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Research Progress in STAT3

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ABSTRACT

STAT3 (Signal Transducers and Activators of Transcription 3) is a transcription and signal transduction protein, which is widely involved in cell proliferation, differentiation, apoptosis and other biological phenomena. It is closely related to cancer. Recently, we found that STAT3 is also involved in epilepsy, Alzheimer and other diseases. Here, we make a review on the structure and signal pathway of STAT3, as well as the associated diseases and some related drugs for patients.

Keywords: Signal Transducers and Activators of Transcription, STAT3 structure, Signaling pathway, Related disease

Abbreviations: STATs: Signal Transducers and Activators of Transcription; mTOR: Mammalian target of rapamycin; JAKs: Janus kinase; CNTF: Ciliary neurotrophic factor; AD: Alzheimer's disease; MAPK: Mitogen activated protein kinases; Trks: Tropomyosin receptor kinase

INTRODUCTION

STATs (Signal Transducers and Activators of Transcription) families have seven members, STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5 and STAT6. It was first discovered in 1993 by James Darnell et al., when they studied the molecular mechanism of IFN (interleukin-mediated gene activation). They found that STAT3 not only regulated intracellular signal transduction mediated by various cytokines and growth factors, but also participated in the processes of inflammation, epilepsy, and stem cell self-renewal.

STRUCTURE OF STAT3

In 1994, Akira et al. purified and cloned STAT3 from mouse liver nuclei.STAT3 has a variety of isomers, including STAT3α, STAT3β, STAT3γ and STAT3δ, all of which were located on 17q21.STAT3α,770 amino acids, with a molecular weight of 92KDa, is the main expression form of STAT3 in most cells and participates in the regulation of cell cycle. STAT3β was thought to be a negative STAT3 protein that inhibited transcription by binding to DNA. STAT3 is composed of 4 functional areas: oligomer domain, which mediates the oligomerization of STAT3; the SH2 (Scr co-source region 2) domain mediates the binding of STAT3 to the receptor and the formation of dimer. The DNA binding region, located between amino acids 400-500, mediates the binding of STAT3 protein to specific DNA sites. Furthermore, the carboxyl terminal regulates the transcriptional activity of STAT3, including the 705tyrosine site (Y705) and the 727serine site (S727). It was believed that the activation of STAT3 was based on the phosphorylation of Y705. The phosphorylation of Ser727 was the key to achieve the maximum transcriptional activity of STAT3 [1]. However, some suggested that phosphorylation of S727 did not depend on phosphorylation of Y705[2].

STAT3 RELATED SIGNALING PATHWAY

JAKs/STAT3 signaling pathway

JAKs (Janus kinase) is a family of non-receptor tyrosine kinases. The JAKs/STAT3 pathway can be activated by various cytokines, growth factors, and so on. These activation factors bind to the corresponding receptors on the cell surface to activate JAKs and activated JAKs mediates the phosphorylation of STAT3 by Tyr705, making STAT3 activated. P-STAT3 was depolymerized with the receptor, and interacted with the SH2 region of another STAT protein to form a dimer, then transported to the cell nucleus [3], and immediately interacted with the promoter of a specific target gene (such as the cis-acting element of IFN) to initiate

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transcription[4]and participate in the processes of cell proliferation, differentiation and apoptosis. Na et al inoculated the brain homogenate of mice with ME7 sheep pruritus strain into the brain of C57BL mice, showed that p-jak2, p-stat3 and GFAP were significantly expressed in the hippocampus of the mice. The result also showed that the p-jak2, p-stat3 and GFAP were located in the nuclei of the proliferating astrocytes, indicating that the JAKs/STAT3 pathway was involved in the pathological process of sheep pruritus [5]. Guo's study confirmed that Leptin may played a neuroprotective and stabilizing role in mitochondrial membrane potential through the JAKS/STAT3 pathway [6].

