily reported in male EAE models, and the presence of sex-based differences in BTG2-mediated microglial regulation warrants further investigation.

Acute neuronal injury. In acute neuronal injury, BTG2 plays a complex and context-based dual role. BTG2 primarily exhibits negative effects in models of spinal cord injury and neonatal hypoxic-ischemic brain injury: The early growth response 1 (EGR1)/BTG2 axis is activated in spinal cord injury, and BTG2 serves as a downstream target of EGR1, which promotes neuronal apoptosis by upregulating the pro-apoptotic protein Bcl2-associated X protein (Bax) and enhancing caspase-3 cleavage (50). Similarly, BTG2 exacerbates neuronal death, cerebral infarction and neuroinflammation

in neonatal hypoxic-ischemic conditions through Bax pathway activation. By contrast, BTG2 inhibition improves neurobehavioral outcomes (51). Additionally, by activating the PI3K/AKT/NF-κB pathway, BTG2 drives microglial polarization toward a pro-inflammatory phenotype in T-2 toxin-induced neurotoxicity (52), which aggravates both neuroinflammation and injury (53). Changes in BTG2 expression have been associated with fentanyl exposure-induced neurotoxicity. Fentanyl exposure significantly changes neuronal development and plasticity in zebrafish embryos, primarily affecting the BTG2 gene. Specifically, exposure to 1 and 5 mg/l of fentanyl significantly upregulates the relative expression of the BTG2 gene. BTG2 serves as an important gene that regulates neural development in vertebrates. Therefore, upregulated BTG2 expression may reflect the potential neurotoxic effects of fentanyl exposure on neural development and activity (54).

However, BTG2 exerts neuroprotective effects in certain excitotoxicity models. For instance, BTG2 is significantly upregulated as a stress-response gene during glutamate excitotoxicity, which probably activates cellular repair and protective pathways to prevent damage. This highlights BTG2's protective role in transcriptional reprogramming (55). BTG2 has been identified as a vital co-regulated gene in spinal cord ischemia-reperfusion injury (SCII) and its expression has been strongly associated with SCII repair (56). This functional diversity suggests that the type of injury, cellular environment and the signaling pathways involved all significantly affect BTG2's function in acute neuronal injury. Exposure to chemicals, such as ethinyl estradiol and diethyl phthalate, can dysregulate BTG2 gene expression, and these genes serve as miRNA targets. Gene expression analysis showed BTG2 upregulation after exposure to certain substances (57).

In summary, BTG2 is a crucial regulatory molecule with pathway specificity and pathological context dependency rather than a uniformly protective or harmful factor in acute neuronal injury. Owing to its involvement in multiple processes, such as apoptosis, inflammation and stress responses, BTG2 is critical to understanding injury mechanisms and developing targeted therapy approaches. It is particularly promising for treatment that targets the EGR1/BTG2 axis, miRNA regulation or the modulation of microglial phenotypic switching.

Other neurological diseases. Aberrant BTG2 expression has been strongly associated with several other neurological disorders. BTG2 variants may play a protective role in diabetic neuropathy (58). One of the key upregulated genes, BTG2, may be involved in immune imbalance (59). BTG2 has been identified as a ferritin-related gene and is consistently increased in the brains of patients with epilepsy (18). By controlling antioxidant pathways, BTG2 may affect the course of amyotrophic lateral sclerosis (60). Although its precise role in T-cell immunity remains elusive (61), these strong associations underscore the importance of BTG2 in both the physiology and pathology of the nervous system.

Taken together, BTG2 plays a dual and context-dependent role in neurological disorders; it serves as a molecular switch that directs cellular responses toward either neuroprotection or pathological progression. BTG2 exerts anti-inflammatory and homeostatic effects in microglia, promoting protective phenotypic changes in conditions such as MS and AD. However, it can abnormally activate pro-inflammatory responses through the PI3K/AKT/NF-κB pathway upon exposure to specific toxic stressors. The degree of injury determines how BTG2 functions in neurons: Moderate stressors, such as excitotoxicity, trigger protective transcriptional reprogramming, whereas severe stressors, such as hypoxia-ischemia and spinal cord injury, cause its activity to shift toward pro-apoptotic pathways, such as the EGR1/BTG2/Bax axis. Mechanistically, the factors that 'switch on or off' BTG2's dual functionality operate at multiple regulatory levels. First, the type and strength of upstream activating signals determine the functional outcome: Under severe genotoxic or ischemic stress, p53-dependent activation strongly upregulates BTG2 and promotes pro-apoptotic signaling. By contrast, under sublethal stress or neurotrophic stimulation (e.g., bone-derived neurotrophic factor), NF-κB- or cAMP responsive element binding protein (CREB)-mediated moderate induction favors neuroprotective transcriptional programs. Second, post-translational modifications (PTMs) in the BTG2 protein form a regulatory 'PTM code' that refines its functional output. These modifications include the following: ERK-dependent phosphorylation, which affects its affinity for the CCR4-NOT deadenylase complex and its control over mRNA stability; PRMT1-mediated arginine methylation, which modifies its interaction with transcriptional co-regulators; and ubiquitin-proteasome-dependent degradation, which determines the duration of its activity. Third, BTG2 lacks intrinsic catalytic activity; therefore, its protein interaction network composition largely affects its context-based function: Association with PRMT1 or CCR4-NOT transcription complex subunit 7 (CNOT7) promotes neuroprotective outcomes, whereas excessive interaction with pro-apoptotic transcription factors, such as p53 or Smad, increases pathological signaling. Finally, this switch may be locked into a pathogenic state by the chronic inflammatory, oxidative and metabolic milieu that characterizes neurodegenerative diseases. Nonetheless, it can be reset toward a protective mode by neuroprotective therapies. Furthermore, machine learning approaches have highlighted BTG2 as a potential biomarker for ischemic stroke (62,63), further corroborating its pathological relevance. An increase in miR-146a can alleviate postoperative cognitive dysfunction by inhibiting BTG2 expression. Thus, BTG2 may influence the occurrence and development of postoperative cognitive dysfunction, and miR-146a negatively regulates its expression (64). Furthermore, BTG2 has been listed as one of the genes that affect learning and memory (65).

This functional duality likely results from different cellular conditions and signaling networks that selectively activate BTG2's downstream pathways. Future research should clarify the upstream mechanisms that regulate the 'switch-like' attribute of BTG2 and investigate methods to selectively improve its protective functions in specific pathological contexts by modulating downstream targets, such as p53, cyclin-dependent kinase (CDK) inhibitors or microglial phenotypes. Such studies have the potential to offer new directions for precision treatments in neurological conditions.

In summary, BTG2 serves as a multifunctional and highly accurate regulator in the nervous system. Cell type, pathological stage and molecular environment all have a significant impact on its contribution to disease development, protection, injury response and disease progression (Fig. 2). Because of

