Abstract. Elevated levels of the pro-inflammatory cytokine interleukin-6 (IL-6) have tumor-promoting activity and are associated with poor survival outcomes in many cancers. Additionally, the IL-6/GP130/STAT3 axis has been widely studied due to its pivotal role in tumor development and maintenance in a number of tissue types, including the cerebellum. However, the connection between IL-6 signaling and medulloblastoma progression is largely unexplored. In the present study, we observed that IL-6 induced medulloblastoma cell viability, cell proliferation and glycolysis. Furthermore, it also upregulated the expression of phosphorylated STAT3, indicating that the IL-6/GP130/STAT3 pathway plays a central role in medulloblastoma. The FDA-approved drug bazedoxifene, a blocker of the formation of the hexameric IL-6/IL-6R/GP130 complex, was re-purposed in this study to inhibit the IL-6/GP130/STAT3 signaling pathway. Bazedoxifene not only inhibited IL-6 mediated cell viability and cell proliferation, and increased phosphorylated STAT3 expression, but it also decreased cell glycolysis, demonstrating a certain level of therapeutic efficacy in vitro. Collectively, our findings offer new insight into the molecular mechanism underlying the biological aggressiveness of medulloblastoma, the roles of IL-6 in these processes and a possible efficacious adjuvant therapy for medulloblastoma.

Introduction

Medulloblastoma is the most common malignant pediatric brain tumor, accounting for ~63.7% of all embryonal brain tumors in children and adolescents (1,2). The current consensus recognizes four genetic (molecular) subgroups of medulloblastoma, including Wingless (Wnt), Sonic hedgehog (SHH), and the numerically designated ‘group 3’ and ‘group 4’ (3,4). Therapy regimens using a combination of surgery, craniospinal radiotherapy, and chemotherapy with vincristine, cisplatin and cyclophosphamide result in an overall survival rate of 70-80%; however, survivors are at increased risk to develop long-term sequelae such as neurocognitive impairment, endocrinopathies and neurologic deficits (5‑7). Therefore, medulloblastoma still represents a major clinical challenge in pediatric oncology, and demands the development of targeted approaches with less toxic side effects while preserving therapeutic effectiveness.

Interleukin-6 (IL-6) belongs to a large family of multifunctional cytokines. Besides its functions in inflammation and immune regulation, it plays a crucial role in the development of various types of cancer (8,9), and regulates most of the hallmarks of cancer, including promotion of survival (10,11), proliferation (12,13), angiogenesis (14), and cancer cell invasion and metastasis (15,16); it is also a pivotal contributor to cancer cell metabolism (17,18). Emerging evidence suggests that high serum levels of IL-6 are observed in multiple cancer types, implying a strong association between IL-6 and cancer (19-21).}

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of transcription) pathways via GP130 tyrosine phosphorylation (13,23,24). Mounting evidence indicates that activation of IL-6/GP130/STAT3 signaling is an important event in a number of cancer types and it promotes tumorigenesis by regulating multiple survival signaling pathways in cancer cells (25-27).

In light of the above, inhibition of the IL-6/GP130/STAT3 axis was considered to have therapeutic potential in cancer and IL-6 and IL-6R blocking antibodies (e.g., tocilizumab), JAK inhibitors, and STAT3 inhibitors have been developed and tested (28-32). A number of IL-6 ligand binding antibodies and IL-6R blocking antibodies have been developed and are currently in clinical trials. Among these, a small molecule JAK inhibitor, tofacitinib, and a humanized monoclonal antibody targeting human IL-6R, tocilizumab, have been approved by the FDA (33). However, tofacitinib has the capacity to block the activity of most cytokines, and tocilizumab could cause a dramatic increase in systemic IL-6 levels and an increased risk of infections (34).