mTOR/STAT3 signaling pathway

mTOR (mammalian target of rapamycin) was a highly conserved serine/threonine protein kinase, belonging to the phosphoinositol kinase-related protein kinase family. PI3K/AKT/mTOR signaling pathway was the most studied: growth factor receptor binded the ligand, collecting PI3K p85 regulating sub activated PI3K, then promoting PIP3 generated. Next, PIP3 combined into PDK1 and AKT PH domain structure, then AKT was activated by PDK1, activated AKT then phosphorylated mTOR (thr2448) through direct or indirect ways to make mTOR activated. Activated mTOR phosphorylates the Ser727 site of STAT3 through different pathways, playing an important role in tumorigenesis, epilepsy formation: in Yokogami et al. [7] study, they used CNTF (ciliary neurotrophic factor)to stimulate human neuroblastoma NBFL cells, they observed that the expression of p-mTOR, p70S6 kinase, 4E-BP1 and p-STAT3 (Ser727)were increased. After treatment of NBFL cells with rapamycin, phosphorylation of Ser727 returned to basal levels, suggesting that mTOR mediates the activation of STAT3 (Ser727). However, how mTOR mediates the activation of STAT3 (Ser727) remains unclear: studies have found that the mTORC2 complex can mediate the phosphorylation of STAT3 (S727). Sun et al observed that the mTOR pathway became activated and p-stat3 (Ser727) was overexpressed in bile duct carcinoma SCK cells in vitro. After rapamycin treatment, the number of SCK cells was significantly reduced and the vitality was reduced. When the treatment time of rapamycin was prolonged, the mTORC2 complex was destroyed, while the expression of p-stat3 (Ser727) was significantly reduced [8]. Other studies suggested that mTOR mediated the phosphorylation of STAT3(Ser727) by PKC: Aziz et al. [9] found increased expression of PKC and p-stat3 in the cultured human melanoma cells (wm266-4), glioma cells (T98G), pancreatic cancer cells (panc-1), and lung cancer cells (H1650). When PKC became silence, phosphorylation of ser727 was decreased, accompanied by inhibiting STAT3 binding to DNA and the expression of STAT3 regulated gene, suggesting that PKC mediated phosphorylation of ser727 and expression of STAT3 regulated target genes. The specific mechanism of mTOR mediating STAT3 activation still needs to be further studied to provide more effective treatment for related diseases.

MAPK/STAT3 Signaling Pathway

MAPK (mitogen activated protein kinases) is one of the serine/threonine protein kinases, which is an important signaling system in eukaryotic cells. Growth factors and cytokines bind to receptors to activate Ras. The activated Ras further binds to the amino terminus of Raf-1 and activates Raf-1. Raf-1 phosphorylates serine of MAPK, and activated MAPK phosphorylates Ser727 of STAT3. Xuan et al. found increased expression of p-stat3 (Ser727) and p-p44/42mapk in myocardial cells in a mouse model of myocardial ischemia [10].

NGF/Trks/STAT3 Signaling Pathway

Trks (tropomyosin receptor kinase) mediates the activity of neurotrophic factor (NGF). Recent studies have found that STAT3 is an important downstream molecule in the Trks signaling pathway. NGF binds to the corresponding receptors, including TrkA, TrkB, or TrkC, to induce phosphorylation of STAT3 at ser727, enhancing stat3-DNA binding and transcriptional activity of STAT3. Ng et al found that the expression of STAT3 was blocked by RNA interference technology in PC12 cells (a rat pheochromocytoma cell line). The transcription level of early response gene induced by NGF was reduced, and the expression of cyclin D1 was decreased, thus inhibiting the growth stagnation caused by NGF. When cortical neurons were treated with BDNF (brain-derived neurotrophic factor), phosphorylation of Ser727 and Tyr705 occurred for 5 minutes, but phosphorylation of Tyr705 disappeared after 15 minutes, and the level of Ser727 persisted, indicating that BDNF activated STAT3 of cortical neurons and had a greater phosphorylation effect on Ser727. Inhibition of STAT3 expression attenuates the role of BDNF in promoting axonal growth in primary hippocampal neurons [11].

STAT3 related diseases

Tumour: STAT3 plays an important role in tumorigenesis and malignant transformation. Itis significantly activated in glioma, meningioma, breast cancer, prostate cancer, melanoma, colon cancer and gastric cancer.