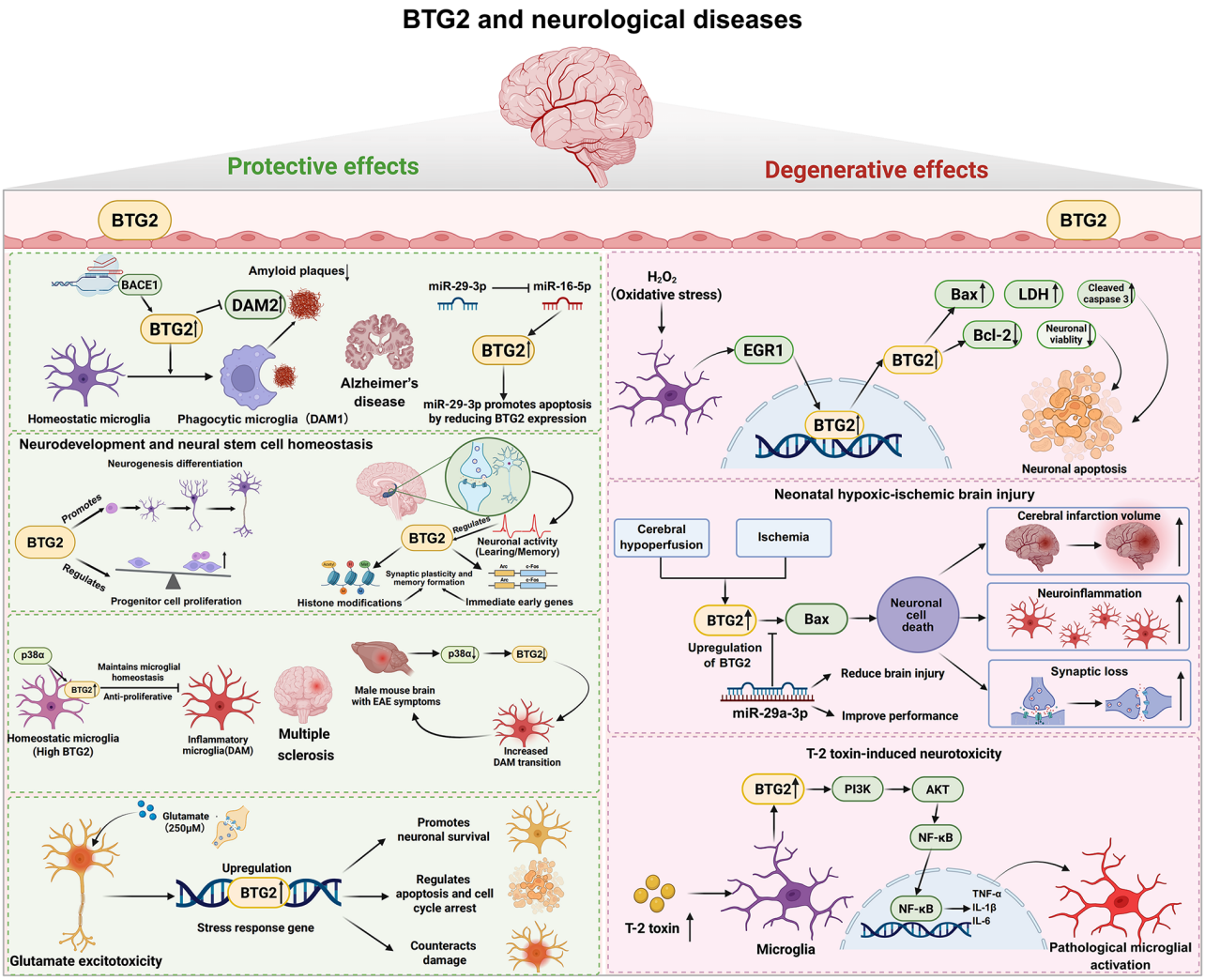

Figure 2. Dual role of BTG2 in neurological diseases. The dual role of BTG2 in the nervous system is categorized into neuroprotection and neurodegenerative changes. Left panel (protective effects): BTG2 protects against Alzheimer's disease; regulates neurodevelopment and neural stem cell homeostasis; and alleviates pathological damage in multiple sclerosis and glutamate excitotoxicity. Right panel (degenerative effects): BTG2 promotes neuronal apoptosis, worsens inflammatory responses and triggers synaptic loss under oxidative stress, ischemic/hypoxic brain injury and T-2 toxin-induced neurotoxicity. Overall, BTG2 modulates key pathways, including BACE1, DAM2, miR-29a-3p/miR-16-5p, EGR1, Bax/Bcl-2 and PI3K/AKT/NF-κB, thereby influencing neuronal survival, inflammation and functional outcomes. BTG2, B-cell translocation gene 2; BACE1, beta-secretase1; DAM1, disease-associated microglia 1; p38α APK, p38 alpha mitogen-activated protein kinase; LDH, lactate dehydrogenase; miR, microRNA; EGR1, early growth response 1; Bax, Bcl2-associated X protein; PI3K, phosphoinositide-3 kinase; AKT, protein kinase B; NF-κB, nuclear factor κ light chain enhancer of activated B cells.

its complexity and central position, BTG2 is a useful target for understanding neurobiological mechanisms and developing novel diagnostic and therapeutic approaches.

4. Cardiovascular diseases

BTG2 contributes to pathological processes in cardiovascular diseases, such as myocardial remodeling, heart failure, atherosclerosis (AS) and cardiomyocyte senescence. It regulates cardiomyocyte apoptosis, inflammatory responses, cell cycle control and vascular smooth muscle cell proliferation, thus affecting cardiovascular homeostasis and disease progression. Changes in BTG2 expression may serve as biomarkers for the prognosis and therapeutic response in these conditions.

Coronary artery disease (CAD) and AS. AS, which is characterized by lipid deposition, inflammatory reactions and vascular wall remodeling, is the core pathophysiological cause of cardiovascular disorders (66). BTG2 is central to the onset and progression of AS.

Researchers at the Drum Tower Hospital affiliated with Nanjing University Medical School (Nanjing, China) discovered a novel signaling pathway wherein chronic angina uses a neuro-immune-epigenetic axis to accelerate AS. Specifically, inflammatory monocytes in the blood and plaques are activated by chronic cardiac pain signals, which leads to elevated BTK protein expression. The SET domain containing 2, histone lysine methyltransferase (SETD2) protein is phosphorylated, histone H3K36me3 modification is strengthened and the transcription and expression of the C-X3-C motif chemokine receptor 1 (Cx3cr1) gene are upregulated. This gene mediates monocyte infiltration into the vascular wall and induces inflammation (67). BTG2 shows promise as a biomarker in CAD and regulates vascular pathological processes. At the cellular level, BTG2 has been associated with both the

osteogenic-like phenotypic switching of vascular smooth muscle cells and coronary artery calcification. In endothelial cells, pro-inflammatory factors induce BTG2 expression. By contrast, the von Hippel-Lindau (VHL) protein may influence endothelial inflammation by modulating BTG2 stability, thereby contributing to AS onset.

Heart injury. BTG2 upregulation adversely affects cardiac damage caused by myocardial infarction and chemotherapeutic drugs (doxorubicin) by promoting cardiomyocyte apoptosis and inflammation, which impairs cardiac function (68). Cardioprotective miRNAs (e.g., miR-322-5p, miR-21, miR-125b-5p and miR-186-5p) directly target and inhibit BTG2, thus alleviating myocardial damage and improving cardiac function (30,36,37,69,70). Patients with acute myocardial infarction show reduced circulating BTG2 levels (30,71), which recover after reperfusion. Therefore, it may serve as a prognostic indicator. Thus, BTG2 is a critical mediator in both ischemic and toxic myocardial injuries and serves as a core downstream target of cardioprotective miRNAs.

Cardiomyocyte proliferation and cardiac regeneration. Beyond its function in myocardial injury, BTG2 serves as a critical cell cycle inhibitor in cardiomyocytes that restricts the heart's ability to regenerate. Together with other cell cycle inhibitors, such as p21 and Meis homeobox 1 (Meis1), the transcription factor T-box transcription factor 20 directly represses BTG2 to promote cardiomyocyte proliferation and post-myocardial infarction cardiac repair (72). This finding positions BTG2 in the context of a broader network of proliferation barriers that should be overcome to achieve cardiac regeneration.

Genetic studies have demonstrated that the deletion or knockdown of Btg1 and BTG2 in neonatal hearts transiently increases the number of mitotic cardiomyocytes without long-term structural defects. Thus, Btg1/2 contribute to postnatal cardiomyocyte cell cycle arrest, and their loss can partially reactivate the proliferative capacity of cardiomyocytes during a developmental window in which regenerative potential still exists (73). Precise delivery to the myocardial injury site can be accomplished by administering a single tail vein injection of an AAV9 vector carrying a targeting short hairpin RNA expression cassette driven by a cardiac-specific promoter (such as cTnT) and targeting BTG2 (in combination with p21 and Meis1), its inherent myocardial affinity and the increased local vascular permeability after myocardial infarction. BTG2-targeted inhibition, either alone or in conjunction with other cell cycle regulators, may be a practical strategy for promoting endogenous cardiac regeneration after injury.

Cardiomyocyte senescence. BTG2 directly regulates cardiomyocyte senescence. The histone methyltransferase suppressor of variegation 39 homolog 2 (SUV39H2) delays cardiomyocyte senescence through the epigenetic downregulation of BTG2. Conversely, the loss of SUV39H2 increases BTG2 levels and accelerates senescence, whereas BTG2 knockdown can reverse this phenomenon (74). Thus, BTG2 drives the cardiomyocyte senescence program, and targeting it may help combat cardiac aging and associated dysfunction. Transient efficacy and potential off-target effects limit small interfering RNA-based knockdown approaches; Therefore, these findings should be interpreted cautiously and validated through complementary genetic approaches, such as CRISPR-based knockout models, in the future. BTG2 has been identified as a novel Myc target gene, which negatively affects myocardial hypertrophy. It inhibits myocardial hypertrophy by interacting with the Ccr4-Not enzyme-mediated deadenylation complex and suppresses cytoplasmic RNA levels (75).

