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Review

# Roles of the Mammalian SBNO Family in Development, Inflammation, Immunity and Cancer

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**ABSTRACT:** The mammalian Strawberry notch homolog (SBNO) family comprises SBNO1 and SBNO2, two large proteins with conserved DExD/H-box and helicase C-terminal domains. Their adenosine triphosphate (ATP) hydrolysis and nucleic acid unwinding activities have not been demonstrated using purified proteins. This review evaluates their reported functions according to the strength of genetic, biochemical, cellular, and patient-derived evidence. SBNO1 has been implicated in trophectoderm specification, stem-cell proliferation, neuronal development and genome maintenance, and liver cancer. SBNO2 participates in inflammatory feedback, osteoclast fusion, macrophage antimicrobial activity, and repair after acute lung injury in defined experimental settings. Loss-of-function studies also support a requirement for SBNO2 in selected signal transducer and activator of transcription 3 (STAT3)-driven hematological malignancy models. Crohn's disease-associated variation in SBNO2 isoform usage links host genetics to macrophage antimicrobial function. These findings support roles for SBNO proteins in transcriptional regulation, while the contributions of interacting partners and chromatin context remain incompletely defined. Differences in their reported functions do not establish functional specialization; potential overlap, complementarity, and compensation remain unresolved. Defining biochemical activities, isoform-specific functions, and cellular recruitment mechanisms will be necessary to assess their therapeutic potential.

**Keywords:** Strawberry notch homolog; SBNO1; SBNO2; Transcriptional regulation; Development; Inflammation; Immune homeostasis; Cancer

## 1. Introduction

*Strawberry notch* was initially identified in a Drosophila developmental genetic screen. Mutations produced several developmental abnormalities resembling impaired Notch function and showed genetic interactions with *Notch* and related genes [1]. Subsequent work established that *Strawberry notch* encodes an evolutionarily conserved nuclear regulator rather than a transmembrane Notch-family receptor. During

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development of the Drosophila wing margin, it acts downstream of Notch and contributes to the expression of multiple target genes [2]. These findings framed the Strawberry notch homolog (SBNO) family as closely connected to Notch signaling without being a core component of the canonical pathway and suggested that its members may also participate in other regulatory programs.

The mammalian SBNO family consists mainly of SBNO1 and SBNO2. Zebrafish have one *sbno1* gene and two *sbno2* paralogs, *sbno2a* and *sbno2b*. During early embryogenesis, *sbno1* and *sbno2a* are broadly expressed and later become enriched in the central nervous system, although their regional expression patterns do not completely overlap. In contrast, *sbno2b* is detected predominantly in non-neural tissues, ventral mesoderm, and hematopoietic regions [3]. These expression patterns indicate differences in spatial and temporal regulation among zebrafish SBNO family members, but do not by themselves establish functional specialization [3]. Early evidence for mammalian *SBNO1* came from expression profiling of reeler mouse embryos [4]. The human *SBNO2* coding sequence was first reported as the brain-derived complementary DNA (cDNA) clone KIAA0963 [5], whereas its functional characterization began with studies of the interleukin-10 (IL-10)/signal transducer and activator of transcription 3 (STAT3) anti-inflammatory pathway [6].

SBNO1 and SBNO2 are large helicase-like proteins of approximately 150 kDa that contain highly conserved DExD/H-box and helicase C-terminal domains. Related sequence motifs occur in animal, plant, and bacterial proteins, providing sequence-based support for the proposed ATPase- or helicase-like activity of the family [3,7]. Sequence and domain homology alone, however, do not establish enzymatic function. Adenosine triphosphate (ATP) hydrolysis and nucleic acid unwinding by SBNO1 or SBNO2 have not been demonstrated in purified-protein assays. Current evidence instead supports roles as transcriptional co-regulators that participate, in a cell-type-dependent manner, in complexes linking sequence-specific transcription factors, chromatin, and the basal transcriptional machinery [6–10].

This review focuses on mammalian SBNO1 and SBNO2, mainly summarizing evidence from mouse models, human cells, and patient studies; findings from Drosophila and zebrafish are primarily used to provide research history and evolutionary context. This review assesses the functions and disease associations of the SBNO family based on the type and strength of supporting evidence. Targeted loss of function in cells or animals, phenotype analysis, and rescue with wild-type proteins or defined isoforms can support causal inference. Protein interactions and chromatin occupancy help establish a regulatory framework but do not, on their own, prove that every binding site is a direct functional target. Patient-tissue expression, genome-wide association, deoxyribonucleic acid (DNA) methylation, and multi-omics screens primarily generate disease-related hypotheses that require validation in defined cell types and experimental contexts. This distinction is particularly important for *SBNO2* because IL-10 induces its expression in Toll-like receptor (TLR)-stimulated mouse and human macrophages [6], and interleukin-6 (IL-6), together with its soluble receptor, increases *SBNO2* expression in cultured mouse and human astrocytes [11]. Elevated SBNO2 expression in diseased tissue may therefore reflect either a pathogenic contribution or a compensatory response [12]; expression data alone cannot establish its functional role. The following sections review the discovery, protein features, expression patterns, physiological functions, disease associations, and proposed mechanisms of SBNO1 and SBNO2 and identify the principal questions that remain unresolved. An overview of the reported functions, representative pathways, and disease associations of SBNO1 and SBNO2 is provided in Figure 1.