Neurologic tumors: A growing evidence indicates that STAT3 participate in the glioma development: LO et al used immunohistochemical method to detect malignant glioma patient specimens, found STAT3 were activated in 60% malignant glioma patients, and associated with malignant degree, human malignant glioma and neural tube cell tumor cells in vitro also found high expression of STAT3. In JSI - 124 (a JAK2 / STAT3 inhibitors) treatment of malignant glioma cells, found that the expression of STAT3 target gene significantly reduced, and limited tumor cell growth, apoptosis increases [12]. Activation of STAT3 has also been found in glioma mice [13]. Magrassi observed significantly increased levels of JAKs and STAT3 in meningioma specimens [14]. Recent studies have found that STAT3 expression in grade II and III meningioma is significantly

increased compared with type I, and STAT3, mek-1 /MAPK and PI3K/AKT/mTOR pathways are co-expressed in meningioma II/III [15], indicating that STAT3 is not only involved in the occurrence of nervous system tumors, but also closely related to the malignant transformation of tumors.

Other tumors: Bone marrow fibrosis patients often suffered JAK2 V617F point mutations, causing JAK2/STAT3 abnormal activation. Recent studies have found that when PI3K/AKT/mTOR inhibitors and JAK2 tyrosine kinase inhibitors were used, may cause cultured CD34 + primary myeloma cells dying [16]. It suggested that to inhibit the differentiation of hematopoietic progenitor cell in bone marrow fibrosis, may treat bone marrow fibrosis. In the study of breast cancer, it was found that by inhibiting the expression of STAT3 through RNA interference technology, the breast cancer formation process of BALB/c mice induced by 4T1 cells would be inhibited, indicating that STAT3 plays an important role in the occurrence of breast cancer [17]. In colon cancer cell line SW480, STAT3 was continuously activated, and inhibition of STAT3 activity by oligonucleodeoxynucleotides would lead to SW480 cell death [18].Combined application of PI3K inhibitor and STAT3 inhibitor is effective for KRAS mutant cell lines SNU-1,SNU-601 and SNU-668 in gastric cancer, which can induce apoptosis [19].

Epilepsy

Astrocyte hyperplasia is the most common pathological change after central nervous system injury (such as cerebral ischemia, epilepsy) [20]. More and more studies have found that STAT3 plays an important role in the proliferation and differentiation of astrocytes after brain injury, and epilepsy is a common brain injury disease.

Xu et al. [21] found that the expression of p-STAT3 and GFAP was significantly increased by immunohistochemistry in the hippocampus of pirocarpine-induced epilepsy rats and brain tissue specimens of epileptic patients, and the positions of p-stat3 and GFAP were similar. After the rats were treated with AG490 (an inhibitor of JAK2/STAT3 signal), the contents of p-stat3 and GFAP were significantly reduced. By using Immunofluorescence, they confirmed that GFAP located in the cytoplasm of human astrocytes in the temporal cortex, while p-STAT3 was located in the cytoplasm and nucleus of astrocytes, providing reliable evidence for STAT3 involves in epileptic astrocyte proliferation. Choi et al. [22] simulated epileptic seizures by intramuscular injection of Marine acid into MSD rats. The Immunohistochemistry results showed that STAT3 expression in the hippocampus of rats in the control group was low, while the nucleus of CA3 and dentate gyrus in the experimental group showed strong immune activity of STAT3 [22]. In MSD rats simulating cerebral ischemia, Kim et al. found that STAT3 was highly expressed in the molecular layer and portal region of the dentate gyrus and the hippocampus CA1 region, and located in astrocytes[23]. Hiroko Nobuta et al. observed postmortem brain tissue with neonatal cortical injury and found that STAT3 was generally activated in proliferated astrocytes [24], which provided a new idea for children with cortical malformation. Hofmann et al. used MSD rats to simulate entorhinal cortex damage and observed similar phenomena [25]. These experiments provide evidence for the involvement of STAT3 in astrocyte proliferation after brain injury and provide evidence for the treatment of epilepsy.

