**Bevacizumab Promotes Cancer Cell Migration by Activation of STAT3**

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). It binds to all isoforms of VEGF-A, blocks the activation of endothelial cell surface VEGF receptors (VEGFR1 and VEGFR2), and finally leading to the regression of tumor vascularization and inhibition of the tumor nutrition supply. Bevacizumab was the first anti-angiogenesis agent approved by the US Food and Drug Administration for the treatment of metastatic colorectal cancer, in 2004. It is currently widely used as the first- or second-line treatment option for many types of cancer including metastatic colorectal, breast, ovarian, non-small cell lung, metastatic renal cell carcinomas, and glioblastoma multiforme (Hurwitz et al., 2004; Willett et al., 2004; Wedam et al., 2006; Cohen et al., 2007; Garcia et al., 2008; Hainsworth et al., 2012; Duran et al., 2014) Although bevacizumab combined with chemotherapy or radiotherapy dramatically reduces tumor size and prolongs the progression-free survival, the therapeutic effect is not sustained.

Tumors can relapse with a poor prognosis (Iwamoto et al., 2009; Mrugala, 2009; Narayana et al., 2009), and it has no statistically significant influence on the overall survival of patients with cancer (Desjardins et al., 2008; de Groot et al., 2010; Keunen et al., 2011; Piao et al., 2012; Piao et al., 2013; Ishida et al., 2014). However, there is currently very little information available on the underlying mechanisms involved in the actions of this drug.

Therefore, in this study, we examined the direct effects of bevacizumab on different cancer cell lines using the wound healing and transwell invasion assays. Then, we performed a pathway inhibition assay to determine the specific signaling pathway mechanisms that play a dominant role in bevacizumab-induced migration and invasion of cancer cells. Finally, we explored the underlying molecule mechanisms using quantitative real-time polymerase chain reaction (qPCR), western blot analysis, and enzyme-linked-immunosorbent assay (ELISA). In conclusion, we found that bevacizumab exerts differential effects on the cell migration of different cancer cell lines, and promotes migration via the IL-6/STAT3 signaling pathway.

**Materials and Methods**

**Cell culture**

Four cancer cell lines including three head and neck squamous cell carcinoma (WSU-HN6, CAL27, and Tca83) and one cervical carcinoma (HeLa) were used to investigate the effects of bevacizumab (San Francisco, CA, 2009; de Groot et al., 2010; Keunen et al., 2011; Piao et al., 2012; Piao et al., 2013; Ishida et al., 2014). However, there is currently very little information available on the underlying mechanisms involved in the actions of this drug.

**Abstract**

There are numerous clinical cases indicating that long-term use of bevacizumab may increase the invasiveness of tumors. However, to date, little is known about underlying molecular mechanisms. Therefore, the purpose of our study was to investigate effects of bevacizumab in four cancer cell lines (WSU-HN6, CAL27, Tca83, and HeLa). It was found to promote migration and invasion in the WSU-HN6 and Tca83 cases, while exerting inhibitory effects in CAL27 and HeLa cells. The signal transducer and activator of transcription (STAT) 3 inhibitors niclosamide and S3I-201 inhibited the STAT3 signal pathway, which is activated by bevacizumab. These inhibitors also substantially blocked bevacizumab-induced migration of WSU-HN6 and Tca83 cells. Bevacizumab upregulated interleukin (IL)-6 and phosphorylated (p)-STAT3 expression time-dependently. Therefore, we propose that bevacizumab has differential effects on the migration of different cancer cell lines and promotes migration via the IL-6/STAT3 signaling pathway.

**Keywords:** Bevacizumab - STAT3 - migration - pathway inhibition - interleukin-6

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Genentech, USA) on the migration and invasion of cancer cells. The cells were cultured in Dulbecco’s modified Eagle’s medium (DMEM, Gibco, Carlsbad, CA, USA) or Roswell Park Memorial Institute 1640 medium (RPMI 1640, Gibco) supplemented with 10% fetal bovine serum (FBS, Gibco) at 37°C in a 5% CO₂ atmosphere. Cells in the mid-logarithmic phase were used in the subsequent experiments.