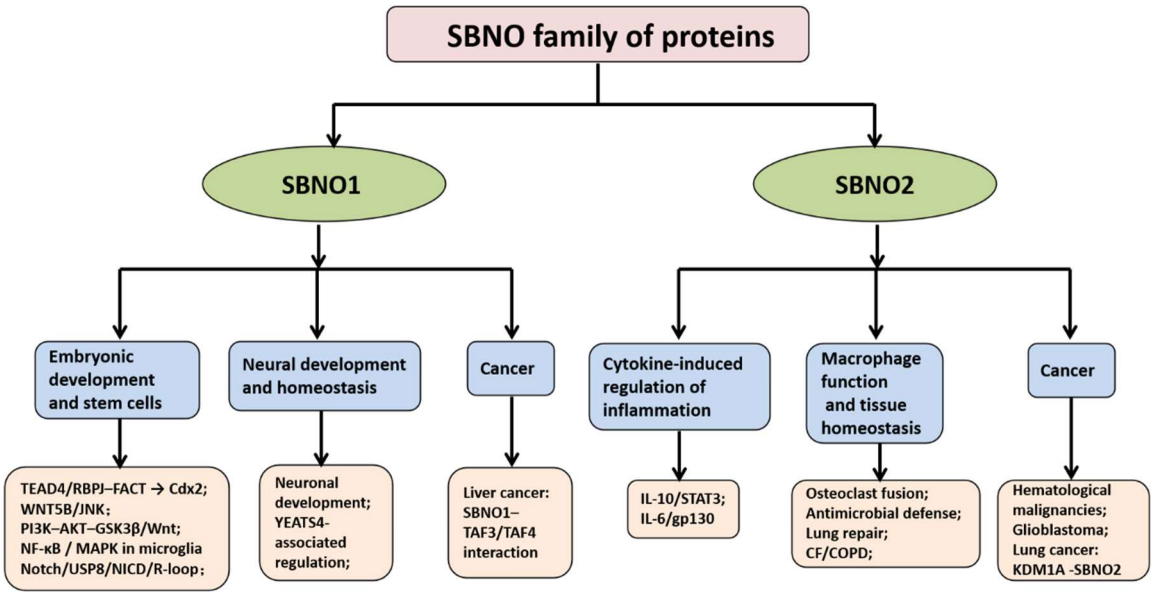


**Figure 1.** Overview of the reported functions, representative pathways, and disease associations of SBNO family proteins.

## 2. SBNO1 as a Nuclear Transcriptional Co-Regulator in Development and Disease

### *2.1. Protein Features and Expression*

SBNO1, also known as MOP-3 (monocyte protein 3), is one of the two principal mammalian SBNO proteins. Baba et al. found that *Sbno1* was markedly downregulated in Reelin-deficient reeler mouse embryos and was expressed mainly in the developing central nervous system, suggesting that its expression may be regulated by Reelin signaling [4]. The canonical human SBNO1 protein comprises 1393 amino acids, has a predicted molecular mass of approximately 154 kDa, and is predominantly nuclear [13,14]. Although its conserved domains led to its early classification as an superfamily 2 (SF2) helicase-like protein, the available functional studies more strongly support a role in nuclear transcriptional and chromatin regulation.

At the ribonucleic acid (RNA) level, *SBNO1* is broadly expressed across human tissues and shows tissue-enhanced expression in the testis. Human Protein Atlas data indicate relatively high expression in the testis, bone marrow, cerebellum, retina, thyroid, skeletal muscle, and several lymphoid tissues, with lower expression in tissues including the gallbladder, choroid plexus, lung, heart muscle, pancreas, pituitary gland, salivary gland, and adrenal gland [13,15]. In mice, *Sbno1* is detectable in preimplantation embryos [7] and remains highly expressed in the developing central nervous system, adult brain, and testis [4]; SBNO1 is also detected in neonatal testes and spermatogonial stem cells [16]. Zebrafish *sbno1* is broadly expressed early in development and later becomes enriched in the central nervous system [3]. These observations define potential sites of SBNO1 activity, but RNA abundance cannot substitute for functional analysis at defined developmental stages and in specific cell types.