STAT3 also promoted the differentiation of neural stem cells (NSCs) into astrocytes: Cao et al. inoculated NSCs with Cre recombinant adenovirus vector in vitro, and RT-PCR showed that the level of stat3 mRNA was significantly lower than that of the control group, confirming the inhibitory effect of Cre on STAT3 function. Compared with the empty vector group, the mRNA level of GFAP was significantly reduced. Western-Blot showed that the change of GFAP protein was consistent with the expression of STAT3, indicating that STAT3 was involved in the differentiation of neural stem cells into astrocytes [26].

Alzheimer's disease (AD)

In AD, Tyk2/STAT3 signal pathway involved in neuronal death caused by amyloidβ.However, the level and activity of STAT3 in AD remains controversial: in vitro experiments, folic acid, improve AD related memory defects and neuron death by the activation of STAT3 in the hippocampus [27]. Recently, in hippocampus and cortex of AD patients and APP/PSI transgenic mice, P-STAT3 were observed highly expressed, which showed that excessive expression of STAT3 cause neuronal cell death [28].

Other related diseases

Some studies founded that P-STAT3 had been linked to atherosclerosis, inflammatory bowel disease and rheumatoid arthritis. Mice with stat3 knocked out were given a diet that caused arteriosclerosis, and adipose streak formation was reduced compared with wild-type mice [29].Significant activation of STAT3 was observed in the intestinal epithelial cells of patients with inflammatory bowel disease [30]. Increased STAT3 activity was observed in mice with rheumatoid arthritis, which may be related to IL-6 stimulation [31].

Inhibitors

Direct inhibitors One class of inhibitors is to inhibit the binding and transcriptional function of STAT3 to DNA, resulting in decreased cell activity and induced apoptosis: LL-3 is a small molecular complex. Mice inoculated with malignant glioma U87 cells were found to prolong the survival time, which may be an ideal drug for the treatment of malignant glioma [32]. Static can effectively inhibit the activity and expression of STAT3 in head and neck squamous cell carcinoma, reducing the survival and proliferation of tumor cells, and increasing the sensitivity to radiotherapy [33]. Another type of inhibitor is peptide aptamer, which is only

composed of 12-20 amino acids. It can block the formation of STAT3 protein dimer [34] and selectively induce cell growth inhibition and apoptosis through cells. Malignant glioma cells are very sensitive to this purified peptide aptamer [35], which is expected to be a drug for the treatment of malignant glioma. Another inhibitor is oligonucleotide, which synthesizes DNA homologous to the DNA attached to transcription factors [36] and competitively inhibits STAT3, thereby terminating transcription [36].

Indirect inhibitors

Indirect inhibitors can block the STAT3 signaling pathway by disrupting extracellular ligand- receptor interactions or by blocking upstream tyrosine kinase stimulating molecules: for example, AG490-an inhibitor of JAK1/2, can inhibit JAK activation, which is an upstream substance of STAT3, then reduce STAT3 activation. It was found that AG490 inhibited the proliferation of glioblastoma cells and induced apoptosis by reducing the anti-apoptotic protein levels of Bcl-xl, Bcl-2 and Mcl-1[37]. Similarly, the inhibitors of Interleukin, such as Sorafenib, Sunitinib, or Vandertanib have been used in clinical trials to mediate antitumor effects by reducing STAT3 activity.

CONCLUSION

As an important transcription factor, STAT3 can be involved in many biological processes, such as cell proliferation, differentiation and apoptosis. In pathological conditions, it can be activated through different pathways to participate in the occurrence and development of the disease. In view of the different disease pathogenesis research and development of the corresponding drugs for the treatment of diseases such as cancer, epilepsy will greatly promote the development of medical level. Further studies are needed to provide a scientific basis for these diseases' prevention and control strategies.

