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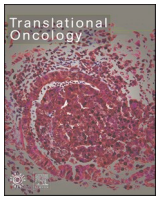

Review Article

Inhibition of STAT3: A promising approach to enhancing the efficacy of chemotherapy in medulloblastoma

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ABSTRACT

Medulloblastoma is a type of brain cancer that primarily affects children. While chemotherapy has been shown to be effective in treating medulloblastoma, the development of chemotherapy resistance remains a challenge. One potential therapeutic approach is to selectively inhibit the inducible transcription factor called STAT3, which is known to play a crucial role in the survival and growth of tumor cells. The activation of STAT3 has been linked to the growth and progression of various cancers, including medulloblastoma. Inhibition of STAT3 has been shown to sensitize medulloblastoma cells to chemotherapy, leading to improved treatment outcomes. Different approaches to STAT3 inhibition have been developed, including small-molecule inhibitors and RNA interference. Preclinical studies have shown the efficacy of STAT3 inhibitors in medulloblastoma, and clinical trials are currently ongoing to evaluate their safety and effectiveness in patients with various solid tumors, including medulloblastoma. In addition, researchers are also exploring ways to optimize the use of STAT3 inhibitors in combination with chemotherapy and identify biomarkers that can predict treatment that will help to develop personalized treatment strategies. This review highlights the potential of selective inhibition of STAT3 as a novel approach for the treatment of medulloblastoma and suggests that further research into the development of STAT3 inhibitors could lead to improved outcomes for patients with aggressive cancer.

Introduction

Medulloblastoma is a type of malignant brain tumor that mainly affects children. It arises from the cerebellum, which is the part of the brain responsible for coordinating movement and maintaining balance [1]. Medulloblastoma is a fast-growing cancer that can spread to other parts of the brain and spinal cord, making it a life-threatening condition if not treated promptly.[2] Medulloblastoma accounts for approximately 15% to 20% of all childhood brain tumors, and it is the most common malignant brain tumor in children [3]. The incidence of medulloblastoma varies by geographic region, with higher incidence rates reported in North America and Western Europe than in other parts of the world [4]. In the United States, medulloblastoma accounts for approximately 7% of all childhood cancers, with an estimated 500-600 new cases diagnosed each year [5]. The incidence rate of medulloblastoma in the United States is approximately 0.5–1.0 cases per 100,000 children under the age of 15 [6]. The cause of medulloblastoma is still not fully understood, but there are some genetic and environmental factors that may increase the risk of developing this type of cancer [7]. Symptoms of medulloblastoma can vary depending on the location and size of the tumor, but they often include headaches, vomiting, dizziness, and problems with balance and coordination [8].

The signal transducer and activator of transcription (STAT3) is a transcription factor comprising several distinct domains that orchestrate its activation and function [9]. STAT3 is a 770-amino acid-long protein with six domains shown in Fig. 1. The structural organization of STAT3 consists of an N-terminal domain (1–130 amino acids) responsible for protein–protein interactions and nuclear localization, followed by a coiled-coil domain (131–320 amino acids) that mediates dimerization. Adjacent to this, a DNA-binding domain (321–465 amino acids) is essential for sequence-specific DNA recognition, followed by a linker region (466–585 amino acids). The linker domain connects the DNA-binding domain to the Src homology 2 (SH2) domain (586–688 amino acids), which plays a crucial role in receptor tyrosine kinase

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recognition and phosphorylation. Finally, a C-terminal transactivation domain (689–770 amino acids) regulates target gene transcription [10–12].

STAT3 activation involves phosphorylation at a tyrosine residue in the SH2 domain, leading to dimerization, nuclear translocation, and subsequent gene regulation, making it a pivotal component in mediating cellular responses to various cytokines and growth factors [13]. The SH2 domain of STAT3 is essential for the activation and dimerization of the protein; the majority of STAT3 inhibitors target this domain [14]. A variety of amino acid residues, such as Arg609, Ser613, Glu614, Asp618, and Leu662, are implicated in inhibitor binding [15] as shown in Fig. 2. To avoid STAT3 activation, small compounds are designed to bind to the SH2 domain containing the tyrosine residue to compete with the natural ligands. To avoid STAT3 activation, small compounds that are made to resemble the phosphorylated tyrosine residue may compete with natural ligands for binding to the SH2 domain [16]. Numerous peptides and small compounds have been researched as possible STAT3 inhibitors. These substances frequently act to obstruct STAT3′s capacity to bind to the DNA and activate target genes, as well as to interfere with the protein–protein interactions necessary for STAT3 dimerization [17,18].

There are two isoforms of STAT3: the full-length STAT3α and the truncated STAT3β [19]. STAT3α is the main mediator of interleukin 6 (IL-6)-type cytokine signaling [20]. It has non-redundant roles, such as modulation of cellular responses to IL-6 and mediation of interleukin 10 (IL-10) function in macrophages. STAT3β is a distinct isoform of STAT3 that differs from STAT3α by the replacement of the C-terminal transactivation domain with a unique 23-amino acid sequence [21]. STAT3β is generally thought to act as a dominant negative factor. It is a truncated isoform that lacks the 55-residue C-terminal transactivation domain of STAT3α [22]. STAT3β can rescue the embryonic lethality of a STAT3-null mutation and can by itself induce the expression of specific STAT3 target genes. STAT3β has unique and specific functions, such as the regulation of cell migration and invasion [23]. STAT3β demonstrates distinct intracellular dynamics with prolonged nuclear retention, mapping to its unique C-terminal end [24].

The activation of the STAT3 pathway is initiated by the binding of extracellular ligands, such as cytokines, to their respective cell surface receptors [25]. These ligand–receptor interactions trigger a cascade of intracellular signaling events that ultimately result in the activation of STAT3 [26]. One of the key signaling pathways that activate STAT3 is the Janus kinase (JAK)-signal transducer and activator of the transcription (STAT) pathway. JAKs are cytoplasmic tyrosine kinases that are associated with cytokine receptors. Ligand binding activates JAKs and leaves phosphorylated tyrosine residues on the cytoplasmic tail of the receptor which [26] in turn, creates docking sites for STAT proteins, which are then phosphorylated by JAKs. Phosphorylated STAT proteins form dimers, translocate to the nucleus, and bind to specific DNA sequences, thereby regulating gene expression to promote cell proliferation, survival, and migration in cancer cells, making them an attractive target for cancer therapy [27]. Another signaling pathway that activates STAT3 is the phosphatidylinositol 3-kinase (PI3K)-AKT pathway. PI3K is a lipid kinase that is activated by growth factors and cytokines [28]. Activated PI3K generates phosphatidylinositol-3,4,5-trisphosphate (PIP3), to which Akt binds, bringing it into active conformation, which is then phosphorylated by 3-phosphoinositide-dependent kinase 1 (PDK1) and is a mechanistic target of rapamycin (mTOR) complex 2 (mTORC2) to activate AKT [29]. AKT, in turn, phosphorylates and activates various downstream targets, including STAT3. The inactivation of the STAT3 pathway is mediated by several negative regulators, including protein tyrosine phosphatases (PTPs), suppressors of cytokine signaling (SOCS), and protein inhibitors of activated STAT (PIAS) [30]. PTPs are enzymes that dephosphorylate tyrosine residues on proteins. They play a crucial role in terminating signaling pathways by removing phosphate groups from phosphorylated proteins.[31] Several PTPs have been shown to regulate the STAT3 pathway, including SHP1, SHP2, and PTPN11 [32].