### *2.2. Roles in Embryonic Development and Stem Cells*

SBNO1 is essential for mouse preimplantation development. Whole-body deletion of *Sbno1* arrests embryos at a morula-like stage, prevents normal blastocoel formation, reduces proliferation, and increases cell death. Loss of SBNO1 has relatively limited effects on most inner cell mass markers but markedly suppresses the trophectoderm genes *Cdx2*, *Eomes*, and *Krt8* [7]. This pattern indicates a selective role in lineage-specific transcription rather than a general requirement for embryonic gene expression. In *Sbno1*-deficient embryos, nuclear localization of YAP, TEAD4, and RBPJ is largely preserved, yet *Cdx2* fails to be activated normally. SBNO1 occupies the *Cdx2* regulatory region and interacts with TEAD4, RBPJ, and the facilitates chromatin transcription (FACT) complex, including its subunits SSRP1 and SPT16,

suggesting that it may connect signal-responsive transcription factors to chromatin-associated transcriptional machinery at regulatory sites where nuclear Notch and Hippo effectors converge [7].

A glutamate-to-glutamine substitution at the conserved E437 residue within the DExH-like region abolished SBNO1-dependent reporter activation. Moreover, expression of the human SBNO1 E437Q mutant in mouse zygotes induced developmental arrest at the 8- to 12-cell stage and reduced *Cdx2* expression [7]. These findings establish the functional importance of this conserved region, but they do not constitute a knockout-rescue experiment and do not identify E437 as a catalytic residue. Adenosine triphosphate (ATP) hydrolysis and nucleic acid unwinding by the wild-type or mutant protein have not been measured. Protein stability, nuclear localization, and interaction capacity should therefore be compared before the E437 phenotype is assigned to loss of enzymatic activity. Likewise, reduced *Cdx2* alone may not explain the entire embryonic phenotype; combined rescue of several trophectoderm regulators will be needed to determine whether SBNO1 controls a single dominant target or a broader lineage program.

Beyond preimplantation development, SBNO1 has been implicated in spermatogonial stem-cell proliferation. Morpholino-mediated *Sbno1* knockdown reduced spermatogonial proliferation and *Wnt5b* messenger RNA (mRNA) abundance in cultured neonatal mouse testes and spermatogonial stem cells. Reduced c-Jun N-terminal kinase (JNK) phosphorylation was demonstrated in the cultured testes, whereas β-catenin immunostaining was not detectably altered in either system [16]. These findings are consistent with involvement of noncanonical Wnt signaling, but do not establish that WNT5B/JNK signaling mediates the proliferation defect or that SBNO1 directly controls *Wnt5b* transcription.

SBNO1 is also abundant and predominantly nuclear in mouse brain tissue and neural stem cells. In neural stem cells, it has been linked to changes in the phosphoinositide 3-kinase (PI3K)–protein kinase B (AKT)–glycogen synthase kinase 3 beta (GSK3β) and Wnt/β-catenin pathways and promotes proliferation through the PI3K-AKT-GSK3β/Wnt-β-catenin axis [17]. SBNO1 overexpression also alters the biological activity of small extracellular vesicles derived from neural stem cells; these vesicles suppress nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) signaling in microglia, reduce neuroinflammation, and promote recovery after experimental stroke [17]. Together with the spermatogonial stem-cell findings [16], these results suggest that SBNO1 can be associated with distinct Wnt branches in different cellular contexts. Direct transcriptional targets and the relative contribution of vesicle-mediated signaling nevertheless remain to be defined.

A recent study in embryonic mouse cortical neural stem cells linked SBNO1 to Notch-dependent stem-cell maintenance. Naranbaatar et al. reported separate interactions of SBNO1 with RBPJ and USP8 in cell-based assays. When the Notch intracellular domain (NICD) and RBPJ were co-expressed, SBNO1 and USP8 synergistically enhanced *Hes5* promoter activity. Conditional deletion of *Sbno1* in embryonic mouse cortical neural stem cells reduced the neural stem-cell population and caused premature neuronal differentiation. Furthermore, USP8 overexpression increased NICD protein levels, whereas SBNO1 overexpression reduced R-loop enrichment at the *Hes5* promoter. Based on these findings, the authors proposed that SBNO1 may enhance Notch target-gene transcription by facilitating USP8-mediated NICD stabilization and R-loop resolution at the *Hes5* promoter [18]. These findings extend the functional evidence for SBNO1 in neural progenitors, but whether SBNO1 directly catalyzes R-loop unwinding remains to be established.

### *2.3. Neural Development and Homeostasis*

SBNO1 function in the postnatal nervous system is strongly dependent on cell type and developmental stage. The protein is expressed mainly in neurons and is particularly abundant in motor-related populations, including layer V cortical neurons and motor nuclei of the brainstem [19]. Neuron-specific deletion of *Sbno1* does not markedly disrupt cortical layering or neurogenesis but impairs cortical projection fibers and dendritic development and causes spastic paralysis [20]. These data support a direct role in axonal and

dendritic growth in differentiated neurons rather than a phenotype caused solely by reduced neural-progenitor proliferation.