Wound healing assay

The cultured cells that attained a confluent monolayer were treated with mitomycin (30 μg/mL) for 3 h, and then wounded by scratching across the well with a 200-μL pipette tip. The decidual cells were removed with phosphate-buffered saline (PBS) and cultured in a serum-free medium containing 100 μM bevacizumab. At the indicated time points following the wounding, the monolayer was photographed at 10× magnification using an inverted microscope and the relative speed of the cell movement was calculated by measuring the distance the cancer cells moved.

Transwell invasion assay

The cell invasion assays were performed using a transwell chamber plate with an 8-μm pore polycarbonate membrane (Millipore, Bedford, MA, USA) coated with 100 μL of 25 μg/mL matrigel (BD, Minneapolis, MN, USA) overnight. The cells were pretreated with mitomycin (30 μg/mL) for 3 h, trypsinized, and then seeded at 1 × 10⁶ cells/well in 0.1 mL of serum-free medium in the upper chamber of the plate in the presence or absence of 100 μM bevacizumab. A total of 0.5 mL of medium supplemented with 20% FBS was added to each well of the lower chamber. At the indicated times following incubation, the cells were fixed with 95% ethanol and stained with 1% crystal violet (Sigma-Aldrich, Saint Louis, MO, USA). The cells in the upper chamber were wiped off, and the invading cells that adhered to the bottom of the membrane were photographed using light microscopy at 20 x magnification (Olympus, Tokyo, Japan). Then, the cell invasiveness was evaluated by measuring the number of invading cells.

Pathway inhibition assay

The cells were cultured following the same procedure used in the wound-healing assay (2.2), except that the cells were pre-incubated with niclosamide, an inhibitor of the STAT3, Notch1, WNT, and mammalian target of rapamycin (mTOR) pathways. In addition, DAPT, XVA939, GSK690693, and S3I-201 (Sigma-Aldrich), which are inhibitors of the Notch1, WNT, pan-Akt, and STAT3 pathways, respectively were also used at a concentration of 100 μM for 1 h prior to bevacizumab treatment. The optimal concentration of each inhibitor that can inhibit the pathway without affecting the cell viability was determined in our previous experiments. RNA and protein samples were harvested from the treated cells for qPCR and western blot analysis.

qPCR

Total RNA was extracted from the tumor cells using the TRIzol reagent (Invitrogen, Carlsbad, CA, USA) and the complementary (c) DNA was synthesized by reverse transcription using the reverse transcription system (Promega, St. Louis, MO, USA). The relative qPCR was performed using the SYBR green master mix (Roche, Basel, Switzerland). All the PCR reactions were performed in a total volume of 20 μL containing 10 μL of SYBR green PCR master mix, 50 ng cDNA, and 250 nM of each primer. Primer sequences were 5'-GTGAGGAAACAGCCAGACG-3' and 5'-TACATTTGCGAGAGGCC-3' for IL-6, and 5'- GCATGGAGTCTGTGCGCAT-3' and 5'- GCATGGAGTCCGTGGCAT-3' for β-actin. The relative expressions of the target genes were calculated using the 2ΔΔct method.

Western blot analysis

Cells were harvested and lysed in RAPI assay buffer (Applygen Technologies, China). Then, 30 μg of protein was separated using 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred onto a polyvinylidene fluoride membrane. The membrane was then blocked with 5% nonfat milk in Tris-buffered saline (TBS) containing 0.5% Tween-20 (TBST buffer) for 1 h and incubated overnight at 4°C with following antibodies: anti-phosphorylated STAT3 (p-STAT3, 1: 1000, Genetex, Irvine, CA, USA), anti-total STAT3 (t-STAT3, 1: 1000, Genetex), matrix metalloproteinase 1 (MMP1, 1:1000, Epitomics, Burlingame, CA, USA), MMP13 (1:1000, Epitomics), MMP14 (1:1000, Epitomics), β-actin (1:1000, internal control; Santa Cruz Biotechnology, Santa Cruz, CA, USA). After immunoblotting with HRP-linked secondary antibodies, Immunoreactive bands were visualized with an enhanced chemiluminescence reagent (Applygen Technologies, Beijing, China).

Enzyme-linked immunosorbent assay (ELISA)

The WSU-HN6 cells were cultured in the presence of bevacizumab (100 μg/mL), and at the indicated times samples of the supernatant were collected and analyzed in duplicate using a human IL-6 and VEGF ELISA kit (Neobioscience Technology, Shenzhen, Guangzhou, China). This experiment was repeated thrice, and the results were obtained from three independent experiments.