Currently, new uses of classical small molecules are playing a critical role in drug discovery. In our previous studies, the FDA-approved drug bazedoxifene was re-purposed as a novel small molecular inhibitor of trimetric IL-6/IL-6R/GP130 complex, suppressing tumor growth and inducing apoptosis in human cancer cells and a xenograft model (35,36). Herein, we investigated the efficacy of bazedoxifene on the IL-6/IL-6R/GP130 pathway and its effects on medulloblastoma cells. Targeting the IL-6/GP130/STAT3 axis using bazedoxifene inhibited IL-6 enhanced cell viability, proliferation, glycolysis and reduced clonogenicity in colony formation. These results suggest that bazedoxifene is a potent inhibitor against the IL-6/GP130/STAT3 signaling pathway and may be of use clinically.

Materials and methods

Cell culture and reagents. The medulloblastoma cell lines (DAOY and UW288) were provided by Dr Corey Raffel (The Research Institute at Nationwide Children's Hospital). Cells were maintained in 1X Dulbecco's modified Eagle's medium (DMEM) with 4.5 g/l L-glutamine and sodium pyruvate (Mediatech, #10013 C v) supplemented with 10% fetal bovine serum (FBS) (Atlanta Biologicals, #S11150), and 1% penicillin/streptomycin (P/S) (Sigma, #P0781) in incubators set at 37˚C and aired with 5% CO₂.

The reagents in the study were as follows: recombinant human IL-6 (Cell Signaling Technology, #8904SF), bazedoxifene (Sigma, #PZ0018), 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) dye (20 µl, 5%, w/v) was added to each well. Subsequently, the plates were incubated at 37˚C for 4 h. Thereafter, DMF solubilization solution (150 µl) was then added to each sample with gentle shaking overnight. Absorbance was measured at 595 nm. Combination index (CI) was calculated by CompuSyn software. Bazedoxifene (10 and 15 μM) is combined either with the STAT3 inhibitor, BP-1-102 (5, 10 and 15 μM), or the GP130 inhibitor, SC144 (5, 10 and 15 μM), in UW288 and DAOY cells.

Cell proliferation assay. Cell proliferation was measured using Bromodeoxyuridine (BrDU) Cell Proliferation assay kit (Cell Signaling Technology, #6813S). Eight thousand cells per well were seeded in 96-well plates in triplicate and allowed to adhere overnight. Cells were treated with serial dilutions of IL-6 or drugs in serum-free medium and incubated at 37˚C for 24 h. The following day the medium was changed to 1X BrDU solution prepared in 0% FBS medium and incubated for 1 h at 37˚C to induce cell proliferation and BrDU incorporation during S-phase. The rest of the procedure was performed according to the manufacturer's instructions. The BrDU incorporation was measured at 450 nm using a microplate reader.

Western blot assay. Medulloblastoma cell lines (DAOY and UW288) were washed with cold PBS and harvested with a rubber scraper after treatment. Cell pellets were kept on ice and lysed for 20 min in cell lysis buffer (Cell Signaling Technology, #9803) containing protease inhibitor cocktail and phosphatase inhibitors. The lysates were cleared by centrifugation, and the supernatant fractions were collected. Cell lysates were then separated by 10% SDS-PAGE and subjected to western blot analysis with 1:1,000 dilution of primary antibodies and 1:1,000 horseradish peroxidase-conjugated secondary antibodies. Antibodies against the following were used for western blotting: phosphorylated STAT3 (Y705), STAT3, phosphorylated p44/42 MAPK (ERK1/2) (Thr202/Tyr204), ERK, phosphorylated AKT (Ser473), AKT, phospho-S6 ribosomal protein (Ser235/236), cyclin D1, and GAPDH. All primary and secondary antibodies were purchased from Cell Signaling Technology. GAPDH served as the loading control in all experiments. Membranes were analyzed using SuperSignal™ West Femto Maximum Sensitivity Substrate (Thermo, #34096).