Other cardiovascular diseases. BTG2 plays multifaceted roles in cardiovascular diseases (Fig. 3). Because of its capacity to control RNA metabolism in hypertrophic cardiomyopathy, BTG2 has an anti-hypertrophic impact in cardiac hypertrophy by inhibiting pathological growth (76). Additionally, clinical data highlight an association between BTG2 and the regulation of myocardial energy metabolism and hypertrophy. Furthermore, BTG2 is implicated in calcific aortic valve disease and myocardial ischemia-reperfusion injury (IRI), and pathways, such as the long non-coding RNA ZFAS1/miR-186-5p axis, regulate its expression (70,77). Notably, BTG2 plays a 'dual role' in cardiac diseases: In most injury models, BTG2 upregulation is detrimental but beneficial in preventing pathological hypertrophy. Therefore, therapeutic strategies targeting BTG2 necessitate precise design based on the disease context.

5. Inflammatory and autoimmune diseases

BTG2 is a crucial regulatory factor and biomarker for inflammatory, immune and metabolic diseases. It maintains T-cell quiescence by promoting mRNA deadenylation (78), thereby preventing autoimmune reactions. BTG2 expression and function depend on the disease context, and its strong correlation with pathological conditions in organs, such as the pancreas and bone, has established BTG2 as a core node in research on inflammatory disease diagnosis and immune regulation.

Acute pancreatitis (AP). BTG2 is a key downstream target of 3'-tRNA-derived fragment, threonine, anticodon AGT in the pathophysiology of AP and substantially contributes to pancreatic acinar intracellular trypsinogen activation mediated by this tRNA-derived fragment (79). Various stressors and physiological signals can rapidly induce BTG2 expression in pancreatic tissue. These stimuli include the following: DNA damage and genotoxic stress from ionizing radiation or chemotherapy, oxidative stress from reactive oxygen species accumulation and hypoxia/ischemia, endoplasmic reticulum stress owing to high-load synthesis of pancreatic enzymes or insulin; pro-inflammatory cytokine stimulation such as TNF-α and IL-1β during pancreatitis or islet inflammation, excessive sugar- or free fatty acid-induced metabolic lipotoxicity and glucotoxicity, and growth factor signaling (e.g., EGF) or mechanical trauma during acute pancreatic injury. Through p53-dependent or -independent signaling and NF-κB signaling, these stimuli quickly upregulate BTG2, which regulates cell cycle arrest, DNA repair and apoptosis. Specifically in AP, rapid BTG2 overexpression is driven by premature trypsinogen activation, acinar cell injury and the ensuing inflammatory cascade, underscoring its role as a critical stress-response gene. BTG2 is markedly overexpressed in pancreatic tissues during the acute phase and may regulate

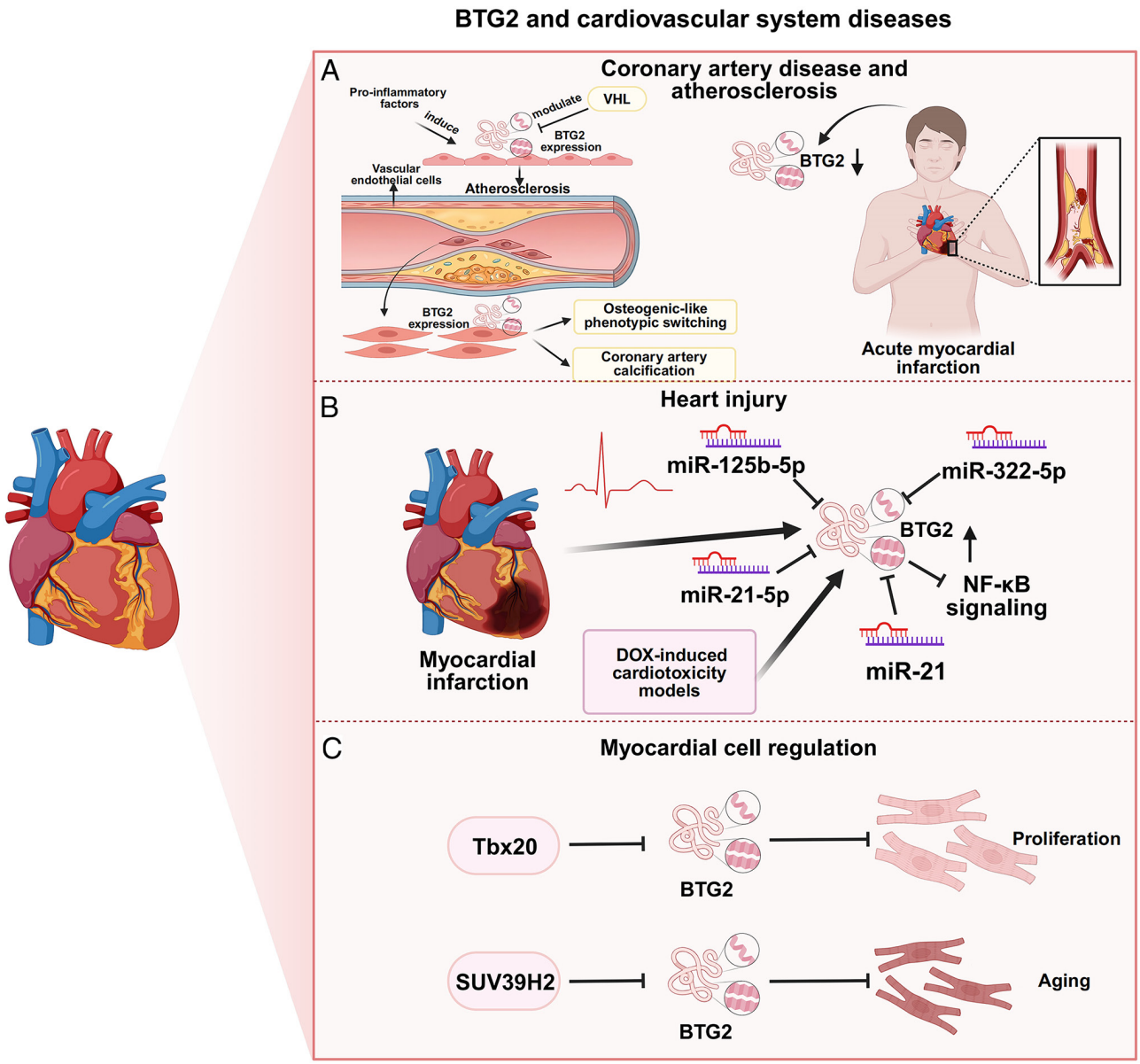

Figure 3. Mechanism of action of BTG2 in cardiovascular diseases. The regulatory role of BTG2 has been illustrated across three types of cardiovascular pathological processes. (A) Coronary artery disease and atherosclerosis: Atherosclerosis is triggered by pro-inflammatory factors that induce BTG2 expression in vascular endothelial cells, which is regulated by the VHL protein. BTG2 upregulation drives osteogenic-like phenotypic change in vascular smooth muscle cells, leading to coronary artery calcification. Additionally, patients with acute myocardial infarction have significantly low circulating BTG2 levels. (B) Heart injury: In myocardial infarction and DOX-induced cardiotoxicity models, miR-125b-5p, miR-21-5p and miR-21 regulate cardiac injury by specifically inhibiting BTG2 expression. miR-322-5p suppresses BTG2, whereas the NF-κB pathway negatively affects BTG2 expression. (C) Cardiomyocyte regulation: The transcription factor Tbx20 inhibits BTG2 expression, thereby promoting cardiomyocyte proliferation and restoring BTG2-mediated suppression of cardiomyocyte proliferation. Likewise, the histone methyltransferase SUV39H2 inhibits BTG2, thereby suppressing cardiomyocyte senescence. BTG2, B-cell translocation gene 2; miR, microRNA; DOX, doxorubicin; VHL, von Hippel-Lindau; Tbx20, T-box transcription factor 20; SUV39H2, suppressor of variegation 39 homolog 2.

cell death through potential anti-apoptotic activity. Thus, it serves as a crucial but poorly understood molecular link between early protease activation and subsequent cell injury repair. In AP, upregulated BTG2 expression aggravates tissue injury by promoting oxidative stress, exacerbating mitochondrial damage and inducing pancreatic acinar cell apoptosis. Elevated BTG2 levels have been directly correlated with disease severity (80). Notably, the pancreas exhibits a substantial upregulation of PC3/TIS21/BTG2 mRNA in response to inflammatory stressors, such as AP. Similar overexpression patterns are observed in the liver and kidneys. Both AP and renal SCII entail apoptosis, and PC3/TIS21/BTG2 has inherent anti-apoptotic activity. Therefore, it may be hypothesized that this protein plays a critical regulatory role in apoptosis within the pancreas, liver and kidneys (81). Collectively, BTG2 may serve as a downstream effector within inflammatory stress cascades, besides showing promise as a therapeutic target for acute inflammatory conditions, including AP (80,81).