Role of STAT3 in medulloblastoma pathogenesis

The STAT3 pathway is activated in medulloblastoma and has been implicated in the development and progression of this tumor. Several studies have shown that STAT3 activation is associated with increased proliferation and survival of medulloblastoma cells [33]. STAT3 was highly activated in medulloblastoma samples, and its expression was

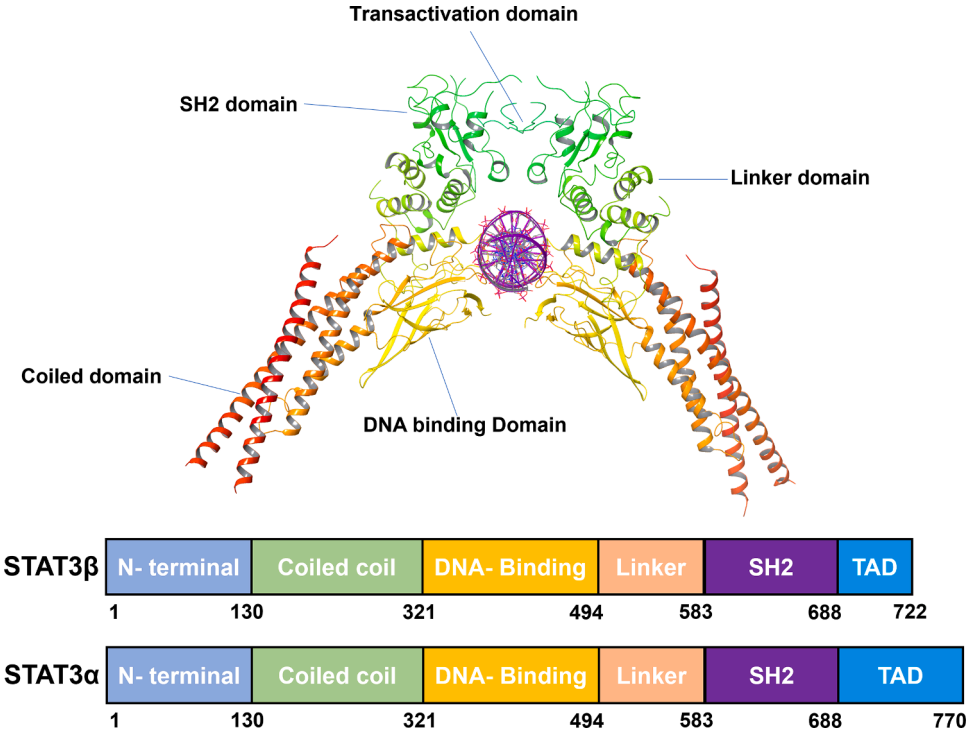


Fig. 1. Structural organization of STAT3 [161].

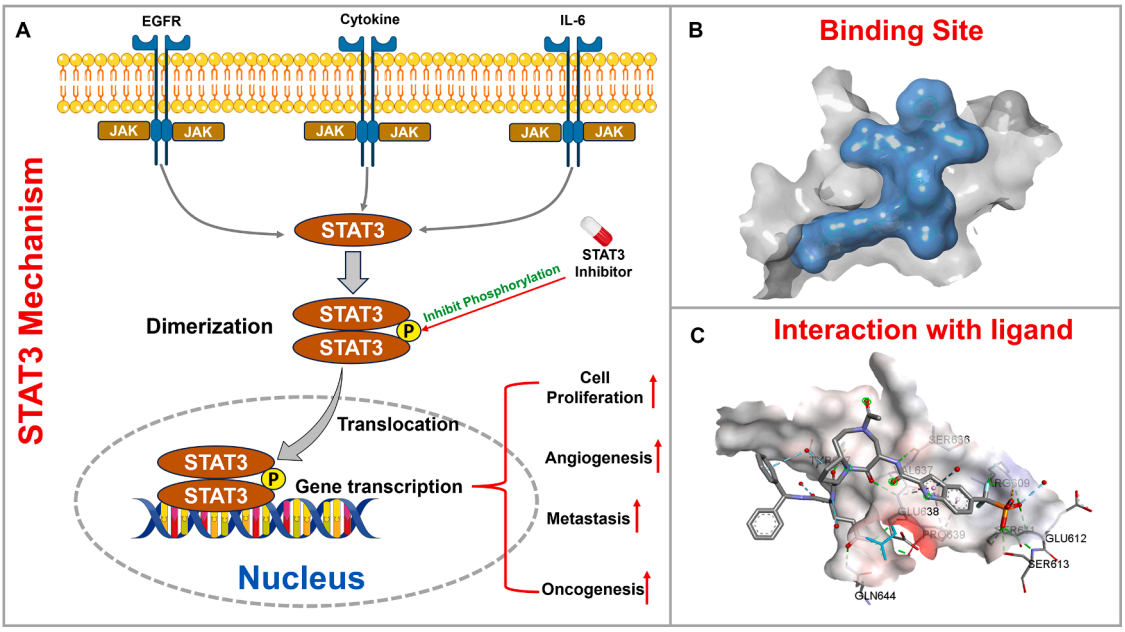


Fig. 2. (A) This diagram illustrates the mechanism of STAT3. Upon cytokine stimulation, JAK activates STAT3 through phosphorylation. Phosphorylated STAT3 forms dimers and translocates to the nucleus, initiating specific gene expression. (B) Binding site. (C) Interaction with ligand.

significantly associated with poor overall survival [34]. The researchers also found that inhibition of STAT3 using small-molecule inhibitors or short hairpin RNA (shRNA)-mediated knockdown led to decreased proliferation and increased apoptosis in medulloblastoma cells [35]. Another study found that cytokine IL-6, a known activator of the STAT3 pathway, was highly expressed in medulloblastoma samples [36]. The researcher showed that IL-6 promoted medulloblastoma cell proliferation and survival through activation of the STAT3 pathway [37]. In addition, STAT3 has been shown to interact with other signaling pathways that are dysregulated in medulloblastoma. For example, STAT3 has been shown to interact with the sonic hedgehog (SHH) pathway, which is commonly dysregulated in medulloblastoma [38]. Another study found that STAT3 was required for the proliferation of SHH-driven medulloblastoma cells and that inhibition of STAT3 led to decreased tumor growth in a mouse model of the medulloblastoma [39] mechanism of STAT3, shown in Fig. 3.