Statistical analysis

Each experiment was performed in triplicate, and the results were obtained from three independent experiments. All the data were analyzed using the statistics for the social sciences (SPSS) 13.0 software, and are expressed as mean±standard deviation (SD). The differences between groups were examined using the Student’s t tests or an analysis of variance (ANOVA), as appropriate. P<0.05 was considered statistically significant.

Results

Bevacizumab exerted differential effects on the migration of different cancer cell lines

The wound healing assay was conducted to investigate the direct effects of bevacizumab on the migration of
cancer cells. The results showed that different cancer cell lines exposed to bevacizumab for 12 h responded differently. The migration speed of the WSU-HN6 and Tca83 cells increased from 7.82±3.52 and 5.85±0.81 μm/h to 12.60±2.03 and 7.98±1.05 μm/h, respectively while that of the CAL27 and HeLa cells decreased from 15.78±3.76 and 2.31±0.42 μm/h to 10.64±1.13 and 1.39±0.19 μm/h, respectively (Figure 1A&D, $P<0.05$).

**Bevacizumab affected invasiveness of cancer cell lines**

The transwell invasion assay was performed to test the effects of bevacizumab on the invasiveness of cancer cell lines. Following treatment with bevacizumab for 24 h, the relative number of invading cells was 1.67±0.23 and 1.50±0.18 fold higher in WSU-HN6 and Tca83 cells, respectively than the number in the corresponding control groups ($P<0.05$). However, for the CAL27 and HeLa cell lines, the relative number of invading cells in the bevacizumab-treated groups was 0.53±0.11 and 0.39±0.14 times lower, respectively than the number in the control group (Figure 1B&D, $P<0.05$). These results indicate that while bevacizumab enhanced the migration and invasion of the WSU-HN6 and Tca83 cells, it inhibited the movement of the CAL27 and HeLa cells.

**Determination of pathways mediating the bevacizumab-induced enhancement of cancer cell migration**

The results of the invasion assay prompted us to explore the mechanisms of the bevacizumab-induced increase in migration and invasiveness we observed in the WSU-HN6 and Tca83 cells. To determine the pathways involved, we performed a pathway inhibition assay using inhibitors associated with cell migration. Following a 12-h treatment in bevacizumab, the increase in migration observed with the WSU-HN6 cells was higher at a speed of 11.87±1.39 μm/h, than that observed in the control group at 7.06±3.82 μm/h ($P<0.05$). The pretreatment of the cells with niclosamide prior to bevacizumab treatment, significantly reduced the migration of the WSU-HN6 cells to 0.79±0.92 μm/h ($P<0.05$). Similarly, the relative migration speed and Tca83 cells and inhibits that of CAL27 and HeLa cells. (B) Bevacizumab promotes the invasiveness of WSU-HN6 and Tca83 cells and inhibits that of CAL27 and HeLa cells. (C&D) Quantitative measurement of the relative migration speed and the invading cell number of WSU-HN6, Tca83, CAL27, and HeLa cells. Data are expressed as mean±SD, n =3, $*P<0.05$, compared with corresponding controls.

**Figure 1. Bevacizumab has Differential Effects on the Migration and Invasiveness of Different Cancer Cell Lines.** (A) Bevacizumab promotes the migration of WSU-HN6 and Tca83 cells and inhibits that of CAL27 and HeLa cells. (B) Bevacizumab promotes the invasiveness of WSU-HN6 and Tca83 cells and inhibits that of CAL27 and HeLa cells. (C&D) Quantitative measurement of the relative migration speed and the invading cell number of WSU-HN6, Tca83, CAL27, and HeLa cells. Data are expressed as mean±SD, n =3, $*P<0.05$, compared with corresponding controls.

Bevacizumab promotes the migration of WSU-HN6 and Tca83 cells and inhibits that of CAL27 and HeLa cells. The migration speed of the Tca83 cells increased 1.37-fold more than that of the control group. The migration speed of Tca83 cells treated with a combination of bevacizumab and niclosamide decreased 0.21-fold more than that of cells treated with bevacizumab alone. This speed was even slower than that of the untreated control cells ($P<0.05$). Therefore, we concluded that niclosamide substantially inhibited the bevacizumab-induced migration, which indicates this effect could be mediated via the STAT3, WNT, Notch1, or Akt/mTOR pathways.