Glycolysis. Extracellular L-lactate was detected in cultured cells using Glycolysis Cell-Based assay kit (Cayman, #600450). Assays were performed following the manufacturer's instructions. Cells (1x10⁵) per well were seeded in 96-well plates in triplicate and allowed to adhere overnight. Cells were treated with IL-6 or with the other agents under study in the presence of 0% FBS. After 48-h incubation, 10 µl of supernatant from each well was transferred to the corresponding wells on the new plates. Reaction solution (100 µl) containing assay buffer, glycolysis assay substrate, glycolysis assay cofactor, and glycolysis assay enzymatic mixture was added to each well with gentle shaking for 30 min at room temperature, after which the absorbance was read at 490 nm.
Colony forming cell assay. Clonogenic capacity was evaluated according to the protocol of Franken et al. (37). Cells were treated with bazedoxifene (10, 15 and 20 µM) and SC144 (10, 15 and 20 µM) for 16 h. After treatment, cells were harvested and reseeded on 6-cm plates with a drug-free medium for an additional incubation of 2 weeks. Colonies were fixed with methanol and stained with crystal violet dye (0.1% w/v).

Statistical analysis. All results are shown as the means ± standard error of the mean (SEM). The difference between two groups was analyzed using the Student’s t-test. All statistical analyses were conducted on the GraphPad Prism 5.0 software (P<0.05, P<0.01, P<0.001).

Results

IL-6 promotes cell viability in medulloblastoma cells. It is well established that elevated serum levels of IL-6 are associated with aggressiveness of many human cancers, including pancreatic, prostate and breast cancer (19-21). To evaluate the association of IL-6 and medulloblastoma, we tested the influence of exogenous IL-6 on the viability of medulloblastoma cells as determined using the MTT assay. DAOY and UW288 cells were treated with different doses of recombinant human IL-6 (0-25 ng/ml), and incubated for 48 h. As a result, stimulation of the cell viability was significantly enhanced in DAOY and UW288 cells, which was significant at 10 ng/ml IL-6 (Fig. 1A).

IL-6 promotes cell proliferation and upregulates the expression of phosphorylated STAT3 in medulloblastoma cells. To further evaluate the association of IL-6 and medulloblastoma, we tested the impact of exogenous IL-6 on the proliferation of medulloblastoma cells using a BrdU incorporation assay, which determines changes in cell proliferation rates over time by measuring cell DNA incorporation. DAOY and UW288 cells were exposed to different concentrations of IL-6 (0-25 ng/ml) for 24 h. As shown in Fig. 1B, increased incorporation of BrdU into DNA was observed in these two cell lines in response to IL-6, which was significant at 10 ng/ml IL-6, indicating that IL-6 induced cell proliferation of DAOY and UW288 cells.

Bazedoxifene impairs IL-6 mediated cell viability in medulloblastoma cells. The FDA-approved drug bazedoxifene is well known as a selective estrogen receptor modulator (SERM); it also exhibits antitumor activity (35,36). We evaluated whether bazedoxifene could suppress cell viability mediated by IL-6 in DAOY and UW288 cells. Cells were pre-treated with different concentrations of bazedoxifene (5, 10 and 20 µM) for 4 h followed by stimulation of exogenous IL-6 (10 ng/ml) for 48 h. As a result, stimulation of the cell viability was significantly enhanced in DAOY and UW288 cells, which was significant at 10 ng/ml of IL-6 (Fig. 1A).
these two cell lines. SC144 and BP-1-102 effectively inhibited IL-6-induced cell viability (Fig. 2A). To evaluate any possible synergism between bazedoxifene, BP-1-102 and SC144, we calculated CI values of bazedoxifene and BP-1-102, as well as bazedoxifene and SC144 in both UW288 and DAOY cells. The results indicated no synergistic effects.

Bazedoxifene inhibits IL-6 induced cell proliferation in medulloblastoma cells. To assess whether bazedoxifene could inhibit cell proliferation induced by IL-6 in medulloblastoma cells, we pretreated DAOY and UW288 cells for 4 h using different concentrations of bazedoxifene (5, 10 and 20 µM) and then added exogenous IL-6 (10 ng/ml) to stimulate cell proliferation for 24 h. Cell proliferation was determined by using BrdU incorporation and the results are presented in Fig. 2B. Cell proliferation was inhibited in a dose-responsive manner with the largest recorded for 20 µM. We also compared the inhibitory effects of bazedoxifene with those of the GP130 inhibitor, SC144, and the STAT3 inhibitor, BP-1-102 on IL-6 induced cell proliferation of DAOY and UW288 cells (Fig. 2B), and found that these agents inhibit IL-6-induced medulloblastoma cell proliferation.