Medulloblastoma stem cells (MBSCs) are a subpopulation of cells within the tumor responsible for tumor initiation, progression, and recurrence. The STAT3 pathway is critical in the regulation of MBSCs. One study found that STAT3 was highly expressed in MBSCs and that its inhibition led to decreased self-renewal and tumor-initiating capacity of MBSCs [40]. The researchers also showed that STAT3 inhibition led to increased differentiation of MBSCs into non-tumorigenic cells [41]. Another study found that the cytokine leukemia inhibitory factor (LIF),

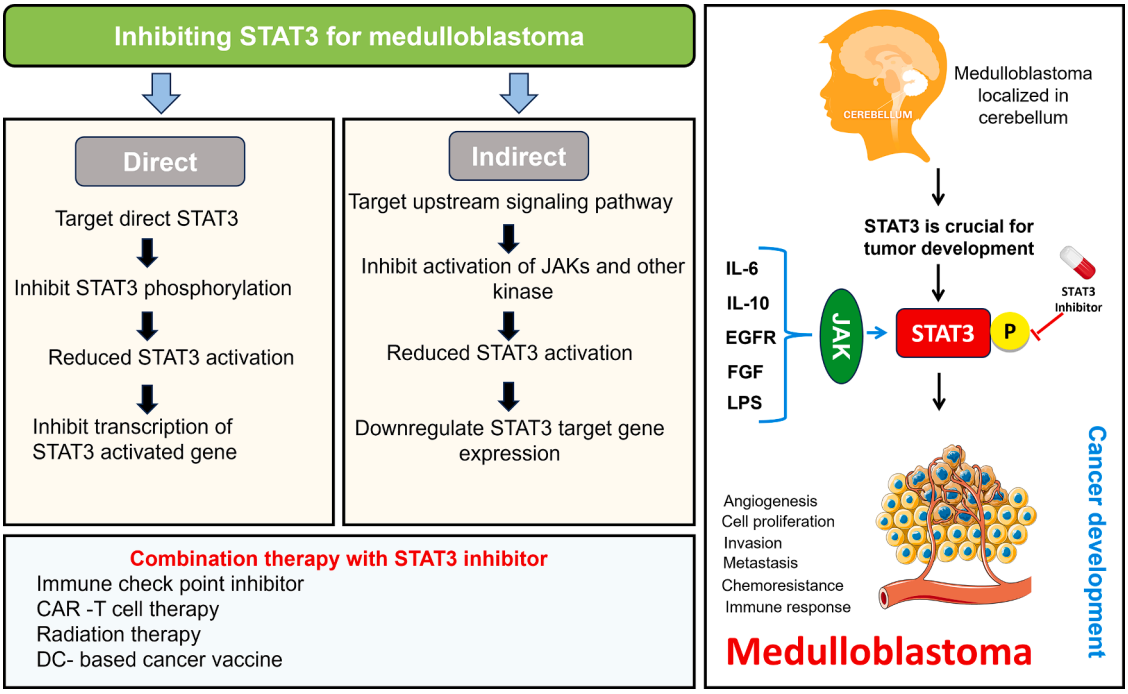


Fig. 3. Mechanisms by which STAT3 inhibitors act on medulloblastoma [162].

which is known to activate the STAT3 pathway, was highly expressed in MBSCs and showed that LIF promoted the self-renewal and survival of MBSCs through activation of the STAT3 pathway [42].

Targeting STAT3 is a new direction for treating medulloblastoma

Targeting STAT3 has emerged as a promising therapeutic strategy for the treatment of medulloblastoma. The activation of the STAT3 pathway in medulloblastoma is associated with increased proliferation, survival, and stemness of tumor cells, as well as resistance to chemotherapy and radiation therapy [43]. Therefore, targeting STAT3 can potentially overcome these limitations and improve the efficacy of current treatment modalities [44].

One of the key advantages of targeting STAT3 is its specificity for tumor cells. While the STAT3 pathway is activated in medulloblastoma, it is not active in normal brain tissue [42]. This differential activation provides a therapeutic window for selectively targeting tumor cells while sparing normal tissue. This specificity can minimize the side effects associated with conventional chemotherapy and radiation therapy, which often result in significant damage to healthy tissue. Several preclinical studies have demonstrated the potential of targeting STAT3 in medulloblastoma [45], and of targeting STAT3-sensitized medulloblastoma cells for chemotherapy and radiation therapy. Stattic, a small-molecule inhibitor of STAT3, has shown promising results in preclinical studies. Treatment with Stattic led to decreased tumor growth and increased survival in a mouse model of medulloblastoma [46]. Furthermore, combination therapy with Stattic and cisplatin was found to be more effective than monotherapy [47]. Another approach to targeting STAT3 is through the use of monoclonal antibodies. The use of monoclonal antibodies targeting IL-6 could be a potential strategy to suppress STAT3 signaling pathway [48]. Siltuximab, an IL-6 neutralizing monoclonal antibody, is undergoing clinical trials for treatment of ovarian, colorectal, pancreatic, lung, and head and neck cancer for its potential to target IL-6R/JAK/STAT3 signaling pathway [49]. In addition to small-molecule inhibitors, other approaches to targeting STAT3 like targeting upstream signaling molecules that activate STAT3, as well as developing novel delivery systems to improve the efficacy and specificity of STAT3 inhibitors are being explored [12]. Overall, targeting STAT3 has emerged as a promising therapeutic strategy for the treatment of medulloblastoma. Its specificity for tumor cells, ability to sensitize tumor cells to chemotherapy and radiation therapy, and potential for combination therapy make it an attractive target for further development. However, more research is needed to optimize the delivery and dosing of STAT3 inhibitors and to better understand the potential side effects associated with targeting this pathway [50].