Periodontitis. BTG2 shows significantly upregulated expression in the gingival tissues of patients with periodontitis, and its levels are positively correlated with disease severity (82).

BTG2, a direct target of miRNA-125a-5p, forms the miR-125a-5p/BTG2 regulatory axis, which may contribute to inflammatory responses and necroptosis via the MAPK pathway (83). Notably, BTG2 expression is strongly associated with immune cell infiltration (e.g., memory B cells and macrophages) and has been validated as a high-performance diagnostic biomarker (84) for periodontitis in multiple machine learning models [area under the curve (AUC) >0.95] (85). Analysis of the Gene Expression Omnibus database suggested that BTG2 serves as a key intermediate gene that links diabetic kidney disease (DKD) and periodontitis. BTG2 is a differentially expressed gene in both DKD and periodontitis. Compared with healthy conditions, patients with DKD show low BTG2 expression. In addition, it has been associated with proteinuria. Furthermore, decreased BTG2 expression has been related to podocyte migration and apoptosis. It may regulate autophagy by inhibiting the mTORC1 pathway, thereby suppressing EMT and influencing the interplay between periodontitis and DKD (35).

Osteoarthritis. Integrative bioinformatics and machine learning approaches have highlighted BTG2 as a diagnostic biomarker for osteoarthritis (86), which reflects its possible role in inflammatory joint degeneration (62,87,88).

BTG2 expression is markedly downregulated in the synovial tissues of patients with osteoarthritis. As a core node in the competitive endogenous RNA (ceRNA) network, it contributes to synovial inflammatory responses by regulating immune cell infiltration (e.g., activated dendritic cells, T cells and macrophages). Similar to its role in periodontitis, BTG2 has shown significant diagnostic value in osteoarthritis, where the diagnostic models based on BTG2 demonstrated high predictive accuracy (AUC values ranging from 0.902 to 0.942) (87).

In summary, BTG2 contributes to a complex regulatory network within inflammatory responses across inflammatory diseases through differential expression, participation in regulatory pathways (e.g., miRNA-mediated gene silencing and MAPK signaling) and modulation of the immune microenvironment. BTG2 offers a novel molecular foundation for disease diagnosis, prognosis evaluation and treatment target selection as a possible biomarker for inflammatory diseases. However, more thorough research and experimental validation are warranted to determine its mechanisms of action in different diseases.

Fungal infection. Research on *Candida* infections identified BTG2 as one of the potential hub genes (89). This finding aligns with growing evidence that BTG2 is central to the regulation of inflammatory processes across pathological conditions, possibly through the modulation of pro-inflammatory cytokine production, immune cell activation and the NF-κB pathway. Inflammation constitutes a central mechanism underlying host defense against *Candida* infections. Thus, the identification of BTG2 as a hub gene further underscores its potential relevance in inflammatory response during fungal pathogenesis. However, its specific role and mechanisms underlying this condition require further experimental validation.

Rheumatoid arthritis (RA). BTG2 expression is markedly elevated in the synovial tissue of patients with RA and correlates with the degree of inflammation. In experimental arthritis models, mice with myeloid cell-specific BTG2 deletion demonstrated more severe joint degeneration and higher levels of inflammatory cytokines (90), indicating that BTG2 offers protection against excessive inflammatory response.

Inflammatory bowel disease (IBD). IBD is a striking example of the pivotal role of BTG2 in immune homeostasis. BTG2 is a crucial regulator of intestinal barrier integrity and epithelial cell turnover, both of which are critical factors in the development of illness. It is highly expressed in intestinal epithelial cells. Because BTG2 regulates Wnt/β-catenin signaling, a master route that controls intestinal stem cell function and mucosal repair, its loss substantially increases susceptibility to dextran sulfate sodium-induced epithelial injury and severely compromises regenerative potential. Furthermore, BTG2 is essential for preserving T-regulatory cell (Treg) function and serves as a critical checkpoint that restricts unwarranted autoimmune activation by modulating Treg-mediated immunosuppression (91). Taken together, these findings suggest that BTG is a key, complex regulator of immune tolerance that connects epithelial defense mechanisms and adaptive immune regulation. This finding underscores BTG2's potential as a therapeutic target for immune-mediated disorders.

6. Metabolic diseases

Type 2 diabetes (T2D), hypertension, obesity, hypercholesterolemia and metabolic dysfunction-associated steatotic liver disease have been identified as a global health burden over the last 3 decades (92). Furthermore, BTG2 has been closely associated with metabolic diseases.

Diabetes and insulin resistance. BTG2 has a multifaceted, context-dependent and tissue-specific function in insulin homeostasis (93,94). In T2D, upregulated BTG2 expression is strongly associated with pancreatic β-cell stress and dysfunction. It modulates the pancreatic and duodenal homeobox 1 transcription factor, thus increasing insulin gene expression and secretion. Furthermore, it has been linked to the PI3K-AKT pathway. However, aberrant BTG2 expression in tissues, such as the liver, exacerbates insulin resistance and disrupts glucose homeostasis, potentially by activating gluconeogenesis in certain hepatic conditions. This increases blood glucose and decreases insulin tolerance (95). Conversely, in adipose tissue, decreased BTG2 expression has been associated with insulin resistance in obesity. BTG2 knockdown increases lipid accumulation, suggesting that it plays a protective role in preserving insulin sensitivity (96). Notably, its rs6682221 variant has a protective function and considerably lowers the risk of diabetic neuropathy in patients with T2D (58). Furthermore, BTG2 serves as a diagnostic biomarker for calcific aortic valve disease in these patients (77).

Obesity, wound healing and angiogenesis. BTG2 serves as a strong anti-obesity factor by inhibiting adipogenesis, promoting lipolysis and preserving β-cell function. In obesity, miRNAs (such as miR-222 and miR-146b) and the Stat3 pathway downregulate BTG2 expression in adipose tissue (96-98). This decrease weakens its protective effects, accelerating lipid

accumulation, adipose tissue growth and insulin resistance, all of which promote the transition from obesity to T2D. Critically, the islet β-cell decrease in this phase is regulated by the miR-146b/BTG2 axis. miR-146b suppresses BTG2, which promotes β-cell apoptosis and inhibits proliferation, whereas BTG2 overexpression reverses these effects (98). Restoring BTG2 expression with the use of Stat3 antagonists or miRNA inhibitors is a possible therapeutic strategy for obesity management (96). Apart from its core metabolic roles, BTG2 relieves obesity and diabetes-associated impairments in angiogenesis and wound healing. It promotes endothelial cell proliferation and migration, enhances mTOR signaling and enhances blood flow recover (99). The miR-409-3p/BTG2 axis serves as a key regulatory pathway that can restore angiogenic capacity in obese and diabetic models (99).

In summary, BTG2 is a crucial regulator at the nexus of metabolic and vascular health. Its tissue-specific and context-dependent actions, which range from β-cell protection (by preventing apoptosis and promoting proliferation) and insulin sensitivity modulation to anti-adipogenic and pro-angiogenic effects, highlight its dual potential as a biomarker and a therapeutic target for T2D, obesity and associated vascular complications.

7. Other system-specific diseases

Hepatic diseases. Apart from its function in liver fibrosis, BTG2 is widely expressed in the liver and contributes to various physiological and pathological processes (100). Under typical metabolic conditions, it influences hepatic defense against oxidative stress by activating the NFE2 like bZIP transcription factor 2 pathway (101). Additionally, it serves as a key component of the growth hormone pathway, working in tandem with YY1 and CREBH to promote hepatic gluconeogenesis and sustain glucose homeostasis (102,103).

However, BTG2 exerts context-dependent dual effects in liver injury. For example, BTG2 downregulation impairs hepatic defense in hookworm infection (40). Conversely, its upregulation during IRI may exacerbate tissue damage (104-106). Likewise, a study using on recombinant AAV-based liver-targeted gene knockdown models have demonstrated BTG2 expression in Kupffer cells, hepatocytes and endothelial cells. BTG2 upregulation during IRI has been associated with inflammatory responses and tissue injury (107). Notably, the liver-specific knockdown of BTG2 reduces its mRNA and protein levels by >50% and confers protection during injury. Similar pro-inflammatory or pro-apoptotic effects have been observed in drug-induced liver injury (DILI), partial hepatectomy and aging liver (108-110). BTG2 upregulation may cause damage by modulating the TNF-α pathway, affecting immune cell function, participating in DNA damage responses (111) or promoting apoptosis. Furthermore, changes in intracellular metabolism and gene expression, including changes in BTG2, may facilitate the co-induction of specific DILI through incompatible bavachin and icariin in the presence of TNF-α (109).