SBNO1 also supports neuronal genome stability. *Sbno1* loss causes cortical thinning, DNA damage, and neuronal apoptosis and markedly reduces expression of the DNA repair-associated chromatin regulator *Yeats4*. Restoration of YEATS4 partially rescues DNA damage and cell death [21]. SBNO1 may therefore maintain mature neurons through at least two separable processes: transcriptional programs required for neurite growth and complex connectivity, and YEATS4-associated genome maintenance required for long-term survival. The rescue data implicate the SBNO1-YEATS4 axis but do not establish SBNO1 itself as a DNA repair enzyme.

### *2.4. Cancer and Other Disease Associations*

Direct experimental evidence also supports a pro-tumor role for SBNO1 in liver cancer. A 2026 study reported that SBNO1 was upregulated across several tumor types and was markedly increased in human hepatocellular carcinoma and intrahepatic cholangiocarcinoma, with predominant localization in tumor-cell nuclei [8]. *SBNO1* knockdown or deletion reduced cell viability, clonogenic growth, and migration and inhibited tumor growth in multiple mouse liver-cancer models. Mechanistically, SBNO1 interacted with transcriptional regulators including the transcription factor IID (TFIID) components TAF3 and TAF4, and its chromatin-binding sites were concentrated near transcription start sites, consistent with support of oncogenic gene expression [8]. These data establish a functional requirement in the tested liver-cancer models, whereas its importance in other cancers and its therapeutic tractability remain uncertain.

The SBNO1 interactome was not identical across liver-cancer cell lines, underscoring the influence of cellular background. TAF3 and TAF4 were recovered relatively consistently, but promoter-proximal enrichment and protein interaction do not prove that every liver-cancer subtype depends on the same regulatory network [8]. In some patient cohorts, *SBNO1* mRNA and protein abundance were also discordant, so transcript elevation alone should not be used to infer functional dependency. Therapeutic evaluation will require simultaneous assessment of protein expression, genetic requirement, direct target genes, and normal-tissue tolerance in molecularly defined tumor subtypes.

Human genetic and multi-omics studies provide additional, but mainly hypothesis-generating, evidence for disease involvement. In a multigenerational family affected by intellectual disability, the 12q24.22-q24.31 interval containing *SBNO1* showed a run of homozygosity and copy-number-variation signals [22]. A genome-wide association study also linked the intragenic *SBNO1* variant rs7980687 to infant head circumference [23]. Because the structural interval contains multiple genes and a common-variant association does not identify the causal gene, neither finding establishes *SBNO1* as the disease driver. *SBNO1* has also appeared in studies of antipsychotic response in schizophrenia, knee osteoarthritis susceptibility, idiopathic pulmonary fibrosis biomarker discovery, and the plasma peptidome of sepsis [24–27]. These observations lack *SBNO1*-specific perturbation and rescue experiments and should therefore be treated as leads for functional testing rather than causal evidence.

Overall, SBNO1 is best viewed as a context-dependent nuclear transcriptional co-regulator. In preimplantation embryos, it cooperates with Notch- and Hippo-responsive factors to activate the trophectoderm program [7]. In spermatogonial and neural stem cells, it is associated with distinct Wnt signaling branches that support proliferation [16,17]. In differentiated neurons, it promotes neurite development and supports genome maintenance through a YEATS4-associated pathway [20,21]. In liver-cancer cells, it cooperates with basal transcriptional machinery to sustain oncogenic transcription and tumor growth [8]. SBNO1 is therefore unlikely to be a conventional sequence-specific transcription factor. Future work should define its proposed ATPase or helicase activity, cell-specific interaction networks, direct chromatin targets, and tissue-specific functions in development, neurological disease, and cancer. Studies of the reported biological functions and disease associations of SBNO1 are summarized in Table 1.

**Table 1.** Reported biological functions and disease associations of SBNO1.

| Category | References | Research Focus |
|---|---|---|
| Embryonic development and stem cells | Naranbaatar et al. 2026 [18] | Notch-dependent neural stem-cell maintenance |
| | Watanabe et al. 2017 [7] | Trophectoderm specification |
| | Shen et al. 2019 [16] | Spermatogonial stem-cell proliferation |
| | Zhang et al. 2024 [17] | Neural stem-cell proliferation and post-stroke repair |
| Neural development and homeostasis | Erkhembaatar et al. 2022 [20] | Axonal and dendritic growth |
| | Baba et al. 2006 [4] | Reelin-associated expression regulation |
| | Zolzaya et al. 2025 [19] | Postnatal brain expression patterns |
| | Ihara et al. 2025 [21] | Neuronal genome stability |
| | Bulayeva et al. 2015 [22] | Genetic associations with intellectual disability |
| | Taal et al. 2012 [23] | Genetic variation associated with infant head circumference |
| | Guo et al. 2023 [24] | Prediction of antipsychotic treatment response |
| Cancer | Fritzsche et al. 2026 [8] | Liver carcinogenesis and oncogenic transcription |
| | Coppieters et al. 2023 [28] | SBNO1 expression in glioma |
| Other diseases | Novakov et al. 2023 [25] | Knee osteoarthritis susceptibility |
| | Gao et al. 2022 [26] | Candidate biomarkers of idiopathic pulmonary fibrosis |