STAT3 inhibitor in combination with radiotherapy

Radiation therapy has been used in cancer treatment for decades. In medulloblastoma, radiation therapy is typically performed after surgery to remove the remaining cancer cells and it is administered alone or combined with chemotherapy for older children [51]. The combination of different therapeutic strategies may enhance efficacy and reduce nonspecific toxicity due to what otherwise would be high-dose monotherapy [52]. Inhibition of STAT3 in combination with radiotherapy reduces the expression of STAT3 downstream targets, such as Cyclin D1 and Survivin, and induces apoptosis in cancer cells [53]. Combination therapy with STAT3 inhibitors and radiotherapy has shown promise for the treatment of medulloblastoma in preclinical studies. Studies have shown that the combination of the STAT3 inhibitor LLY17 and radiotherapy was more effective at inhibiting tumor growth in a mouse model of medulloblastoma than either treatment alone [54]. While radiotherapy is an effective treatment for medulloblastoma, it can be limited by resistance and toxicity. Targeting the STAT3 pathway can potentially overcome these limitations and enhance the efficacy of radiotherapy [55]. Inhibition of STAT3 leads to decreased DNA repair, increased apoptosis, and decreased survival of medulloblastoma cells exposed to radiation therapy [56]. This suggests that targeting STAT3 can enhance the effects of radiation therapy by reducing the ability of tumor cells to repair DNA damage and increasing their sensitivity to radiation-induced cell death [57]. In one study, treatment with the STAT3 inhibitor Stattic in combination with radiation therapy led to increased survival and decreased tumor growth in a mouse model of medulloblastoma compared with those for either treatment alone [58]. Another study found that treatment with the STAT3 inhibitor S3I-201 in combination with radiation therapy resulted in increased apoptosis and decreased proliferation of medulloblastoma cells [59]. The combination of STAT3 inhibitors and radiotherapy has also been investigated in other types of cancer. In a preclinical study of head and neck cancer, treatment with the STAT3 inhibitor JSI-124 (cucurbitacin I) in combination with radiation therapy led to increased tumor cell death and decreased tumor growth compared with those for either treatment alone [60]. Similarly, a study of breast cancer cells found that treatment with the STAT3 inhibitor OPB-31121 in combination with radiation therapy resulted in increased apoptosis and decreased cell viability [61]. While these preclinical studies are promising, more research is needed to optimize the combination of STAT3 inhibitors and radiotherapy for the treatment of medulloblastoma [62]. This includes determining the optimal dosing and timing of both treatments and evaluating potential side effects.

STAT3 inhibitor in combination with chemotherapy

Several studies have shown that STAT3 inhibitors can synergize with chemotherapy to kill cancer cells in a variety of cancer types, including lung cancer, breast cancer, and pancreatic cancer [63]. Directly targeting STAT3 and/or inhibiting its functions may be a promising strategy for developing safe and effective anticancer therapeutics [64]. Several STAT3 inhibitors have entered clinical trials, and some of them have been combined with chemotherapy to exert synergistic effects in treating triple-negative breast cancer [53]. Combining STAT3 inhibitors with Chimeric Antigen Receptor T (CAR-T) cells can reduce excessive expansion of CAR-T cells and alleviate the cytokine release syndrome (CRS) [65]. In addition, STAT3 inhibition enhances the therapeutic efficacy of immunogenic chemotherapy by stimulating type 1 interferon production by cancer cells. Therefore, combining STAT3 inhibitors with chemotherapy may be a promising strategy for cancer treatment [66].

Combination therapy with STAT3 inhibitors and chemotherapy has also shown promise for the treatment of medulloblastoma in preclinical studies. The effectiveness of chemotherapy in medulloblastoma is limited by toxicity and development of resistance. Targeting the STAT3 pathway can potentially overcome these limitations and enhance the efficacy of chemotherapy. Preclinical studies have shown that inhibition of STAT3 can sensitize medulloblastoma cells to chemotherapy [67]. Inhibition of STAT3 leads to decreased expression of anti-apoptotic proteins, increased apoptosis, and decreased survival of medulloblastoma cells exposed to chemotherapy. This suggests that targeting STAT3 can enhance the effects of chemotherapy by reducing the ability of tumor cells to survive and promoting their death [56].

STAT3 inhibitor in combination with immunotherapy

Currently, one of the most promising methods for treating cancer is immunotherapy. Immune checkpoint blockade (ICB) and CAR-T cells are the major components of this treatment approach, which has produced substantially better outcomes in patients with otherwise incurable malignancies [68,69]. A variety of cancers exploit immune checkpoint malfunction as a defense strategy to evade immune monitoring, enabling the progression of cancer. The notion of enhancing the host immune system as a potential anti-cancer treatment evolved from this belief [70]. The basic processes of cell division, differentiation, angiogenesis, and survival are all impacted by STAT3 [71,72]. In normally functioning cells, brief activation of STAT3 through

phosphorylation allows cytokines and growth factor receptors to convey transcriptional signals to the nucleus [73]. On the other hand, STAT3 attains hyperactivation in most of the cancer malignancies, which results in poor clinical outcome of various cancer therapies [74]. The cancer-associated fibroblasts (CAFs), endothelial cells, tumor cells, and smooth muscle cells make up an extremely multifaceted and varied ecosystem known as the tumor microenvironment (TME) [75,76]. TME is able to accelerate the development of cancer and cause resistance to therapy, especially to cancer immunotherapy [77,78]. Studies indicate that STAT3 is overactive in the TME, including immune cells, CAFs, and cancer cells themselves [79–83]. The increased activity of STAT3 in the TME may have a considerable effect on the immune response against tumors through several pathways. Hyperactivated STAT3 exerts significant immune effects on tumor cells by decreasing the production of immune-stimulating molecules such as chemokines, pro-inflammatory cytokines, and interferons, and increasing the levels of several cytokines and growth factors that include Transforming growth factor-β (TGFβ) and IL-6 [84]. To provide resilience for growth of tumor cells, STAT3 frequently interacts with other signaling pathways, such as nuclear factor kappa B (NF-κB), which is responsible for inflammation-induced carcinogenesis, as well as immune responses against tumors. Cyclooxygenase 2 (COX-2), interleukin 1 (IL-1), IL-6, and interleukin 23 (IL-23) are a few of the molecules that can be stimulated by NF-κB, particularly v-rel avian reticuloendotheliosis viral oncogene homolog A (RELA); they are also implicated in chronic inflammation and cancer development [85–87].

At this point, many levels of STAT3-NF-κB crosstalk have been discovered: (i) With many shared targets involved in cell angiogenesis, proliferation, survival, and metastasis, NF-κB and STAT3 are commonly stimulated in tumor cells and TME-bound immune cells [86]. (ii) By p300-mediated acetylation, STAT3 can extend the retention time of RELA in the nucleus, resulting in continuous activation of NF- κB. (iii) Numerous cytokines, such IL-6, can activate STAT3 and NF-κB at the same time [88]. (iv) Recent research has shown that NF-κB functioning in pancreatic CAFs enhanced CXCL12 expression, protecting malignant cells from immune onslaught [89]. Considering the widely recognized relationship between CXCL12 and STAT3, it is likely that STAT3 is involved in this NF-κB -associated immune escape [90,91]. Additionally, STAT3 is essential for a variety of immune cells that mostly make up the TME. Immunosuppression is brought on by the increased activity of STAT3 in tumor-bound immune cells, which prevents immune responses that are innate and adaptive. Overall, increased STAT3 activity in the innate immune cell subgroup may suppress antigen presentation, reduce the synthesis of pro-inflammatory mediators such as Interferon-gamma (IFNγ), and prevent effector cells from destroying malignancies [92–94].