By contrast, elevated BTG2 expression protects macrophages in non-alcoholic fatty liver disease, exerting anti-inflammatory and antioxidant effects, thereby reducing lipid accumulation and inflammation (112).

In summary, BTG2 functions as a critical regulator of hepatic stress responses, metabolic homeostasis and injury repair. Its protective and detrimental effects largely depend on the pathological context.

Respiratory diseases. BTG2 exhibits differential expression patterns and complex regulatory functions in pulmonary diseases, which demonstrate its context-dependent function in lung pathologies.

BTG2 expression is upregulated in monocytes/macrophages in chronic obstructive pulmonary disease, which may promote pro-inflammatory reactions and contribute to disease progression, corroborating its potential as a biomarker (113). By contrast, the enhancer of zeste 2 polycomb repressive complex 2 subunit-forkhead box O3-miR-34b regulatory axis suppresses BTG2 expression in asthma, reducing BTG2 levels that promote inflammatory responses and disease development (114). BTG2 serves as one of three key exosome-associated biomarkers in obstructive sleep apnea (OSA), which has been associated with intermittent hypoxia and metabolic dysregulation. BTG2 expression is significantly decreased in patients with OSA, which correlates with immune-metabolic imbalance. Mechanistically, BTG2 regulates lipid metabolism by suppressing the STAT3 pathway and downregulating IL-6. Immune profiling further confirms a positive correlation between BTG2 expression and memory B cells and a negative correlation with CD56-bright natural killer cells. Furthermore, low BTG2 levels are related to a high risk of OSA (115).

Collectively, these findings support a 'hypoxia-exosome-immune' triad mechanism where BTG2 regulates immune-metabolic homeostasis. In summary, BTG2 plays a substantial but diverse role in pulmonary inflammatory diseases, and its functional direction and regulatory networks vary across conditions.

Renal diseases. BTG2 is strongly associated with the pathogenesis of renal diseases. It primarily affects immune regulation, cellular stress response and kidney development. With a high centrality score and major regulatory roles that are probably associated with immune pathways, BTG2 may function as a hub gene and a pivotal gene in multi-layer regulatory networks in DN. BTG2 shows promise as a therapeutic target that warrants further investigation, together with other hub genes, such as JUN, CDK inhibitor 1B, VEGFA, phosphatase and tensin homolog, EGFR, MYC and tumor protein 53 (116). Apart from DN, BTG2 has diverse roles in other renal pathologies. For instance, in patients undergoing hemodialysis, a p53-dependent mechanism induces BTG2 expression in skeletal muscles, which reflects cellular responses to DNA damage and oxidative stress from the uremic environment (117). Notably, this p53-BTG2 regulatory axis is not exclusive to hemodialysis. It represents a wider, evolutionarily conserved stress-response pathway that has been implicated in various conditions, including malignancies, neurodegenerative diseases, cardiovascular disorders and metabolic disease, where p53 activation (triggered by genotoxic, oxidative or metabolic stress) in turn induces BTG2 expression. Furthermore, BTG2 expression can be modulated through p53-independent mechanisms, such as TGF-β/Smad signaling, MAPK pathways and Sp1/Sp3 transcription factors,

highlighting the multifaceted signaling network that regulates BTG2 expression across tissues and diseases. BTG2 downregulation, likely regulated by miR-146a-5p, disrupts immune balance in idiopathic membranous nephropathy (118). In renal SCII, BTG2 serves as an NF-κB signaling-responsive gene and as a prognostic marker that mediates both inflammation and cellular stress. This role is critical in transplantation-related SCII, characterized by aberrant BTG2 activation in specific renal cell populations. This feature connects inflammatory signaling to cellular damage (119). Additionally, loss of BTG2 function - particularly in women - reduces nephron numbers and impairs salt-handling capacity in salt-sensitive renal injury, causing severe hypertension and proteinuria (120). Collectively, these findings emphasize the role of BTG2 in the pathophysiology of renal diseases, underscoring its potential as both a biomarker and a therapeutic target across renal conditions. BTG2 is among the four genes used to diagnose lupus nephritis (LN). However, BTG2 expression is high in the control group and significantly downregulated in the LN group. Further gene enrichment analysis highlights the role of BTG2 in biological processes, including phagocytosis regulation, viral infection defense, the activating transcription factor 6-mediated unfolded protein response, neuronal cell homeostasis maintenance and sodium ion transmembrane transport. Additionally, BTG2 is associated with the Toll-like receptor pathway. It has been hypothesized that upregulating BTG2 expression may inhibit the activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome, thereby delaying LN progression (121).

Reproductive system disease. BTG2 plays context-dependent roles in the reproductive system. Elevated BTG2 expression has been associated with diminished potential of oocyte development during *in vitro* fertilization/intracytoplasmic sperm injection in granulosa cells, particularly in women with high antiMüllerian hormone levels (122). It serves as a cell cycle inhibitor in ovarian cell cultures (123). Conversely, high BTG2 expression correlates with greater oocyte retrieval and blastocyst formation rates in endometriosis-related infertility, highlighting its potential as a predictive biomarker (124). Additionally, BTG2 has been implicated in the immune microenvironment of patients with obese polyendocrine metabolic ovarian syndrome, indicating its contribution to disease pathogenesis (125).

Musculoskeletal diseases. The BTG2 gene is central to both intervertebral disc degeneration (IDD) and musculoskeletal disorders. In IDD, BTG2 serves as a high-confidence biomarker that modulates extracellular matrix metabolism and immune responses, thus affecting degeneration (126). Hsa-miR-185-5p regulates BTG2 expression, which is downregulated in degenerated disc tissues (127). Additionally, BTG2 is involved in the ceRNA axis, such as the BTG2/hsa-miR-185-5p/SOCS3 network (126,127), thus serving as a therapeutic target. In musculoskeletal diseases, BTG2 has been associated with sarcopenia, skeletal muscle development, myoblast function and muscle aging. Furthermore, it serves as a diagnostic biomarker in sarcopenia, with elevated expression observed in cellular models. It influences disease progression by regulating muscle stem cell senescence (128). BTG2 has been identified as a critical gene for postnatal muscle growth in the Tianzhu white yak during skeletal muscle development and has functional correlations with genes, such as ankyrin repeat domain 2 (129). BTG2 overexpression suppresses myoblast proliferation while promoting differentiation, which is directly targeted by miR-103-3p (130). BTG2 is a possible treatment target in muscle aging because it induces muscle stem cell senescence, which has been associated with cumulative DNA damage (131). Collectively, BTG2 regulates essential cellular processes in the musculoskeletal system, influencing both disc integrity and muscle function. These processes include proliferation, differentiation, senescence and molecular signaling pathways. These roles underscore the potential of BTG2 as a biomarker and a therapeutic target for musculoskeletal conditions. BTG2 has been identified as one of the key genes that regulates immunity, inflammation and the cell cycle in a model of early-onset spinal curvature (EOS) combined with thoracic functional insufficiency syndrome (TIS) in pigs. Compared with the control group, the EOS + TIS model group demonstrated significantly downregulated BTG2 expression in lung tissue. Therefore, BTG2 may have a negative regulatory function in impaired lung development caused by EOS + TIS (132).

Other diseases. BTG2 has been strongly associated with DNA damage (133), oxidative stress and aging pathways. In a study on ocular disease, BTG2 is activated in the retina of lens-induced myopic guinea pigs, where it promotes DNA damage and apoptosis, resulting in retinal thinning. By contrast, miR-92b-3p exerts protective effects by targeting and suppressing BTG2 expression (134). Concurrently, BTG2 is regulated by both LINC01136 and hypoxia-inducible factor-1α under hypoxic conditions; it inhibits the proliferation of retinal microvascular endothelial cells, which affects neovascularization-related pathological processes (135). MiR-202-3p targets and regulates BTG2 in vascular calcification, thus accelerating calcification progression (136). BTG2 serves as a cell senescence-related gene and a diagnostic biomarker in abdominal aortic aneurysm (137). In urticaria, it contributes to miRNA-mediated post-transcriptional dysregulation and inflammatory signaling (138). In aging models, long interspersed nuclear element-1 RNA regulates BTG2 expression, which has been associated with a disruption of heterochromatin homeostasis (139). Thus, BTG2 is central to non-neoplastic pathological processes, such as DNA damage, aging and metabolic diseases, where it regulates cell cycle, stress responses and metabolic processes (Fig. 4). These findings offer novel directions for understanding the underlying mechanisms and targeted treatment of related conditions.