## 3. SBNO2 as a Context-Dependent Regulator of Inflammation, Immunity and Tissue Homeostasis

### *3.1. Protein Features and Expression*

SBNO2 is the other principal mammalian member of the family. Its coding sequence was initially reported as the brain-derived cDNA clone KIAA0963 [5], and it was subsequently identified as an IL-10/STAT3-inducible nuclear transcriptional co-regulator [6]. The canonical human SBNO2 protein contains 1366 amino acids and has a predicted molecular mass of approximately 150 kDa [14]. *SBNO2* RNA is broadly distributed across human tissues and shows relatively low tissue specificity, with higher abundance in the lung, adipose tissue, spleen, esophagus, kidney, and liver [15,29].

Whole-body *Sbno2* knockout models have produced different viability outcomes. An early study reported embryonic lethality in homozygous mutant mice, whereas independent models generated later survived to adulthood and were used to examine skeletal and central nervous system phenotypes [6,9,12]. The reason for this discrepancy remains unresolved but may reflect differences in the targeted exons or the production of residual truncated proteins. Differences in genetic background may also contribute, although this possibility has not been directly tested. A recent isoform-resolved study focused on two major *SBNO2* transcripts, termed ISO1 and ISO2. Upon ectopic expression in human embryonic kidney 293 (HEK293) cells, both isoforms localized to the nucleus, but they differed in stimulus responsiveness and associated gene networks [30].

In mice, *Sbno2* expression is strongly dependent on stimulus and cellular context. In TLR-stimulated macrophages, IL-10 induces *Sbno2* expression through a STAT3-dependent mechanism [6]. In the inflamed central nervous system, *Sbno2* is expressed predominantly in astrocytes and is regulated by IL-6/glycoprotein 130 (gp130) signaling [11]. Receptor activator of nuclear factor κB ligand (RANKL) induces *Sbno2* in osteoclast precursors, where it contributes to cell fusion [9]. In zebrafish, *sbno2a* is expressed mainly in the central nervous system, whereas *sbno2b* is more prominent in non-neural tissues, ventral mesoderm, and hematopoietic regions [3]. These patterns reinforce the view that SBNO2 function is specified by cell lineage, stimulus, and isoform rather than by a single universal pathway.

### *3.2. Cytokine-Induced Regulation of Inflammation*

Early studies showed that IL-10 induces *SBNO2* expression in a STAT3-dependent manner in TLR-stimulated mouse and human macrophages [6]. In transfected reporter systems, SBNO2 repressed NF-κB-

driven transcription but not interferon regulatory factor 7 (IRF7)-driven transcription [6]. However, *Sbno2*-deficient mouse macrophages retained IL-10-mediated suppression of lipopolysaccharide (LPS)-induced tumor necrosis factor (TNF) production. Their LPS-induced NF-κB DNA-binding activity and inflammatory cytokine production following stimulation with various TLR agonists were also comparable to those in wild-type cells [9]. These findings demonstrate selective repression by SBNO2 in reporter assays but do not establish it as a general inhibitor of endogenous TLR–NF-κB responses.

A separate line of evidence comes from studies of IL-6-driven central nervous system (CNS) inflammation. Hyper-IL-6, a fusion protein comprising IL-6 and its soluble receptor, induces *SBNO2* expression in cultured mouse and human astrocytes [11]. Global deletion of *Sbno2* exacerbated neuroinflammation and neurodegeneration in glial fibrillary acidic protein (GFAP)-IL6 mice. Following hyper-IL-6 stimulation, primary *Sbno2*-deficient astrocytes exhibited enhanced and sustained expression of selected IL-6-responsive genes despite reduced gp130 pathway activation [12]. These findings support a protective feedback role for SBNO2 in this experimental system, although its direct transcriptional mechanism remains unresolved. Because the *in vivo* study used global deletion, these results alone do not permit exclusive attribution of the phenotype to *SBNO2* loss in astrocytes.

Together, these studies support the interpretation that SBNO2 regulates selected transcriptional responses in defined cellular and experimental contexts. The available evidence does not establish a universal anti-inflammatory role or a shared molecular mechanism across these settings. Differences in signaling duration, parallel pathways, chromatin state, or cell-type-specific transcriptional complexes remain possible explanations requiring experimental testing. The principal unresolved questions are which direct regulatory targets and interacting partners of SBNO2 mediate these effects and whether the underlying mechanisms overlap between the two settings.