Furthermore, the other inhibitors including DAPT, XAV939, and GSK690693 did not significantly inhibit the bevacizumab-induced effects in the WSU-HN6 and Tca83 cells. The migration speed of the WSU-HN6 cells exposed to DAPT, XAV939, and GSK690693 was 11.78±1.97, 14.49±1.74, and 15.14±5.43 μm/h, respectively, which was comparable to that of cells treated with bevacizumab alone (11.87±1.39 μm/h). No significant difference was found in the migration of WSU-HN6 cells treated with DAPT, XAV939, and GSK690693 compared to those treated with bevacizumab alone ($P>0.05$). However, the migration of the Tca83 cells was inhibited by DAPT, XAV939, and GSK690693; although the inhibition was lower than that induced by niclosamide. Pretreatment of the Tca83 cells with either DAPT, XAV939, or GSK690693 followed by treatment with bevacizumab, decreased the migration speed by 0.47, 0.45, and 0.72-fold more, respectively than treatment with bevacizumab alone did ($P<0.05$, Figure 2A). These results suggest that the Notch1, WNT, and AKT/mTOR pathways were not the

**Figure 2. STAT3 Mediates the Effects of Bevacizumab-Induced Migration of Cancer Cells.** (A) Niclosamide, the multiple pathway inhibitor, significantly inhibited bevacizumab-induced migration in WSU-HN6 and Tca83 cells. Notch1 pathway inhibitor DAPT, WNT pathway inhibitor XAV939, and Akt pathway inhibitor GSK690693 did not show marked inhibition in WSU-HN6 cells. In Tca83 cells, DAPT, XAV939, and GSK690693 showed the limited effects. (B) S3I-201 significantly blocked bevacizumab-induced migration in WSU-HN6 and Tca83 cells. Each histogram represents the quantitative analysis of the relative mobility of cancer cells at its left side. Data are expressed as mean±SD, n =3, $*P<0.05$ compared with the corresponding controls, $^{*}P<0.05$ compared with the corresponding bevacizumab-alone treated cells.
major mediators of the bevacizumab-induced migration of the WSU-HN6 and Tca83 cells.

**STAT3 plays a crucial role in bevacizumab-induced migration of cancer cells**

Based on the results of the preliminary pathway inhibition study, we decided to confirm the role of phosphorylated (p)-STAT3 in bevacizumab-induced migration of cancer cells using S3I-201, a specific inhibitor of this pathway. The results showed that pretreatment with S3I-201 reduced the bevacizumab-induced migration of the WSU-HN6 and Tca83 cells to 11.16±1.59 and 4.33±1.26 μm/h, compared with that observed in the cells exposed to bevacizumab alone (19.23±2.18 and 9.95±1.32 μm/h, respectively, \( P < 0.05 \), Figure 2B).

**Determination of p-STAT3 expression during bevacizumab-induced cell migration using western blot analysis**

The western blot analysis revealed that both S3I-201 and niclosamide suppressed the bevacizumab-induced increase in the expression of p-STAT3 in WSU-HN6 and Tca83 cells (Figure 3A). Therefore, we ascertained that p-STAT3 plays a crucial role in bevacizumab-induced cell migration.

**Bevacizumab regulates cancer cell migration via IL-6/p-STAT3 signaling**

Next, we sought to determine the mechanisms by which bevacizumab activates the intracellular signaling molecule STAT3. Numerous studies have shown that STAT3 is activated by IL-6-mediated phosphorylation, which causes it to translocate and further regulate the transcription of downstream genes (Wang et al., 2014). Therefore, we used a treatment time-course assay to determine the effects of bevacizumab on the expressions of IL-6 and activation of the STAT3 pathway. Our results showed that bevacizumab upregulated IL-6 mRNA and protein levels as well as p-STAT3 protein expression time-dependently. However, the expression of IL-6 mRNA peaked 12 h after treatment. Therefore, we propose that bevacizumab might activate the STAT3 pathway by upregulation of IL-6 expression (Figure 3B&3C).