8. Discussion

Originally discovered as an antiproliferative gene (8), BTG2 is now recognized as a key regulator of cellular adaptability across a wide spectrum of non-tumor diseases. Over the last 10 years, BTG2 has been identified as a context-sensitive integrator of signals that regulate cell-cycle control, apoptosis, differentiation, inflammatory activation and tissue remodeling rather than only a downstream stress-responsive molecule (140,141). BTG2 deficiency affects various disease states. In the nervous system, BTG2 deficiency impairs hippocampus-based

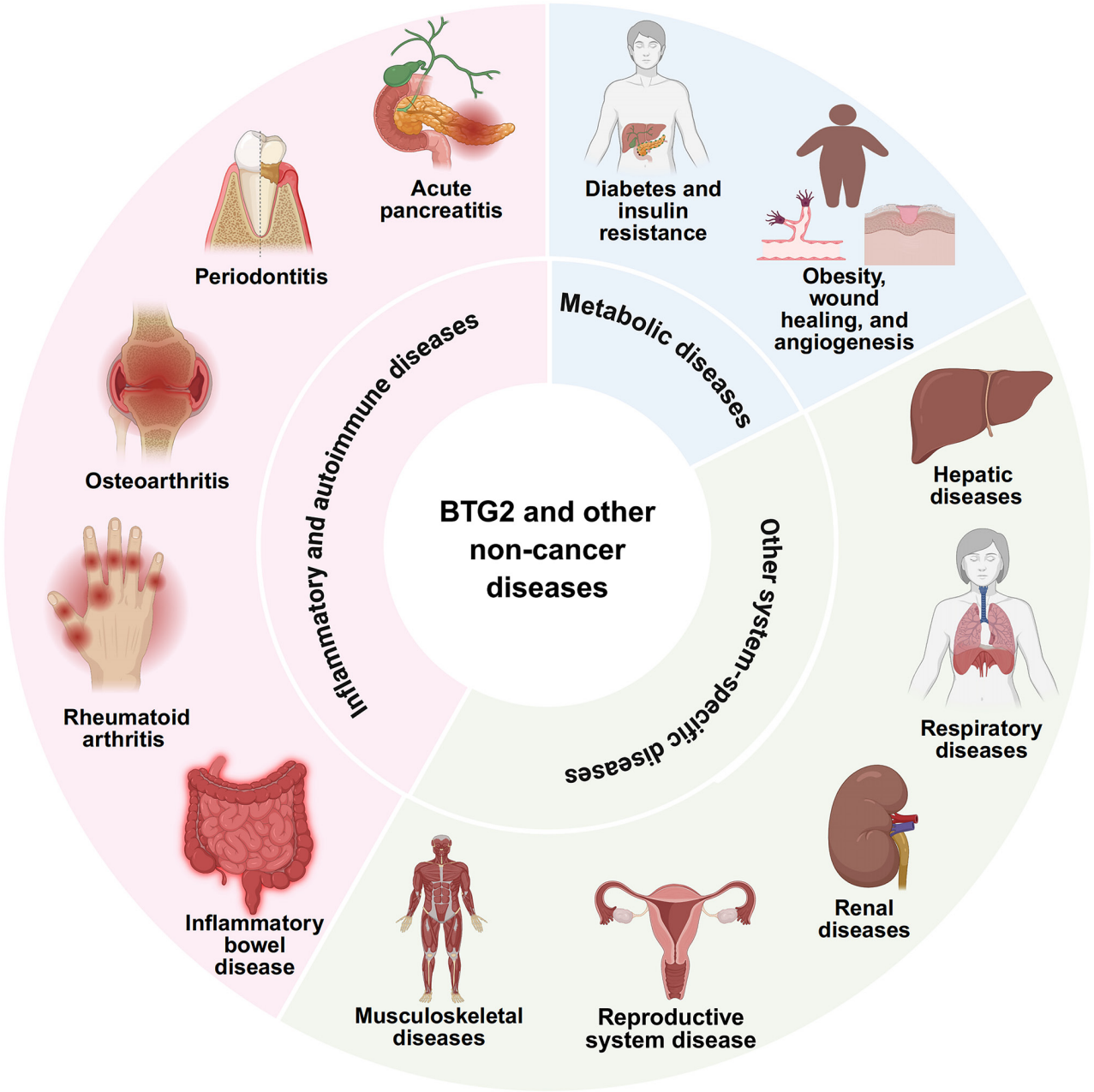

Figure 4. BTG2 and other non-cancer diseases. Non-neoplastic diseases involving BTG2 are categorized into three major groups: i) Inflammatory and autoimmune diseases, ii) metabolic diseases and iii) other system-specific diseases. Inflammatory and autoimmune diseases consist of acute pancreatitis, periodontitis, osteoarthritis, rheumatoid arthritis and inflammatory bowel disease. Metabolic diseases consist of diabetes and insulin resistance, obesity, as well as wound healing and angiogenesis. Other system-specific diseases consist of hepatic diseases, respiratory diseases, renal diseases, reproductive system diseases and musculoskeletal diseases. BTG2, B-cell translocation gene 2.

learning and memory and decreases neurogenesis, indicating its function in neurodevelopment and cognition (142). In terms of metabolism, knockout mice have a higher body weight and lower insulin sensitivity, whereas their fibroblasts proliferate more rapidly and are resistant to p53-dependent cell cycle arrest (14). Notably, podocyte-specific BTG2 deletion in the kidneys markedly attenuates glomerulosclerosis and inhibits EMT, suggesting its pro-fibrotic role (34). This finding is contrary to its regulatory role in oral submucous fibrosis reported in another study (29). Furthermore, BTG2-deficient mouse models with inflammatory injury display unwarranted inflammatory responses, confirming its negative regulatory role in inflammation resolution.

In contrast to other dual-function molecules, such as p53, NF-κB and TGF-β, BTG2 is unique because it is defined, in the context of signal transduction, as a non-catalytic, abundance-driven adapter node located at critical downstream signaling convergence sites. BTG2 functions solely through protein-protein interaction modules, whereas pleiotropic transcription factors, such as p53, NF-κB or TGF-β, decode upstream signals through intrinsic enzymatic activity or DNA-binding domains. Stoichiometric competition between several effectors, particularly the CNOT7/CCR4-NOT deadenylase complex and PRMT1 methyltransferase, controls its biological outputs by transforming graded upstream signals into a quantitative redistribution of molecular interactions.

Thus, to coordinate binary cell fate decisions, BTG2 serves as a quantitative threshold sensor that combines stress intensity and environmental inputs. The dynamic interactome equilibrium formed by the cellular milieu ultimately determines its functional outcome rather than an intrinsic catalytic switch.

One important insight from this review is that a fundamental protective (Table I)-vs.-pathogenic (Table II) paradigm is insufficient to entirely understand BTG2. The possible mechanisms underlying its context-dependent roles are as follows. First, BTG2 consists of inherently disordered non-coding regions, and non-coding RNAs have substantially varied expression profiles across diseases. Second, BTG2 lacks enzymatic activity and is completely dependent on its interacting proteins. Furthermore, BTG2's binding affinity may be impacted by its phosphorylation and methylation, and it might be challenging to highlight the precise sites of differential modification during diseases. Because BTG2 lacks enzymatic activity, it is forced to delegate all functional regulation to its non-coding regions. The complementarity of these two aspects yields a fine-tuned context dependency. Additionally, despite its primary localization in the nucleus, BTG2 can undergo nucleocytoplasmic shuttling under specific conditions. Post-translational modifications, such as phosphorylation and acetylation, as well as associated proteins, such as PRMT1, may regulate its subcellular distribution. Notably, BTG2 primarily functions as a nuclear transcriptional regulator, where it may regulate mRNA decay upon cytoplasmic translocation. This localization-based functional switch likely represents a mechanism underlying the pleiotropic roles of BTG2 across tissues and pathological contexts.

The biological consequences of BTG2 should therefore be interpreted as a context-dependent functional outcome (loss-of-function state) rather than as a direct reflection of its genomic sequence. No naturally occurring damaging BTG2 variants have been identified in human non-cancerous conditions. However, the knockout model demonstrated the importance of wild-type BTG2 for typical renal development and blood pressure regulation, and its function is strongly modulated by the developmental stage, cell type and sex. Therefore, the loss-of-function mutation is vital to clarify these context-dependent mechanisms, showing that the protective effects of BTG2 are not uniform. Instead, they vary based on the biological environment of BTG2. These findings provide a theoretical framework for understanding the impact of dysregulated wild-type BTG2 expression on disease susceptibility, rather than structural mutation.