### *3.3. Macrophage Function and Tissue Homeostasis*

*Sbno2*-deficient mice exhibit increased bone mass and reduced bone turnover. Early osteoclast differentiation is largely preserved, but precursor fusion, multinucleation, and bone-resorptive capacity are impaired [9]. These findings identify osteoclast fusion as a principal SBNO2-dependent step. RANKL induces *Sbno2* through c-Fos/Jdp2; SBNO2 then associates with TAL1 and relieves TAL1-mediated repression of the dendritic cell-specific transmembrane protein (DC-STAMP) promoter, allowing microphthalmia-associated transcription factor (MITF) to promote DC-STAMP transcription and precursor fusion [9]. In this setting, SBNO2 acts through transcriptional derepression rather than classical corepression. In an overexpression-based reporter assay in HEK293 cells, SBNO2 dose-dependently relieved TBX18-mediated transcriptional repression, further indicating that the direction of its regulatory output depends on the surrounding transcriptional complex and cellular context [10].

Isoform-resolved analysis has expanded understanding of SBNO2 in inflammatory bowel disease. In human monocytes and monocyte-derived macrophages, IL-10 preferentially induces the noncanonical ISO2 isoform, whereas LPS induction of ISO2 depends partly on autocrine IL-10 [30]. Co-expression networks link ISO1 more strongly to cytokine, interferon, and inflammatory responses, while ISO2-associated networks are enriched for autophagy, lysosomal, and antimicrobial processes. Crohn's disease-associated variants are linked to reduced ISO2 expression or transcript usage. *SBNO2* depletion impairs macrophage control of intracellular Salmonella enterica serovar Typhimurium, whereas re-expression of SBNO2, particularly ISO2, improves antimicrobial activity [30]. Multi-omics integration has also nominated *Sbno2* as an inflammatory bowel disease candidate gene [31]. Nevertheless, analyses of total gene expression have not established disease causality, and *in vivo* studies are still required to determine how specific isoforms, cell types, and microbial contexts influence intestinal inflammation.

Recent animal work suggests an additional role in tissue repair after sepsis-associated acute lung injury. In a mouse model of LPS-induced lung injury, *Sbno2* was markedly upregulated in tissue-resident alveolar

macrophages. Genetic loss of *Sbno2* or antibody blockade weakened macrophage-mediated protection of alveolar epithelium, whereas intratracheal delivery of recombinant SBNO2 promoted epithelial regeneration and reduced lung injury [32]. The study provided evidence that tissue-resident alveolar macrophages can release SBNO2 into the alveolar space. However, its release mechanism, extracellular molecular form, epithelial receptor or uptake pathway, and requirement under endogenous conditions remain unclear [32].

In chronic human airway disease, the current evidence is predominantly epigenetic and associative. In sputum from patients with cystic fibrosis, methylation at the *SBNO2*-associated cytosine-phosphate-guanine (CpG) site cg18608055 was positively associated with lung function [33]. A related association was identified in peripheral blood from individuals with chronic obstructive pulmonary disease [34]. These respiratory studies did not examine whether methylation at this locus alters *SBNO2* expression or mediates changes in pulmonary function [33,34]. A separate copper-related epigenome-wide association study reported a significant association between cg18608055 methylation and *SBNO2* expression in blood leukocytes [35]. This association does not establish a causal effect of methylation on *SBNO2* expression or a mechanism mediating changes in pulmonary function.

### *3.4. Cancer*

*SBNO2* is a direct transcriptional target of activated STAT3 in selected hematological malignancy models. *SBNO2* knockdown impairs cell proliferation or survival in models of STAT3-mutant natural killer-cell leukemia and nucleophosmin–anaplastic lymphoma kinase (NPM–ALK)-positive T-cell anaplastic large cell lymphoma [36]. These perturbation results support a functional dependence on SBNO2 in the models examined. Separately, in the NPM-ALK-positive patient cohort, high SBNO2 expression was associated with shorter relapse-free survival ($p = 0.0066$), whereas the overall-survival difference was not statistically significant ($p = 0.17$) [36]. This clinical association alone is insufficient to establish a causal mechanism or confirm the prognostic value of SBNO2. The downstream molecular basis of cellular dependence on SBNO2 also remains incompletely defined.

SBNO2 expression is elevated in human glioblastoma tissue, providing evidence of disease-associated expression changes. SBNO2 overexpression produced different phenotypes across patient-derived glioblastoma stem-like cell models [28]. These findings indicate that cellular responses to increased SBNO2 levels are model-dependent, but do not establish a consistent functional dependence on endogenous SBNO2 in these models or a uniform growth-promoting role for SBNO2.