It has been demonstrated that increased expression of immune checkpoint molecules such as Cytotoxic T-lymphocyte associated protein 4 (CTLA-4), Programmed cell death 1 (PD-1), and Programmed death-ligand 1 (PD-L1) helps tumor immune escape. There is a lot of evidence that STAT3 can control these immune checkpoint molecules directly or indirectly. By interacting directly with the promoters of PD-1, PD-L1, and PD-L2 genes, STAT3 functions as a transcription factor that can boost gene expression [95–98]. In addition, it has been discovered that STAT3 can indirectly stimulate the production of immune checkpoint molecules by altering several signaling mechanisms. According to reports, PD-1 overexpression in Clusters of differentiation 4 (CD4+) T cells increases the expression of STAT3 mRNA by an unidentified process, and this is necessary for the synthesis of Interleukin 17 (IL-17) and TGFβ1 [99]. In CD4+ T cells, PD-1 can reduce the TCR's ability to activate the PI3K/Akt pathway [100]. Given that PI3K/Akt is a transcriptional regulator of STAT3, it is likely that PD-1 indirectly increases STAT3 activity via PI3K inhibition. In addition to indicating that STAT3 is involved in anti-tumor immunity, the inverse relationship of immune checkpoint molecules and STAT3 offers a possible method for enhancing the effectiveness of the existing immune checkpoint inhibitors [101]. The inclusion of STAT3 inhibitors can increase curative effectiveness and simultaneously decrease resistance to ICB immunotherapy, which is an optimistic finding of paired STAT3 and immune checkpoint blocking. Hematologic malignancies' anti-cancer treatments have been transformed by CAR-T cell therapy, an immunotherapeutic strategy that is quickly gaining popularity. The primary tumor stromal component CAFs influence the extracellular matrix, secrete soluble molecules, promote angiogenesis and metastasis, and suppress anti-tumor immune responses, which all lead to the development of cancer and treatment failure [102]. Recent research has shown that Leukemia inhibitory factor (LIF), among other cytokines, can activate STAT3 in CAFs [103]. Due to the overstimulation of STAT3, CAFs produce different immunosuppressive agents such as C-C Motif Chemokine Ligand 2 (CCL2), Vascular endothelial growth factor (VEGF), TGFβ, IL-6, and EGF, which is responsible for their pro-oncogenic activity [104,105]. It is becoming clearer that STAT3 signaling has a role in CAR-T treatment. Chronic lymphocytic leukemia patients that responded to anti-CD19 CAR-T cells exhibited higher IL-6/STAT3 levels, which encouraged the growth of CAR-T cell therapy, according to transcriptomic profiling [106]. Accordingly, a new anti-CD19 CAR-T cell with STAT3 stimulation demonstrated higher CAR-T cell proliferation and decreased terminal differentiation, and provided superior anti-cancer effects [106]. These results imply that stimulation of STAT3 in CAR-T cells has a positive effect. As discussed earlier, STAT3 excessive stimulation in tumor stroma suppresses the immune system and may result in a rise in the production of specific cytokines and growth factors. In light of this, constitutive production of a variety of cytokines, including IL-6 and IL-10, may raise the likelihood of severe side effects of CAR-T treatment [107]. Therefore, there have been some efforts to integrate STAT3 inhibitors with CAR-T treatment to increase its stability and anti-tumor effects while reducing CAR-T cell toxicity *in vivo*. Several human malignancies cause increased STAT3 activation, which serves as a key signaling link for tumor cells and TME constituent cells, particularly tumor-infiltrating immune cells. Addressing STAT3 thus seems to have various advantages, including decreased intrinsic tumor cell growth, greater immunosuppressive interaction within the TME, and increased anti-tumor effects of immune cells invading the tumor. Due to these outcomes, STAT3 has emerged as an intriguing prospective approach to the treatment of cancer [84].

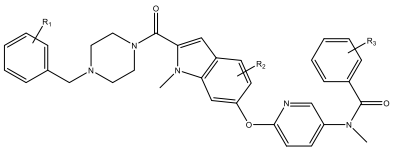
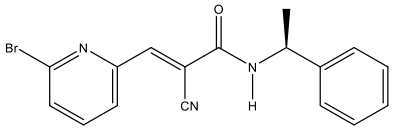
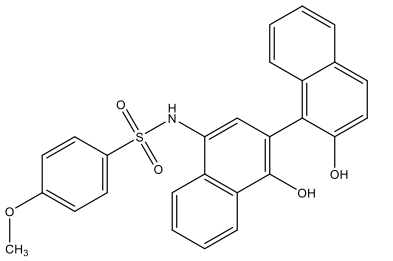
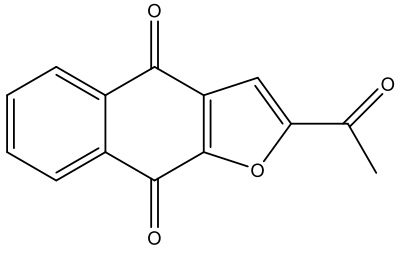
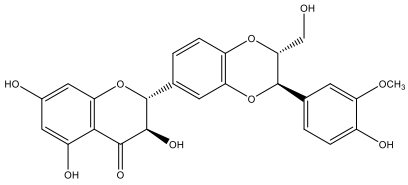
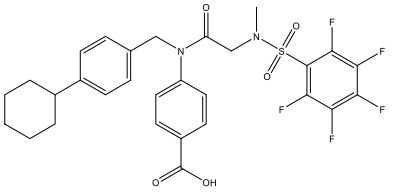
The combination of a STAT3 inhibitor with immunotherapy could yield several benefits:

- Enhanced immune response: STAT3 inhibition may restore immune cell function and improve their ability to recognize and attack tumor cells.
- Reduced tumor growth: Blocking STAT3 could hinder tumor cell proliferation and survival, making them more susceptible to immune attack.
- Improved immune infiltration: STAT3 inhibition might increase immune cell infiltration into the tumor, bolstering the effectiveness of immunotherapy.
- Reduced immunosuppression: STAT3 inhibition can modulate the tumor microenvironment, reducing factors that suppress the immune response.

Various STAT3 inhibitors under development

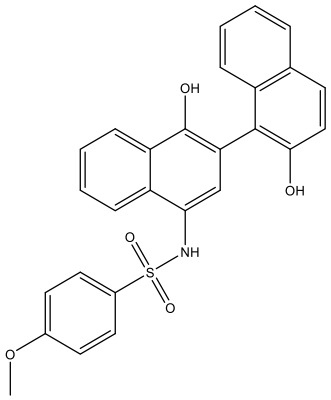
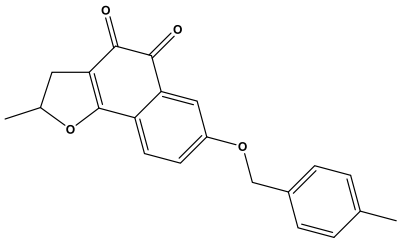
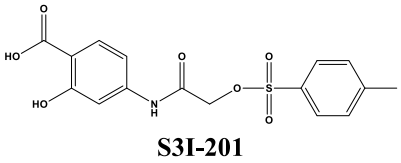
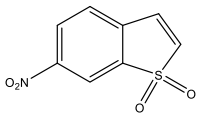
Several STAT3 inhibitors are currently under clinical trial. Some of the small-molecule inhibitors that have entered clinical trials include STAT3 Inhibitor C188-9 (TTI-101) and STAT3 Inhibitor WP1066. These inhibitors are being tested for their safety and efficacy in treating various types of cancer, including head and neck cancer and other solid tumors. The development of STAT3 inhibitors is a promising area of research, and various novel approaches are being explored to overcome the challenges associated with targeting STAT3. List of various STAT3 inhibitors under development is shown in Table 1.