Importantly, this seeming duality should not be regarded as a contradiction that weakens the relevance of BTG2; rather, it clarifies a profound principle of BTG2 biology. BTG2 dysregulation maintains its relevance for biomarker development and therapeutic investigation in most non-tumor disorders because it is functionally interpretable and directionally consistent. Determining the prevalent pattern of BTG2 dysregulation within a particular microenvironmental and temporal context is still crucial for precision medicine, even in circumstances with bidirectional effects. More generally, the potential that BTG2 exhibits dual-threshold or U-shaped functional activity implies that it may serve as a dose-sensitive homeostatic rheostat, with positive or negative outcomes arising when expression deviates from an optimal range.

Beyond this context dependence, this review promotes a more comprehensive conceptualization of BTG2 as a molecular hub located at the interface of multiple pathological systems. The BTG2-centered neuro-immune-epigenetic axis is a particularly compelling framework. Through the BTK-SETD2-H3K36me3-Cx3cr1 cascade, chronic cardiac nociceptive signaling activates inflammatory monocytes in AS. By contrast, VHL-dependent regulation of BTG2 stability modulates endothelial inflammatory responsiveness (143-145). Downstream of p38alpha signaling, BTG2 is a marker of microglial homeostasis in MS, and its decrease facilitates the change from a homeostatic to a disease-associated inflammatory state (49). By contrast, BTG2 upregulation during the transformation from homeostatic microglia to phagocytic DAM1 states is associated with attenuated amyloid pathology in AD (42). Taken together, BTG2 is not merely an immune activation marker but also a regulatory node that facilitates the functional coupling of neural cues, immune-state transitions and epigenetic remodeling. Therefore, BTG2 may help determine whether neuroimmune responses continue to be adaptive or shift toward chronic pathology.

The metabolic-epigenetic-fibrosis network is a second conceptual axis that emerged from this review. BTG2 appears to play a similar central role in this network. In OSF, arecoline-driven metabolic reprogramming induces YY1 lactylation at K183, which enhances PU.1 activity, promotes BTG2 upregulation, and drives fibroblast senescence and collagen deposition. This pathway serves as a striking example of how metabolic disruption can be transformed into epigenetic instructions, which are subsequently translated into fibrotic remodeling via BTG2. BTG2 plays a similar integrative role in metabolic disease, where it helps maintain hepatic glucose homeostasis by suppressing gluconeogenic enzymes through the action of histone deacetylase (100,146). Collectively, BTG2 functions as an active mediator through which metabolic and epigenetic disturbances yield long-lasting pathological consequences, rather than merely as a passive responder to metabolic stress.

Chronic sterile inflammation, extracellular matrix remodeling and fibrosis, oxidative stress and mitochondrial dysfunction, cellular senescence and senescence-associated secretory phenotype, vascular dysfunction and microcirculatory abnormalities, and shared signaling pathways (TGF-β, NLRP3, Wnt, Hippo and mTOR) are the possible features among fibrotic diseases, neurological disorders and cardiovascular diseases. These commonalities point to a potential vicious cycle model involving 'chronic stress-inflammation-remodeling'. However, further research is warranted to clarify the precise shared characteristics of these diseases and the regulatory roles of BTG2. This study investigated the bidirectional effects of BTG2 on fibrosis, the nervous system and the cardiovascular system. Further research is necessary to determine whether this could be attributed to the comparable pathogenic mechanisms among these diseases. BTG2 expression is frequently associated with disease progression and clinical outcome in the aforementioned conditions, underscoring its growing relevance as a mechanistic determinant and a translationally meaningful biomarker.

The function of BTG2 in maintaining immune and tissue homeostasis is a recurrent theme that unites these

Table I. The 'protective' function of BTG2 in non-tumor diseases.

Disease category	Specific disease/ situation	Key cell/tissue types	Protection mechanism-core function	Main regulatory pathway/axis	Biological effects and significance
Fibrotic disease	DN (partial model)	Kidney tissue	Overexpression can inhibit mTORC1, enhance autophagy and suppress EMT	mTORC1/ autophagy pathway	Reduces kidney fibrosis and protects kidney function (35)
	OSF (early stage)	Oral fibroblasts	Early upregulation may limit excessive fibroblast activation	Initial stress response	Delays the progression of fibrosis (29)
Nervous system disease	Alzheimer's disease	Microglia	As a DAM1 phenotypic transition marker, promotes amyloid protein clearance	BACE1 deficiency-related pathways	Reduces amyloid plaque burden and exerts neuroprotective effects (42)
	Multiple sclerosis	Microglia	Maintenance of microglial homeostasis and inhibition of inflammatory phenotype transformation	p38α MAPK pathway	Reduces neuroinflammation and slows disease progression (49)
	Glutamate excitotoxicity	Neuron	Stress-induced upregulation, activation of cellular protection and repair pathways	Stress response and transcriptional reprogramming	Counters excitotoxicity and promotes neuron survival (55)
Cardiovascular disease	Pathological myocardial hypertrophy	Cardiomyocyte	Inhibition of pathological growth, anti-hypertrophy	Related to RNA metabolism regulation	Prevention of pathological remodeling in heart failure (76)
Inflammatory/ autimmune diseases	RA	Myeloid cells	This deficiency leads to more severe joint damage and inflammation	Suppression of excessive inflammatory responses	Maintains joint immune homeostasis and protects bone tissue (90)
	IBD	Intestinal epithelial cells/ regulatory T cells	Maintenance of intestinal barrier function and enhancement of Treg suppressive capacity	Wnt/β-catenin pathway	Reduces intestinal inflammation and promotes epithelial repair (91)
Metabolic disease	T2D	Fat cells	Maintenance of insulin sensitivity and reduction of fat accumulation	Regulated by miR-146b and Stat3	Improves insulin resistance and combats obesity-related metabolic disorders (96-98)
	Obesity/diabetes and wound healing	Endothelial cells	Promotion of angiogenesis and improvement of blood flow	miR-409-3p/ BTG2 axis	Accelerates tissue repair and reduces complications (99)
Hepatic disease	Non-alcoholic fatty liver disease	Hepatic macrophages	Anti-inflammatory and antioxidant effects	Protective pathways within macrophages	Reduces fatty accumulation and inflammation in the liver (112)

BTG2, B-cell translocation gene 2; miR, microRNA; mTORC1, mTOR complex 1; BACE1, beta-secretase 1; DAM1, disease-associated microglia 1; p38α APK, p38 α mitogen-activated protein kinase; Wnt, Wingless-related integration site; Stat3, signal transducer and activator of transcription 3; DN, diabetic nephropathy; OSF, oral submucous fibrosis; AD, Alzheimer's disease; MS, multiple sclerosis; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; T2D, type 2 diabetes; EMT, epithelial-mesenchymal transition.

Table II. The 'destructive' function of BTG2 in non-tumor diseases.

Disease category	Specific disease/ situation	Key cell/tissue types	Break mechanism/core functionality	Main regulatory pathway/axis	Biological effects and significance
Fibrotic disease	Focal segmental glomerulosclerosis	Podocytes	Promotion of EMT and fibrosis via a Smad3-dependent mechanism	TGF-β/Smad3 pathway	Leading to podocyte damage and loss, accelerating glomerulosclerosis (34)
	Diabetic nephropathy (tubules)	Proximal tubule cells	High expression correlates positively with EMT and fibrosis	SGLT2i-downregulated Smad3 pathway	Drives tubulointerstitial fibrosis and promotes disease progression (33)
	Submucosal fibrosis of the oral cavity (advanced stage)	Oral fibroblasts	Induces cellular senescence and promotes excessive collagen deposition	Arecoline → YY1 lactylation → PU.1 → BTG2 pathway	Leading to tissue stiffness, functional impairment and an increased risk of cancer (29)
Nervous system disease	Spinal cord injury/hypoxic-ischemic brain injury	Neurons	Activation of the EGR1/BTG2/Bax axis, promoting apoptosis	EGR1/BTG2/Bax apoptotic axis	Exacerbation of neuronal death, expansion of the infarct area and deterioration of neurological function (50)
Cardiovascular disease	Neurotoxicity of T-2 toxin	Microglia	Induces pro-inflammatory polarization of microglia	PI3K/AKT/NF-κB pathway	Exacerbates neuroinflammation, leading to secondary neuronal damage (53)
	Regulation of cardiomyocyte aging	Cardiomyocyte	SUV39H2 epigenetically downregulates BTG2, delaying aging	SUV39H2/BTG2 axis	Fights heart aging, maintains heart function (74)
	Acute myocardial infarction/ myocardial ischemia	Cardiomyocytes	Upregulated to promote cardiomyocyte apoptosis and inflammation	Inhibited by miR-21, miR-125b-5p	Exacerbates myocardial injury, leading to worsening cardiac function (30,36,37,69,70)
Inflammatory/ autoimmune diseases	Acute pancreatitis	Pancreatic acinar cells	Upregulation promotes oxidative stress, mitochondrial damage and apoptosis	tRF3-Thr-AGT/BTG2 axis	Exacerbates pancreatic tissue necrosis and is associated with disease severity (79)
	Chronic obstructive pulmonary disease	Monocytes/ macrophages	Upregulation may enhance pro-inflammatory responses	Associated with inflammatory signaling pathways	Exacerbates airway inflammation and promotes disease progression (113)
	Asthma	Airway-associated cells	EZH2-mediated epigenetic silencing leads to downregulation of expression and promotes inflammation	EZH2-FOXO3-miR-34b axis	Involved in airway hyperresponsiveness and the development of inflammation (114)
Metabolic disease	Type 2 diabetes (liver)	Hepatocytes	Abnormal upregulation may exacerbate insulin resistance and gluconeogenesis	Associated with hepatocyte stress pathways	Disrupts blood glucose homeostasis and exacerbates metabolic disorders (95)
Eye diseases	Myopic retinopathy	Retinal cells	Activates and promotes DNA damage and apoptosis	miR-92b-3p/BTG2 axis	Leads to retinal thinning and functional impairment (135)