In addition, we also sought to determine the genes that are regulated by the STAT3 pathway, and may contribute to bevacizumab-induced cancer cell migration. qPCR and western blot assays were used to determine the levels of the cell migration-associated genes including matrix metalloproteinases (MMPs), integrins, adhesive molecules, and cytoskeleton genes following treatment of cells with bevacizumab and bevacizumab plus S3I-201 (Figure 4). However, the results revealed that the changes in the levels of all the genes analyzed in the WSU-HN6 and Tca83 cells exposed to the same treatment were either minimal or incomparable to each other. Therefore, these effects appeared not to be meditated by the bevacizumab-induced STAT3 pathway. At this point in the study, we were still unable to elucidate the specific target genes regulated by the bevacizumab-mediated STAT3 pathway.

**Figure 3. Bevacizumab Regulates Cancer Cell Migration Via IL-6/p-STAT3 Pathway.**

(A) Western blot results showed that p-STAT3 expression was induced by bevacizumab, and this effect was suppressed by S3I-201 and niclosamide in WSU-HN6 and Tca83 cells. (B) Western blot analysis showed that bevacizumab induced the expression of p-STAT3 time-dependently. Densitometric analysis of immunoblots from three separate determinations of p-STAT3 expression after bevacizumab treatment. The p-STAT3 signal was normalized with total (t)-STAT3. Data are expressed as mean ± SD, n=3. * \( P < 0.05 \) compared with p-STAT3 expression level at 0 h. (C) qPCR and ELISA results showed that bevacizumab induced the IL-6 mRNA and secreted protein in time-dependently.

**Figure 4. Matrix Metalloproteinases (MMPs) are not Involved in the Bevacizumab-Induced Cancer Cell Migration Mediated Via the p-STAT3 Pathway.**

Western blot results showed that, compared with corresponding untreated cells, the expressions of MMP-1, -2, -9, -13, and -14 were not affected significantly in bevacizumab-treated WSU-HN6 and Tca83 cells. After cells had been pretreated with S3I-201, the expression levels of MMP-1, -13, and -14 were slightly down-regulated in bevacizumab-treated WSU-HN6 and Tca83 cells. Meanwhile, MMP-9 expression results obtained in the bevacizumab-treated WSU-HN6 and Tca83 cells were not comparable. These results indicate that MMPs do not significantly affect the process of bevacizumab-induced cancer cell migration.

**Figure 5. Bevacizumab Completely Neutralized Vascular Endothelial Growth Factor (VEGF) Secreted By Cancer Cells.**

Cells were treated with 100 μg/mL bevacizumab for 24 h following pretreatment with or without S3I-201, the specific STAT3 pathway inhibitor for 1 h. An ELISA was used to analyze the secreted protein collected from the supernatant. Results showed that secreted VEGF markedly decreased after bevacizumab treatment.
Discussion

Bevacizumab inactivates the available extracellular VEGF-A, thereby blocking the activation of the VEGF receptor and its downstream pathway, and slowing angiogenesis (Carmeliet et al., 2011). Bevacizumab is primarily believed to influence the physiological behavior of endothelial cells, which express high levels of VEGFR1 and VEGFR2. However, in this study, we investigated whether bevacizumab has a biological effect on the behavior of tumor cells of epithelial origin. Before we did this study, we firstly tested the VEGF binding activity of bevacizumab by detection of VEGF secretion via ELISA. Our results showed that 100 µg/mL bevacizumab could completely neutralize VEGF secreted by WSU-HN6 and Tca83 cells, which indicates that bevacizumab does have the anti-angiogenic function (Figure 5). This result is supported by Simon’s study (Simon et al., 2014). Next, we detected the effect of bevacizumab on cancer cell migration. Our results clearly showed that, bevacizumab directly affected the migration of tumor cells of epithelial origin but not endothelial cells in vitro, which indicates that it may have other functions rather than anti-angiogenesis. Similar results were obtained in a previous study showing that bevacizumab enhanced the proliferation and invasiveness of glioblastoma cells in vitro (Simon et al., 2014). Conversely, in another study evaluating the influence of bevacizumab on the proliferation, migration, survival, and gene expressions of different cancer cell lines, the measurable response detected was limited (Hein et al., 2013).