REFERENCES

1. Wen Z, Zhong Z, Darnell JE (1995) Maximal activation of transcription by Stat1 and Stat3 requires both tyrosine and serine phosphorylation. Cell 82: 241-250.
2. Sakaguchi M, Oka M, Iwasaki T, Fukami Y, Nishigori C (2012) Role and regulation of STAT3 phosphorylation at Ser727 in melanocytes and melanoma cells. J Invest Dermatol 132: 1877-1885.
3. Minami M, Inoue M, Wei S, K Takeda, M Matsumoto, et al. (1996) STAT3 activation is a critical step in gp130-mediated terminal differentiation and growth arrest of a myeloid cell line. Proc Natl Acad Sci USA 93: 3963-3966.
4. Zhong Z, Wen Z, Darnell JE (1994) Stat3: A STAT family member activated by tyrosine phosphorylation in response to epidermal growth factor and interleukin 6. Science 26: 95-98.
5. Na YJ, Jin JK, Kim JI, Choi EK, Carp RI (2007) JAK-STAT signaling pathway mediates astrogliosis in brains of scrapie-infected mice. J Neurochem 103: 637-649.
6. Guo Z, Jiang H, Xu X, Duan W, Mattson MP (2008) Leptin-mediated cell survival signaling in hippocampal neurons mediated by JAK STAT3 and mitochondrial stabilization. J Biol Chem 283: 1754-1763.
7. Yokogami K, Wakisaka S, Avruch J, Reeves SA (2000) Serine phosphorylation and maximal activation of STAT3 during CNTF signaling is mediated by the rapamycin target mTOR. Curr Biol 10: 47-50.
8. Hong SM, Park CW, Cha HJ, Kwon JH, Yun YS, et al. (2013) Rapamycin inhibits both motility through down-regulation of p-STAT3 (S727) by disrupting the mTORC2 assembly and peritoneal dissemination in sarcomatoid cholangiocarcinoma. Clin Exp Metastasis 30: 177-187.
9. Aziz MH, Hafeez BB, Sand JM, DB Pierce, Aziz SW, et al. (2010) Protein kinase Cvarepsilon mediates Stat3Ser727 phosphorylation, Stat3-regulated gene expression, and cell invasion in various human cancer cell lines through integration with MAPK cascade (RAF-1, MEK1/2, and ERK1/2). Oncogene 29: 3100-3109.
10. Xuan YT, Guo Y, Zhu Y, Wang O, Rokosh G, et al. (2005) Role of the protein kinase C-epsilon-Raf-1-MEK-1/2-p44/42 MAPK signaling cascade in the activation of signal transducers and activators of transcription 1 and 3 and induction of cyclooxygenase-2 after ischemic preconditioning. Circulation 112: 1971-1978.
11. Ng YP, Cheung ZH, Ip NY (2006) STAT3 as a downstream mediator of Trk signaling and functions. J Biol Chem 281: 15636-15644.
12. Lo HW, Cao X, Ali-Osman F, Hu Zhu (2008) Constitutively activated STAT3 frequently coexpresses with epidermal growth factor receptor in high-grade gliomas and targeting STAT3 sensitizes them to Iressa and alkylators. Clin Cancer Res 14: 6042-6054.
13. Weissenberger J, Loeffler S, Kappeler A, Kopf M, Lukes A, et al. (2004) IL-6 is required for glioma development in a mouse model. Oncogene 23: 3308-3316.
14. Magrassi L, De-Fraja C, Conti L, G Butti, L Infuso, et al. (1999) Expression of the JAK and STAT superfamilies in human meningiomas. J Neurosurg 91: 440-446.
15. Johnson MD, O'Connell M, Vito F (2009) Increased STAT-3 and synchronous activation of Raf-1-MEK-1-MAPK, and phosphatidylinositol 3-Kinase-Akt-mTOR pathways in atypical and anaplastic meningiomas. J Neurooncol 92: 129-136.
16. Fiskus W, Verstovsek S, Manshouri T (2013) Dual PI3K/AKT/mTOR inhibitor BEZ235 synergistically

enhances the activity of JAK2 inhibitor against cultured and primary human myeloproliferative neoplasm cells. Mol Cancer Ther 12: 577-588.