Table 1
Various STAT3 inhibitors under development.

Inhibitor Name	Cancer Type	Brief Description	Phase of Development	Ref
 **OPB-31121**	Advanced solid tumor, and hepatocellular carcinoma	• Antitumor activity demonstrated, Unfavorable pharmacokinetic profile. • The DLTs were grade 3 vomiting, grade 3 diarrhea, and grade 3 lactic acidosis. • Thrombocytopenia, Neutropenia.	**Status** Phase II (Ongoing) **NCT number** NCT00955812 NCT01406574	[1,2]
 **WP1066**	Recurrent glioblastoma, Metastatic malignant neoplasm in the brain	• Antitumor activity demonstrated, • More effective with radiation therapy. • Grade 1 nausea and diarrhea in 50% of patients.	**Status** Phase II (Recruiting) **NCT number** NCT05879250 NCT04334863	[3]
 **TTI-101**	Breast cancer, Hepatocellular carcinoma, head and neck squamous cell carcinoma	• Antitumor activity demonstrated, • No dose limiting toxicities. • Diarrhea was the only TRAE observed in ≥30%	**Status** Phase II (Recruiting) **NCT number** NCT05440708, NCT03195699	[4,5]
 **Napabucasin (BBI608)**	Glioblastoma, Advanced Malignancies, Colorectal Cancer	• Antitumor activity demonstrated. • AEs included grade 1/2 diarrhea, nausea, abdominal cramps, and vomiting. • No DLTs was observed	**Status** Phase II (Ongoing) **NCT number** NCT02315534 NCT01775423 NCT02753127	[10, 11]
 **Silibinin**	Brain metastasis (BM) from non-small-cell lung cancer (NSCLC), Breast Cancer	• Antitumor activity demonstrated. • Mild allergic reactions, urticaria • Mild laxative symptoms have been reported	Preclinical	[6,7]
 **SH-4-54**	Chronic myeloid leukemia (CML)	• Inhibited the growth of CML cell lines. • SH-4-54 effectively inhibited the phosphorylation of STAT3. • Specific toxicity and side effects of SH-4-54 are not reported	Preclinical	[8]

(*continued on next page*)

Table 1 (*continued*)

Inhibitor Name	Cancer Type	Brief Description	Phase of Development	Ref
 **C188-9**	Head and neck squamous cell carcinoma	• Strong antitumor effect on HNSCC • C188-9 was well tolerated in mice. • Showed good oral bioavailability. • No specific toxicity reported	Preclinical	[9]
 **LYW-6**	Colorectal cancer	• STAT3 phosphorylation in tumor inhibited on xenograft models. • Reduce the metastasis in tail-lung metastasis models.	Preclinical	[12]
 **S3I-201**	Gastric cancer	• Strong anti-proliferation activity demonstrated on gastric cancer cells. • Enhancement in growth inhibition with dacomitinib	Preclinical	[13, 14]
 **Stattic**	Breast cancer, Pancreatic cancer	• Potently and selectively inhibits STAT3 activation and nuclear translocation. • No specific toxicity reported	Preclinical	[15, 16]

STAT3 in polarization of macrophages in medulloblastoma

The complicated process of macrophage polarization, which gives rise to different activation states, is generally believed to be controlled by a number of intracellular signaling molecules and their associated pathways [108,109]. Furthermore, STAT3 controls macrophage polarization to carry out a variety of critical functions in both healthy and malignant human tissues, including angiogenesis, proliferation, differentiation, and survival, as well as immune system regulation [64]. There is a crosstalk between different signaling pathways like PI3K/Akt/mTOR, MAPK, and AMPK during the STAT3-dependent macrophage polarization process [110].

The JAK/STAT pathway is activated by cytokines and growth factors, which are secreted glycoproteins acting as intercellular messengers. These factors bind specialized cell surface receptors on target cells which have intracellular domains that are constitutively coupled to members of the JAK family, which includes JAK1, JAK2, JAK3, and TYK2. The cytokine-receptor engagement activates JAK which phosphorylates the tyrosine residues on the cytoplasmic tail, which in turn causes auto/transphosphorylation. This phosphorylation forms binding sites for latent cytoplasmic STATs, which are then drawn to the receptor complex and phosphorylate themselves by the action of tyrosine-phosphate-binding SH2 domains. Finally, the phosphorylated STATs separate from the receptors, form a dimer in the cytoplasm, and travel to the nucleus, where they bind to the target gene's promoter region to start the transcription of that gene [111]. Through JAK/STAT signaling, the multifunctional protein STAT3 affects human metabolism, immunological inflammation, and damage repair. It is controlled by numerous cytokines and growth factors [112]. Research on the function of JAK/-STAT3 in macrophage polarization has demonstrated that this system can either be stimulated or inhibited to improve macrophage M2 polarization, depending on the disease. However, STAT3 activation often promotes macrophage M2 polarization [110].

According to research on tumor conditions including glioma and ovarian cancer, JAK/STAT3 signaling axis activation promotes M2 macrophage polarization and influences the course of the disease by either activating or suppressing associated cytokines [113–117]. The two distinct sets of data indicate that, in addition to the diversity of STAT3 and macrophages, other factors that may influence macrophage polarization include immune cells, tumor cells, the JAK/STAT3 pathway, multiple cytokines, chemokines, immune cells, and interaction between diverse signaling pathways in macrophages [118,119]. The pattern of macrophage polarization may depend on how these parameters are balanced. IL-6 and IL-10 are the two most prominent regulatory cytokines of the JAK/STAT3 signaling pathway. IL-6 is found abundantly in the TME and is a vital cytokine that promotes tumor cell cycle

development and inhibits apoptosis [120]. IL-6 promotes the JAK/-STAT3 signaling pathway by interacting with host cell receptor complex glycoprotein 130/IL-6 receptor (IL-6R) [121]. According to recent studies, IL-6/JAK/STAT3 may be expressed directly in tumor cells and promote tumor cell proliferation, differentiation, and metastasis. It may also be present in macrophages and affect the beginning and development of disease indirectly through macrophage M2 polarization [122]. As a result, by blocking this signaling pathway, macrophage polarization to the M2 sub-type can be blocked, which in turn suppresses pro-tumor related cytokines including IL-6, IL-10, and VEGF production, which will eventually restrict the advancement of the tumor condition [123].