Table II. Continued.

Disease category	Specific disease/ situation	Key cell/tissue types	Break mechanism/core functionality	Main regulatory pathway/axis	Biological effects and significance
Vascular diseases	Vascular calcification	Vascular smooth muscle cells	Regulated by miR-202-3p, promoting osteogenic phenotypic conversion	miR-202-3p/BTG2 axis	Promotes vascular wall calcification, increasing the risk of cardiovascular events (136)

EMT, epithelial-mesenchymal transition; TGF-β, transforming growth factor β; SGLT2i, sodiumglucose cotransporter 2 inhibitors; BTG2, B-cell translocation gene 2; EGR1, early growth response 1; SUV39H2, suppressor of variegation 39 homolog 2; FOXO3, forkhead box O3; tRF3ThrAGT, 3'-tRNA-derived fragment, threonine, anticodon AGT; PI3K, phosphoinositide-3 kinase; AKT, protein kinase B; NF-κB, nuclear factor κ light chain enhancer of activated B cells; EZH2, enhancer of zeste homolog 2; Bax, Bcl2-associated X protein; miR, microRNA; FSGS, focal segmental glomerulosclerosis; DN, diabetic nephropathy; SCI, spinal cord injury; HIE, hypoxic ischemic encephalopathy; COPD, chronic obstructive pulmonary disease.

disease states. By controlling mRNA deadenylation via the CCR4-NOT complex, BTG2 maintains T-cell quiescence, thereby reducing aberrant immune activation and preventing loss of self-tolerance (147). Through myeloid cell-specific mechanisms, BTG2 inhibits unwarranted inflammatory signaling in RA (90), whereas its deficiency in IBD compromises epithelial resilience, increases susceptibility to injury and impairs mucosal healing (91). Its immunological relevance is further increased by its role in regulatory T-cell biology. Collectively, these findings position BTG2 as a protector of homeostatic balance, whose dysregulation may contribute to inflammatory amplification, poor resolution and tissue recovery failure. This homeostatic function may represent the shared denominator underlying the seemingly heterogeneous role of BTG2 across organ systems.

The growing relevance of BTG2 is equally notable from a translational viewpoint. Multiple studies support its use as a diagnostic or prognostic biomarker across diseases. However, several concerns (including its strong context-dependent and bidirectional effects, as well as the absence of standardized detection protocols) must temper enthusiasm for its clinical translation. Furthermore, BTG2 expression should be interpreted consistently across diseases owing to its strong context dependence.

This concept has major ramifications for treatment timing, dose calibration and patient stratification. BTG2 levels have important guiding value from a therapeutic perspective. For instance, high BTG2 expression has been significantly associated with histological remission in IBD. Thus, monitoring BTG2 expression after treatment may indicate mucosal healing. In DKD, reduced BTG2 expression correlates with proteinuria, and stratifying patients based on BTG2 levels may facilitate early intervention to delay DKD progression. BTG2 is markedly downregulated in OSA and its future integration with indicators, such as BTG3, may facilitate molecular subtyping. The dynamic evaluation of disease status and the accurate prediction of complication risk are the main rationale for BTG2-based stratification analyses. To evaluate and standardize its therapeutic applicability, more clinical investigations are required because existing research is still in the exploratory stage. Thus, disease-specific, ideally cell-type-aware, interpretive frameworks are warranted for any therapeutically relevant application.

Although intrinsically complicated, BTG2's therapeutic implications are equally promising. Preclinical evidence indicates that BTG2 can be modulated through multiple modalities, including miRNA-based approaches, such as miR-21 (148), miR-25-3p, miR-29a-3p, miR-322-5p and miR-409-3p. Targeting BTG2-related pathways using physiologically adaptable methods is further demonstrated by exosome-mediated delivery systems, such as IFN-gamma-primed exosomes derived from mesenchymal stromal cells in myocardial infarction models. In parallel, BTG2-associated signaling systems in cardiotoxicity and renal fibrosis appear to be influenced by clinically proven drugs, such as SGLT2i and traditional Chinese medicine formulations (33,68). Therefore, BTG2-centered therapies may be achievable through both direct and indirect mechanisms. However, indiscriminate activation or suppression may pose a risk because BTG2 functions in a context-sensitive and possibly dose-dependent manner. Therefore, rather than relying on universal assumptions of benefit, therapeutic research must shift toward cell-selective, temporally controlled and pathway-informed methods.

Despite the advancements synthesized in this review, there are several limitations. First, while rigorous validation in human tissues and prospective clinical research is still limited, a substantial proportion of evidence stems from bioinformatic analysis, cell culture and animal models. Second, the mechanism of action of BTG2 in certain disease domains remains incompletely understood. Third, BTG2's intrinsically disordered C-terminus presents a major obstacle to structural characterization and logical drug discovery, even though it is probably essential to the protein's ability to interact with many binding partners and coordinate several pathways. Thus, the field is still in its early stages of mechanistic maturation, despite the growing conceptual and translational relevance of BTG2.

Likewise, the most crucial priorities for further research are determined by these limitations. To advance the science, a quantitative, spatiotemporally resolved understanding of

BTG2 biology must replace static and binary models. The BTG2 interactome should be systematically mapped across cell states, tissues and disease situations using advanced proteomics and single-cell multi-omics, while clarifying the upstream regulatory circuits and post-translational modifications that regulate its stability and signaling capacity. Dissecting the stage-dependent roles of BTG2 during disease progression will require conditional and inducible genetic systems with cell-type specificity and temporal control.

Furthermore, the identification of expression thresholds that differentiate between adaptive and pathogenic BTG2 activity, the delineation of downstream pathway outputs across expression states and the development of dynamic monitoring strategies that record BTG2 trajectories rather than depending solely on single-timepoint measurements will all be crucial. Large-scale, multicenter validation of BTG2-based biomarker panels is warranted to support clinical implementation. Furthermore, future research should entail combination strategies that target BTG2 along with its upstream regulators or downstream effectors for optimizing therapeutic efficacy while minimizing toxicity.

In conclusion, BTG2 has conceptually evolved from a traditional antiproliferative factor into a systems-level regulator of stress adaptation, immune homeostasis and cell-fate determination across non-tumor diseases. Its functions within the neuro-immune-epigenetic axis and the metabolic-epigenetic-fibrosis network underscore its importance as an integrative node in multisystem pathology. Despite substantial mechanistic and translational challenges, existing evidence strongly positions BTG2 as a biologically and clinically important molecule. To comprehensively clarify its potential as a biomarker and a treatment target in refractory non-tumor diseases, a profound understanding of its context-dependent, dose-sensitive and temporally dynamic roles is warranted.

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Authors' contributions

SL was involved in visualization, writing - original draft and writing - review & editing. XL performed visualization and writing - review & editing. ZZ participated in visualization, writing - review & editing, investigation and methodology. LY was responsible for methodology, investigation, and writing - review & editing. YL performed visualization and writing - review & editing. QH was responsible for funding acquisition, supervision and writing - review & editing. Data authentication is not applicable. All authors have 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.

Use of artificial intelligence (AI) tools

The authors declare that no Generative AI was used in the creation of this manuscript.

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