It is noteworthy that we discovered the dual role of bevacizumab, which acted as either an inhibitor or enhancer of cell migration in different cancer cell lines. These paradoxical results are consistent with clinical data. In most cases, patients with cancer benefit from bevacizumab treatment (Keating, 2014). Only a few patients experience the unexpected effects of long-term use of bevacizumab, which include enhanced tumor aggressiveness and propensity to metastasize (Lucio-Eterovic et al., 2009; Miletic et al., 2009; de Groot et al., 2010; Keunen et al., 2011; Piao et al., 2012; Piao et al., 2013; Ishida et al., 2014). Variations in the genetic backgrounds of the different cancer cells or patients may be responsible for the apparent discrepancy in the responses to bevacizumab. However, the underlying mechanisms of these effects currently remain largely unknown, and further studies are required to elucidate them.

Bevacizumab-induced migration of cancer cells prevents some of the cells from being exposed to the therapeutic effects of the drug, thereby impairing the long-term benefits to the patient. In view of the widespread use of bevacizumab in various advanced cancers, there is an urgent need to determine the mechanisms involved in the infiltrative phenotypic changes associated with bevacizumab therapy. Several explanations have been proposed for the bevacizumab-induced migration. For example, the antiangiogenic therapy of bevacizumab may create a more hypoxic tumor microenvironment, which favors the phenotypic changes in the cancer cell lines. In addition, the direct effects of bevacizumab on glioblastoma cell lines in vitro may create the VEGF-A-dependent autocrine loop, which enhances tumor aggressiveness (Simon et al., 2014). These mechanisms explain the phenomenon from different perspectives and might be important in bevacizumab-induced migration; however, the detailed mechanisms have not yet been elucidated. Our results indicate that bevacizumab induces cancer cell migration via the IL-6/STAT3 signaling pathway.

We found that bevacizumab increased the IL-6 and p-STAT3 protein expression time-dependently. The inhibition of STAT3 activation by niclosamide and S3I-201 suppressed the bevacizumab-induced migration of the cancer cell lines ( Siddiquie et al., 2007; Pan et al., 2012). STAT3 is a multifunctional mediator that participates in regulating cell survival, proliferation, metastasis, and differentiation (Chen et al., 2008; Zhou et al., 2014). STAT3 can be activated by the IL-6 and IL-10 family of cytokines as well as by receptor tyrosine kinases such as the epidermal growth factor receptor and non-receptor tyrosine kinases such as Src (Yu et al., 1995; Shao et al., 2003; Grivennikov et al., 2008). The binding of IL-6 induces phosphorylation of the receptor and Janus kinases, which then activates STAT3 (Wang et al., 2014). Enhanced activation of STAT3 is associated with acquired therapeutic resistance, and inhibition of this pathway can reverse drug sensitivity (Gao et al., 2014; Sen et al., 2012).

Regrettably, we were unable to determine the key molecules that are involved in STAT3 activation and promotion of the migration of cancer cell lines. Previous studies showed that bevacizumab stimulates the cellular invasion of surrounding tissue by upregulating the expression of invasion-related molecules like MMP-2, MMP-9, and MMP-14 (Furuta et al., 2014). Lucio-Eterovic found that MMP inhibitors decreased bevacizumab-induced cancer cell migration in vitro, but the effects were not evident in vivo (Lucio-Eterovic et al., 2009). However, in our study, the expressions of MMP-1, -2, -9, -13, and -14 were not affected significantly, and the results obtained in the WSU-HN6 and Tca83 cells were not comparable (Figure 5). These results indicate that some unidentified molecules regulated by STAT3 might play a central role in bevacizumab-induced cancer cell migration.

In conclusion, we found that bevacizumab induces differential effects on the migration of different cancer cells. Bevacizumab promotes the migration of two of the cancer cell lines we investigated mainly through activation of the STAT3 pathway. The therapeutic strategy of combining inhibition of the STAT3 pathway with bevacizumab should be considered as a plausible option in attenuating potential bevacizumab-induced cancer cell migration and survival. However, the functions of the STAT3 pathway and the key molecules associated are complex, and their elucidation was beyond the scope of this study (Pandurangan et al., 2014). Therefore, further studies are required to provide a complete profile of the molecular mechanisms mediating bevacizumab-induced cancer cell migration, including the involvement of the STAT3 pathway.

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