The transcriptional regulator, also known as the "master switch" that controls the production of many pro-inflammatory mediator genes, is called NF-κB. The NF-κB's p65 subunit controls the polarization of macrophage M1. Whenever the Toll-like receptor 4 (TLR4) on the surface of macrophages attaches to lipopolysaccharide (LPS) via a route reliant on the myeloid differentiation factor 88 (MyD88) or the interferon regulatory factor (IRF) 3, the conventional NF-κB pathway is activated [124]. Typically, STAT3 activation is essential for the anti-inflammatory M2 phenotype, whereas NF-κB activation results in an inflammatory macrophage M1 phenotype. Together, these processes regulate responses to diverse microenvironments and preserve M1/M2 homeostasis [125]. (MicroRNA) let7Wb, one of the most significant factors associated with immune system regulation and inflammation, has been shown to affect the TLR4 pathway adversely [126]. The TLR4/NF-κB/STAT3/AKT signaling pathway was found to be responsible for the significant increase in p-STAT3 and p-AKT expression levels in macrophages. In the presence of let-7b inhibitor, STAT3 stimulation completely stopped, suggesting that the TLR4/NF-κB/STAT3/AKT regulatory circuit can regulate the modification of macrophage polarization, a process that causes inflammation [127].

Studies have shown that migration, proliferation, and survival of macrophages depend on the PI3K/AKT signaling system [128]. Numerous human diseases such as heart-related disease, diabetes, cancer, and neurological problems have been related to dysregulation of this signaling system [129–132]. Additionally, research has shown that PI3K/AKT activation enhances STAT3 phosphorylation and nuclear translocation, which helps macrophages polarize toward M2 and has pro-cancer and immunosuppressive effects through the release of many mediators [133,134].

In conclusion, a variety of signaling pathways can control macrophage polarization by influencing STAT3, which then influences the progression of the illness. Consequently, activating or inhibiting these signaling pathways may be able to control the M1/M2 balance and offer fresh treatment options for disorders that are associated with it [110].

Exosomes-based therapies targeting STAT3

Material exchange between cells is required for good communication and cell viability [135]. Recently, extracellular vehicles (EVs), notably exosomes, have emerged as new cell–cell communication mediators in healthy and pathological situations [136]. Exosomes are distinct from other forms of EVs in terms of biogenesis, release mechanisms, size, content, and function; see Fig. 4. Exosomes are generated by the inward budding of early endosome membranes, which later develop into multivesicular structures [137]. Microvesicles (MVs), conversely, are formed by direct outward pinching or budding of the cell's plasma membrane, whereas apoptotic bodies are discharged into the extracellular space by dying cells [137]. Recent research has revealed that tumor-cell-derived exosomes play an important role in communication by transporting numerous biomolecules such as proteins, lipids, DNA, and RNA [138]. The cargo of exosomes closely resembles the intracellular components of their parent cells. Therefore, real-time detection of these exosomal components could provide critical insights for diagnosis, prognosis, and disease monitoring. In a clinical setting, exosomes can serve as diagnostic biomarkers and even as carriers for anticancer drugs. Their clathrin-coated membranes confer exceptional stability and resistance against degradation enzymes, such as RNases, making them an attractive tool for diagnosis and therapy [139]. Exosomes and other extracellular vesicles are essential in regulating a wide range of physiological and pathological cellular processes, which can be utilized for therapeutic purposes [136]. Recently, mesenchymal stem cells (MSCs) derived from various sources, such as bone marrow, adipose tissue, and cord blood, have gained significant attention as potential therapeutic agents with regenerative properties [140]. Studies have shown that in pig and mouse models, MSC-derived exosomes have significant cardio-protective paracrine effects against myocardial ischemia/reperfusion injury [141]. Furthermore, MSC-derived exosomes have been shown to treat pulmonary hypertension by suppressing early inflammation and vascular remodeling. These act by inhibiting

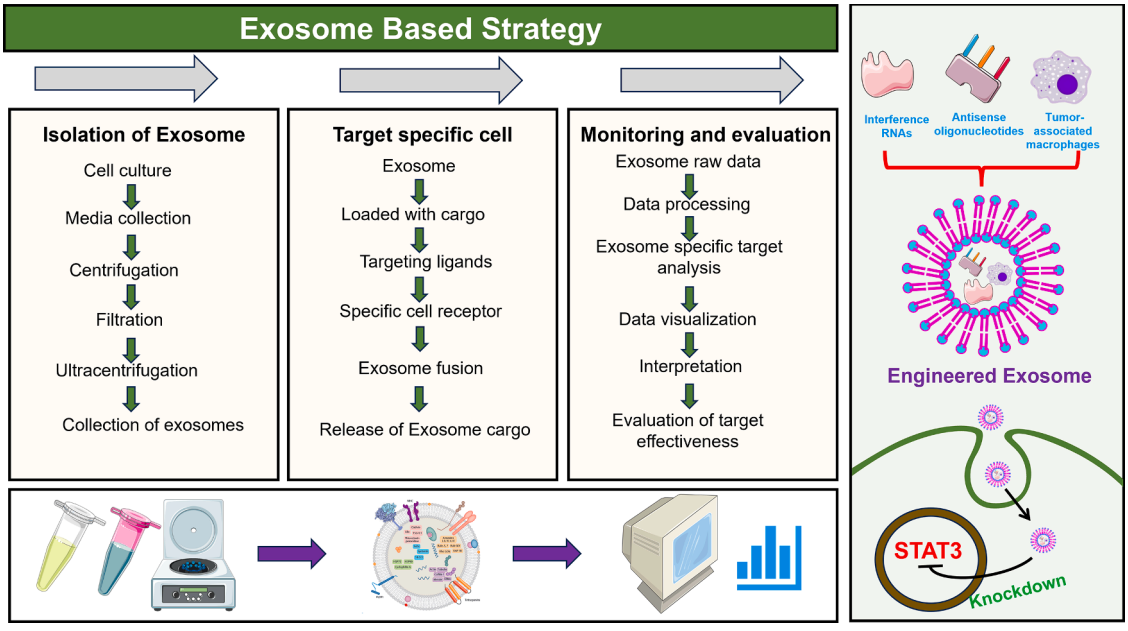


Fig. 4. Workflow for exosome-based strategy used for STAT3 inhibition.

hyper-proliferative pathways, including STAT3 mediated signaling [142]. Another study explored the potential of exosome-based strategies targeting STAT3 for treating neurovascular injuries. Microglia-secreted miR-424-5p is crucial in exacerbating endothelial cell damage and vascular integrity loss during oxygen–glucose deprivation (OGD). MiR-424-5p inhibition mitigated these effects by targeting the FGF2-mediated STAT3 signaling pathway. *In vivo*, mouse experiments confirmed that blocking miR-424-5p reduced neurological dysfunction and endothelial cell injury caused by middle cerebral artery occlusion (MCAO) [143].