The lung cancer study examined tumor-cell-mediated regulation of CD8+ T-cell responses. Lysine-specific demethylase 1A (KDM1A) bound to the *SBNO2* promoter and enhanced *SBNO2* transcription in tumor cells. In the co-culture system, silencing *SBNO2* in tumor cells counteracted the inhibitory effects of KDM1A overexpression on CD8+ T-cell proliferation, chemotaxis, and cytokine production [37]. These findings support a contribution of tumor-cell SBNO2 to the immunosuppressive phenotype in this experimental system, but do not establish a T-cell-intrinsic function of SBNO2. The intermediary signals linking tumor-cell SBNO2 to T-cell responses require further investigation.

Across the settings reviewed, loss-of-function studies, complemented by rescue experiments in some systems, provide functional evidence in defined models [9,12,30,36,37], whereas expression changes and overexpression responses alone do not establish endogenous dependency [28]. Here, context dependence describes observed stimulus-, isoform-, and model-specific responses; it does not imply an established common regulatory mechanism. For example, NF-κB reporter repression [6] must be considered alongside preserved endogenous TLR responses and IL-10-mediated TNF suppression in *Sbno2*-deficient macrophages [9]. ISO2-selective induction and isoform re-expression experiments provide a separate line of evidence concerning macrophage antimicrobial activity [30]. Whether differences in interacting partners

and chromatin targets explain these outcomes remains unresolved. Relevant studies are summarized in Table 2. Direct comparisons with SBNO1 are also needed to assess shared and paralog-specific functions.

**Table 2.** SBNO2 in inflammation, tissue homeostasis, and cancer.

| Category | References | Research Focus |
|---|---|---|
| Regulation of inflammation | El Kasmi et al. 2007 [6] | IL-10/STAT3 induction and transcriptional regulation |
| | Grill et al. 2015 [11] | Inducible expression and localization in CNS inflammation |
| | Syme et al. 2022 [12] | Feedback in chronic IL-6-associated CNS inflammation |
| | Maruyama et al. 2013 [9] | Endogenous TLR–NF-κB responses and IL-10-mediated suppression |
| Macrophage function and tissue homeostasis | Aschenbrenner et al. 2024 [30] | Isoform regulation, antimicrobial activity, and Crohn's disease susceptibility |
| | Maruyama et al. 2013 [9] | Osteoclast fusion and bone homeostasis |
| | Rivera-Reyes et al. 2018 [10] | Supporting evidence on transcriptional complexes |
| | Zhu et al. 2025 [31] | Candidate susceptibility genes in inflammatory bowel disease |
| | Dai et al. 2026 [32] | Alveolar epithelial regeneration and barrier repair |
| | Tost et al. 2026 [33] | Airway methylation and lung function |
| | Bermingham et al. 2019 [34] | Blood methylation and respiratory function |
| | Long et al. 2021 [35] | Supporting evidence on methylation signals |
| Cancer | Brandstoetter et al. 2023 [36] | Dependency in STAT3-driven hematological malignancies |
| | Coppieters et al. 2023 [28] | Glioblastoma expression and model-dependent responses |
| | Pan and Zhang 2026 [37] | Tumor-cell-mediated immune suppression |

## 4. Shared Regulatory Principles and Key Questions

Current evidence does not support a fixed activating or repressive function for SBNO proteins. Their output is more likely determined by stimulus- and lineage-specific recruitment. In mouse preimplantation embryos, SBNO1 cooperates with TEAD4, RBPJ, and the FACT complex in the trophectoderm transcriptional program; in liver-cancer cells, its interaction network includes basal transcriptional regulators such as TAF3 and TAF4 [7,8]. IL-10 induces both *SBNO2* and ETS variant transcription factor 3 (ETV3) in TLR-stimulated macrophages through a STAT3-dependent response [6]. This shared induction should be distinguished from the identification of TAL1 as an SBNO2-interacting protein in studies of osteoclast differentiation [9]. The molecular partners mediating SBNO2-dependent regulation in astrocytes remain to be identified [12]. These observations suggest that the availability of DNA-binding factors, local chromatin state, and signaling kinetics may jointly determine where SBNO proteins are recruited and what transcriptional output follows. Whether the interactions observed in different cell types are mediated by the same SBNO domains remains unknown.

Resolving the molecular function of SBNO proteins first requires direct biochemical analysis. Purified full-length SBNO1, SBNO2 ISO1, SBNO2 ISO2, and mutants in conserved motifs should be compared for nucleotide binding, ATP hydrolysis, and nucleic acid unwinding [7,30]. In cells, interaction maps and chromatin occupancy should be paired with chromatin accessibility and nascent-transcription measurements at near-endogenous protein abundance. Domain-deletion and rescue experiments can then distinguish a potential enzymatic contribution from a scaffolding function. Isoform-specific antibodies or unique mass-spectrometric peptides will also be required to confirm ISO2 production in relevant immune cells under defined stimuli. Only by connecting biochemical activity, molecular interactions, and cellular phenotypes can investigators determine whether SBNO-dependent transcriptional co-regulation requires the proposed enzymatic activity [7,9,30].