17. Ling X, Arlinghaus RB (2005) Knockdown of STAT3 expression by RNA interference inhibits the induction of breast tumors in immunocompetent mice. Cancer Res 65: 2532-2536.
18. Souissi I, Najjar I, Ah-Koon L (2011) A STAT3-decoy oligonucleotide induces cell death in a human colorectal carcinoma cell line by blocking nuclear transfer of STAT3 and STAT3-bound NF-kappaB. BMC Cell Biol 12:14.
19. Park E, Park J, Han SW (2012) NVP-BKM120, a novel PI3K inhibitor, shows synergism with a STAT3 inhibitor in human gastric cancer cells harboring KRAS mutations. Int J Oncol 40: 1259-1266.
20. Seifert G, Schilling K, Steinhauser C (2006) Astrocyte dysfunction in neurological disorders: a molecular perspective. Nat Rev Neurosci 7:194-206.
21. Xu Z, Xue T, Zhang Z (2011) Role of signal transducer and activator of transcription-3 in up-regulation of GFAP after epilepsy. Neurochem Res 36: 2208-2215.
22. Choi JS, Kim SY, Park HJ (2003) Upregulation of gp130 and differential activation of STAT and p42/44 MAPK in the rat hippocampus following kainic acid-induced seizures. Brain Res Mol Brain Res 119: 10-18.
23. Kim SY, Park HJ, Choi JS (2004) Ischemic preconditioning-induced expression of gp130 and STAT3 in astrocytes of the rat hippocampus. Brain Res Mol Brain Res 129: 96-103.
24. Nobuta H, Ghiani CA, Paez PM (2012) STAT3-mediated astrogliosis protects myelin development in neonatal brain injury. Ann Neurol 72: 750-765.
25. Xia XG, Hofmann HD, Deller T, Kirsch M (2002) Induction of STAT3 signaling in activated astrocytes and sprouting septal neurons following entorhinal cortex lesion in adult rats. Mol Cell Neurosci 21: 379-392.
26. Cao F, Hata R, Zhu P (2010) Conditional deletion of Stat3 promotes neurogenesis and inhibits astrogliogenesis in neural stem cells. Biochem Biophys Res Commun 394: 843-847.
27. Yamada M, Chiba T, Sasabe J (2008) Nasal Colivelin treatment ameliorates memory impairment related to Alzheimer's disease. Neuro Psychopharmacol 33: 2020-2032.
28. Wan J, Fu AK, Ip FC (2010) Tyk2/STAT3 signaling mediates beta-amyloid-induced neuronal cell death: implications in Alzheimer's disease. J Neurosci 30: 6873-6881.
29. Gharavi NM, Alva JA, Mouillesseaux KP (2007) Role of the Jak/STAT pathway in the regulation of interleukin-8 transcription by oxidized phospholipids in vitro and in atherosclerosis in vivo. J Biol Chem 282: 31460-31468.
30. Neufert C, Pickert G, Zheng Y (2010) Activation of epithelial STAT3 regulates intestinal homeostasis. Cell Cycle 9: 652-655.
31. Hirano T (2010) Interleukin 6 in autoimmune and inflammatory diseases: a personal memoir. Proc Jpn Acad Ser B Phys Biol Sci 86: 717-730.
32. Fuh B, Sobo M, Cen L (2009) LLL-3 inhibits STAT3 activity, suppresses glioblastoma cell growth and prolongs survival in a mouse glioblastoma model. Br J Cancer 100:106-112.
33. Adachi M, Cui C, Dodge CT (2012) Targeting STAT3 inhibits growth and enhances radiosensitivity in head and neck squamous cell carcinoma. Oral Oncol 48: 1220-1226.
34. Lin L, Hutzen B, Li PK (2010) A novel small molecule, LLL12, inhibits STAT3 phosphorylation and activities and exhibits potent growth-suppressive activity in human cancer cells. Neoplasia 12: 39-50.
35. Borghouts C, Kunz C, Delis N (2008) Monomeric recombinant peptide aptamers are required for efficient intracellular uptake and target inhibition. Mol Cancer Res 6: 267-281.
36. Yu H, Pardoll D, Jove R (2009) STATs in cancer inflammation and immunity: A leading role for STAT3. Nat Rev Cancer 9: 798-809.
37. Senft C, Priester M, Polacin M (2011) Inhibition of the JAK-2/STAT3 signaling pathway impedes the migratory and invasive potential of human glioblastoma cells. J Neurooncol 101: 393-403.