Mesenchymal stromal cell-derived exosomes (MEX) have shown potential in treating pulmonary hypertension. They inhibit early lung inflammation while promoting vascular remodeling. By inhibiting the activation of the STAT3 pathway, MEX significantly reduces hypoxia, and lowers miR-17 levels while raising miR-204, which is typically reduced in pulmonary hypertension. MEX also inhibits STAT3 signaling in pulmonary artery endothelial cells, directly influencing hypoxic vascular cells [144].

A study proposed a unique way to improve glioblastoma (GBM) therapy by employing Angiopep-2 (An2)-functionalized exosomes loaded with small interfering RNA (siRNA) targeting STAT3. GBM treatment with siRNA has several problems, including low absorption, immunogenicity, instability, short circulation time, and limited blood–brain barrier penetration. An Exo-An2-siRNA formulation demonstrated exceptional properties such as increased blood stability, effective cellular uptake, and significant BBB penetration. Exo-An2-siRNA displayed potent *in vitro* anti-GBM activities, protected siRNA, and successfully targeted GBM cells, enhancing tumor inhibition and increased survival in mice with GBM [145]. Formulations such as exosomal curcumin (Exo-cur) and exosomal cucurbitacin I (Exo-JSI124) have been developed by independently encapsulating curcumin and a STAT3 inhibitor named JSI124 into exosomes. When administered intranasally to brain microglial cells, these exosomes caused apoptosis in microglial cells, substantially decreasing LPS-driven brain inflammation. Similarly, Exo-JSI124 slowed tumor growth and increased subject survival in a glioblastoma tumor model [146]. Therefore, exosome-based formulations are used for targeting STAT3 in various applications, including inflammation control and cancer therapy, and offer a promising approach.

STAT3: a potential player in personalized medicine

STAT3 is emerging as a key component of personalized medicine for medulloblastoma patients, offering exciting new therapeutic opportunities [147]. Complete comprehension pertaining to STAT3 activation pathways is still lacking and there is a need for refining STAT3 inhibitors for therapeutic application [148]. Repurposing drugs is another effective way to get STAT3 inhibitors into the clinic quickly [149]. Recently FDA approved compounds like Pyrimethamine and Celecoxib as STAT3 inhibitors, offering new avenues for cancer therapy. Use of STAT3 inhibitors in combination with other targeted therapies or conventional procedures like radiation therapy or chemotherapy could increase treatment efficacy [150]. Certain natural substances, such as salidroside and isoharringtonine, have been found in multiple preclinical investigations to increase the efficacy of STAT3 inhibitors. These compounds have also been shown to exert anti-cancer activity against triple negative breast cancer (TNBC) by preventing STAT3 from binding to DNA. Pectolinarigenin inhibited the migration and invasion of breast cancer cells in vitro and suppressed growth and metastasis of osteosarcoma by inhibiting the STAT3 signaling pathway [53,151]. Numerous other natural products have demonstrated strong anticancer effects by blocking the STAT3 signaling pathway in different types of cancer, including resveratrol, curcumin, alantolactone, curvularin, osthole, piperlongumine, withaferin A, trichothecin, angoline, norcantharidin, 2-O-methylmagnolol, and cosmomycin C. These organic products will reduce STAT3 inhibitor toxicities and side effects, and dramatically maximize their tolerability. In addition, targeted therapy is becoming equally promising in order to ensure better therapeutic approaches and overcome blood-brain barrier, chemoresistance, tumor microenvironment, and cancer stem cells [152–156]. These therapies include drugs aimed at certain pathways, oncoviruses, and modified T-cells. Cancer-specific therapy is based on innovative tailored therapy techniques. Genetic testing is a method to determine the specific abnormalities in a patient's cell of their cancer [157,158]. However, in this situation, it is necessary to use a different procedure to identify the STAT3 expression in the tumor cells before beginning the treatment. This alternative solution must encompass genomic profiling of your tumor to discover some essential mutations or other differences that may influence your response to STAT3 inhibitors and molecular testing to determine the existence of STAT3 and how hard it is working. Also, new ways of targeting STAT3, like aptamers and oligonucleotides, have shown promise in reducing tumor growth. While causing minimal damage, STAT3 also shows much promise as a personalized target, given its involvement in immune infiltration and drug response in cancer [159,160].

Conclusion

Medulloblastoma is an aggressive brain tumor in children which requires prompt attention to avoid fatality. The complex molecular profile is characterized by the activation of STAT3 pathway facilitated by JAK-STAT and PI3K-AKT signaling. Targeting these pathways presents the best hope for curing this devastating disease, and thus more studies are needed to develop new therapies that can ameliorate the prognosis in these severely impacted patients. The process of preclinical testing on Stattic and other STAT3 inhibitors has proven to be encouraging and demonstrates potential for combination therapy. STAT3 inhibitors combined with other modalities of treatment like radiation, chemotherapy, immunotherapy, and exosome-based methods could lead to synergistic effects that would help overcome resistance as well as enhance therapeutic outcomes. There is effective therapy for targeting the STAT3 pathway through an exosome-based method for various applications, including neurovascular injuries and glioblastoma therapy. Nevertheless, there are certain limitations. For example, most of the evidence is based on preclinical research, thus failing to comprehensively capture the mechanistic and physiological consequences on actual pathologies. Therefore, any treatment decisions based on these findings should be made with caution. Additionally, there is a lack of sufficient long-term usage data on safety, efficacy, and patient outcomes, and the majority of reviewed clinical studies are in the developing stages. Future research on STAT3 inhibition in the therapy of medulloblastoma should focus on several aspects. More research should be performed on the molecular processes underlying STAT3 activation and its interaction with other signaling pathways. This will allow for the development of predictable biomarkers and combination therapies. Identifying novel and better STAT3 inhibitors with higher bioavailability and specificity and research on drug delivery systems for selective inhibition of STAT3 in the central nervous system will also be needed for clinical applications.

Availability of data and materials

All the data were from publicly available search engines, namely PubMed, Scopus, and Web of Science. These articles are available online.

CRediT authorship contribution statement

Sachindra Kumar: Writing – review & editing, Writing – original draft, Conceptualization. **Dube Aakash Arwind:** Writing – original draft. **Harish Kumar B:** Writing – review & editing. **Samyak Pandey:** Writing – review & editing. **Raksha Nayak:** Writing – original draft.

Megh Pravin Vithalkar: Writing – original draft. **Nitesh Kumar:** Writing – review & editing. **K Sreedhara Ranganath Pai:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare no conflicts of interest.

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