Disease models should treat cell type, disease stage, and isoform as core experimental variables. Intestinal studies should distinguish circulating monocytes, tissue macrophages, epithelium, and the associated microbial environment [30]. Lung-injury studies should separate tissue-resident from recruited

monocyte-derived alveolar macrophages and analyze injury, inflammatory resolution, and repair as distinct phases [32]. Inducible lineage-specific *Sbno2* deletion combined with targeted ISO2 re-expression could assess microbial control, inflammation, and tissue integrity in the same model. Cancer studies should likewise test tumor-cell dependency and feedback functions in immune cells separately, thereby avoiding attribution of a net whole-body intervention phenotype to a single cellular mechanism [12,30,32,36,37].

These contextual differences also constrain the therapeutic interpretation of SBNO2. Inhibition could impair the growth or survival of selected STAT3-dependent malignancies but might simultaneously compromise inflammatory feedback in astrocytes, antimicrobial activity in macrophages, or repair after alveolar injury [12,30,32,36]. Conversely, current lung-injury data cannot determine whether enhancement of SBNO2-associated repair would affect tumor immune escape [32,37]. Therapeutic studies should therefore restrict intervention by cell type, isoform, and timing and should evaluate preservation of normal-tissue function alongside disease improvement.

The evidence for SBNO-family functions should be stratified rather than extrapolated across models. Genetic perturbation supports roles for SBNO1 in preimplantation embryos, neurons, and liver cancer [7,8,20,21]. Comparatively direct functional evidence supports SBNO2 in osteoclast fusion, chronic IL-6 neuroinflammation, macrophage antimicrobial activity, and selected STAT3-dependent malignancies [9,12,30,36]. The Crohn's disease study links genetic variation, transcript selection, and macrophage phenotype but has not yet shown that the associated variant directly causes intestinal disease *in vivo* [30]. Independent cross-trait and multi-omics analyses have also nominated *SBNO2* as a candidate gene for inflammatory bowel disease [31]. Methylation signals in chronic airway disease [33,34] and expression changes in glioblastoma patient samples [28] remain mainly associative, whereas the hematological and lung-cancer studies combine patient associations with functional perturbation [36,37]. Finally, although tissue-resident alveolar macrophages have been implicated as a source of extracellular SBNO2, its release mechanism, extracellular molecular form, direct target cells, and receptor or uptake pathway remain to be established [32].

## 5. Conclusions

Research on the SBNO family has expanded from Drosophila Notch-related development to mammalian development, immunity, tissue homeostasis, and cancer. The field has also moved from expression surveys and genetic associations toward analysis of transcriptional complexes, chromatin engagement, isoform-specific regulation, and cell-type-specific function. SBNO1 and SBNO2 share similar protein sizes and conserved helicase-like domains, and both localize to the nucleus and cooperate with transcription factors or the basal transcriptional machinery in defined experimental contexts. Functional studies have implicated SBNO1 in trophectoderm specification, stem-cell proliferation, neuronal development and genome maintenance, and liver carcinogenesis [7,8,16,17,20,21]. SBNO2 has been implicated in selected inflammatory responses, macrophage antimicrobial activity, osteoclast fusion, tissue repair, and specific tumor models [6,9,12,30,32,36,37]. These findings document functions reported for each protein in particular experimental settings, but do not, by themselves, establish functional divergence or specialization between the two paralogs. The cited studies generally examine the proteins in different biological systems, with limited direct comparison under matched conditions. Consequently, differences in their reported functions may partly reflect research focus and model selection.

Whether SBNO1 and SBNO2 have overlapping or complementary functions, or whether either protein can partially compensate for loss of the other, remains unresolved. Direct comparisons in the same cellular context, including individual and combined perturbations and reciprocal rescue where feasible, could help assess these relationships and distinguish shared functional requirements from paralog-specific contributions. Neither protein can yet be assigned to a classical helicase category or a single canonical signaling pathway. Instead, SBNO proteins appear to connect signal-dependent transcription factors,

chromatin, basal transcriptional machinery, cell fate, and disease phenotypes. Establishing their direct biochemical activities, recruitment mechanisms, isoform expression, and cell-specific interaction networks will determine whether SBNO1 and SBNO2 can progress from candidate biomarkers and dependencies to mechanistically interpretable and safely actionable therapeutic targets.

## Statement of the Use of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) and DeepSeek to refine language and improve readability. After using these tools, the authors critically reviewed, revised, and verified all content and took full responsibility for the accuracy and integrity of the published article.

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## Author Contributions

H.W. designed the study and prepared the manuscript; Y.L. made important conceptual contributions and revised the manuscript.

## Ethics Statement

Not applicable.

## Informed Consent Statement

Not applicable.

## Data Availability Statement

No new datasets were generated or analyzed for this review.

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## Declaration of Competing Interest

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

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