Bazedoxifene reverses IL-6-induced STAT3 phosphorylation in medulloblastoma cells. STAT3 phosphorylation can be upregulated by exogenous IL-6, therefore, we sought to determine the effect of bazedoxifene on the expression of IL-6 stimulated STAT3 phosphorylation. We pretreated DAOY cells with bazedoxifene (20 µM) for 4 h followed by stimulation with IL-6 (10 ng/ml) for 30 min. As shown in Fig. 3, we observed that IL-6-mediated stimulation of STAT3 phosphorylation was blocked by bazedoxifene in DAOY cells.
These results lend support to bazedoxifene functioning as a potent inhibitor of IL6/GP130/STAT3 phosphorylation in medulloblastoma cells.

Bazedoxifene attenuates IL-6-stimulated glycolysis in medulloblastoma cells. The enhanced flux of glucose to lactate by tumors as compared with normal tissues as previously observed by Warburg and coworkers (38,39). To investigate the effect of IL-6 signaling on glucose metabolism in medulloblastoma cells, we first treated DAOY and UW288 cell lines with recombinant human IL-6 and observed the changes in lactate production. As a result, human IL-6 was shown to promote the uptake of glucose and increased its metabolite, lactate (Fig. 4). Notably, bazedoxifene treatment resulted in a dose-dependent decrease in lactate, indicating that bazedoxifene treatment decreases tumor cell glycolysis, which is mediated through the IL-6 signaling pathway in medulloblastoma cells. We tested whether the GP130 inhibitor, SC144 and the STAT3 inhibitor, BP-1-102 could block glucose metabolism induced by IL-6. As expected, SC144 and BP-1-102 effectively attenuated lactate production in DAOY and UW288 medulloblastoma cells.

Bazedoxifene treatment results in reduced colony formation. To further test the therapeutic potential of bazedoxifene against medulloblastoma cells, a colony forming assay was performed in medulloblastoma cells. We treated DAOY and UW288 cells with bazedoxifene and SC144 for 16 h, followed by re-seeding the same number of viable cells at very low cell densities. After incubation for 2 weeks, cells were then fixed and stained. We found that bazedoxifene effectively reduced the dose-dependent colony forming capacity in DAOY and UW288 cells more potently than SC144 (Fig. 5).

Discussion

Medulloblastoma is an aggressive brain tumor with a high recurrence rate. The primary therapy of medulloblastoma includes maximal tumor resection followed by craniospinal radiotherapy as well as chemotherapy (40,41). Cisplatin and vincristine are two major drugs utilized in the treatment of medulloblastoma (42-44). However, resistance and therapy-associated side-effects limit the therapeutic effectiveness of these agents, which has spawned an intense search for novel, biologically-based therapeutic targets (45). IL-6 is a pleiotropic cytokine that is highly expressed in numerous types of cancer (19-21). Notably, mounting evidence suggests that IL-6 is overexpressed in another brain tumor, glioblastoma multiforme (GBM), where it plays a crucial role in enhancing proliferation, invasion and angiogenesis in vitro (46,47), so IL-6 has been identified as a promising molecular target.
for glioblastoma therapy. Several novel IL-6 inhibitors have been recently developed (48). In our previous study, we found that DAOY and UW288 cells secreted high IL-6 levels (49). However, the importance of IL-6 in the progression of medulloblastoma is poorly established. Herein, we demonstrated that IL-6 significantly stimulated cell viability and cell proliferation of DAOY and UW288 cells. Thus, our data combined with previous studies, support that targeting IL-6 signaling with small-molecule inhibitors is both a viable strategy in medulloblastoma treatment and one that deserves further study.

IL-6 signaling is mediated via its binding to the common signal transducer, GP130, which is part of the hexameric IL-6/IL-6R/GP130 complex that ultimately leads to the activation of JAK. JAK phosphorylates GP130, resulting in the recruitment and activation of STAT3 as well as other downstream factors (SHP2, Ras-MAPK and PI3K) (50). Herein, we observed that IL-6 upregulated the expression of phosphorylated STAT3, but had no significant effect on the phosphorylation of other protein kinase pathways, revealing that IL-6 mediated JAK/STAT3 pathway is specifically upregulated by IL-6 in medulloblastoma cells. Therefore, we hypothesized that targeting of the IL-6/JAK/STAT3 axis could be an effective therapeutic approach for medulloblastoma.

Bazedoxifene is a third-generation SERM with improved selectivity and safety over tamoxifen that is currently approved by the FDA for use in the prevention of postmenopausal osteoporosis (51,52). Madindoline A (MDL-A) inhibits the formation of the hexameric IL-6/IL-6R/GP130 signaling complex, since bazedoxifene is similar structure it led us to re-purpose bazedoxifene and test its anticancer activity in medulloblastoma and it could block IL-6 signaling in this cancer type (35). Additionally, phase III clinical studies demonstrated that bazedoxifene exhibited a favorable reproductive safety profile in postmenopausal women over periods of 3 and 7 years (53,54), which suggests that bazedoxifene is an excellent drug candidate as an IL-6/GP130/STAT3 signaling antagonist. Thus, we investigated the in vitro effects of bazedoxifene in the inhibition of the IL-6/GP130/STAT3 axis in medulloblastoma cells. We showed that blocking the IL-6/GP130/STAT3 axis by bazedoxifene resulted in a significant reduction in medulloblastoma cell viability and proliferation. Notably, another previously reported GP130 inhibitor, SC144, and the STAT3 inhibitor, BP-1-102, also effectively reduced medulloblastoma cell viability and proliferation mediated by IL-6. Furthermore, bazedoxifene inhibited IL-6-mediated STAT3 phosphorylation in DAOY cells, as did the IL-6 signaling pathway inhibitors, SC144 and BP-1-102. Our findings further support our hypothesis that the inhibition of IL-6/GP130/STAT3 signaling pathway is a viable strategy for medulloblastoma therapy.

Enhanced aerobic glycolysis is one of the prominent features of most types of cancer cells, and it is important in the facilitation of cancer cell proliferation energy provision (48,55). Although a recent study has showed that IL-6-mediated promotion of glucose metabolism is dependent on the JAK/STAT3 signaling pathway through the increased expression of hexokinase 2 and 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (PFKRB-3) (56,57), it is unclear whether IL-6 can enhance glycolysis via the IL-6/GP130/STAT3 axis to provide biomass intermediates and energy in medulloblastoma progression. In view of this, targeting the IL-6/GP130/STAT3 pathway to inhibit glycolysis might be a therapeutic approach for medulloblastoma. The present study demonstrated the critical role of IL-6 in medulloblastoma progression and its part in promoting glycolysis. Specifically, downregulation of IL-6/GP130/STAT3 signaling by bazedoxifene treatment reduced IL-6-mediated glycolysis in medulloblastoma cells. Furthermore, the GP130 inhibitor, SC144 and the STAT3 inhibitor, BP-1-102 also decreased IL-6-stimulated glycolysis in medulloblastoma cells, which suggests that this signaling pathway could be a potential target in medulloblastoma treatment. Strikingly, our data demonstrated that the antitumor effects of bazedoxifene through inhibition of colony formation of medulloblastoma cells were more potent than the inhibition by SC144. Additionally, bazedoxifene has been documented with neuroprotective potential, suggesting that it can permeate the blood-brain barrier which is essential for the treatment of brain tumors (58,59).

In conclusion, this study demonstrated that IL-6 plays a critical role in medulloblastoma cell viability, cell proliferation and glycolysis and it promotes medulloblastoma progression, implicating IL-6 signaling as a potential molecular target for medulloblastoma treatment. Furthermore, we found that...
downregulation of the IL-6/GP130/STAT3 pathway using bazedoxifene impairs medulloblastoma cell viability and proliferation, reduces glycolysis and disrupts clonogenicity. Our findings provide preclinical in vitro evidence for a potential therapeutic role of bazedoxifene for medulloblastoma. Additional studies are required to determine optimal strategies for incorporating this agent for use in children with medulloblastoma. In particular, future investigation would be needed in order to evaluate the use of bazedoxifene in combination with other agents.

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