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Review Article

STATs Inhibitors in Cancer Therapy Strategies

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Abstract

Signal Transducer and Activator of Transcription (STAT) can play a role in the growth or inhibition of cancer by regulating cytokine-dependent immunity and inflammation. STATs constitute a group of transcription factors including seven members that were identified about 20 years ago when the interferon gene pathway was examined. STATs link the receptor stimulation with gene transcription and transmit a signal to the corresponding gene. The vital role of this family of signal transducers in cell growth in both normal and malignant conditions makes them interesting targets for cancer therapy strategies. STAT3 in this family acts as an oncogene that plays a role in human cancers. As an important signaling protein, STAT3 may be involved in tumorigenesis, angiogenesis, and cancer cell metastasis as well as chemoresistance. Therefore, STAT3 inhibition is considered a treatment method because its inhibition could be a prospect for cancer treatment without affecting normal cells. Other members of this group of transcription factors are also involved in neoplasia, and the inhibition and/or induction of its function may play role in controlling cancer cell growth or triggering differentiation and maturation induction processes. This paper aims to review the future of targeting STATs family in cancer therapy methods.

Keywords: STAT, STAT3, Cancer, Signaling pathway, Treatment, Inhibition

Introduction

Signal Transducer and Activator of Transcription (STAT) constitute a group of transcription factors that are present in mammalian cells. STAT are involved in downstream signaling of various growth factors and cytokines receptors that were discovered nearly 20 years ago in the study of signaling pathway(s) involved in the interferon gene [1,2].

Despite their role in cytokine responses, members of this family are implicated in cell growth, apoptosis, pro-inflammatory and anti-proliferative effects; therefore, deregulation of this pathway may play role in neoplasia. Studies about the potential induction or inhibition of one or more of these protein classes can theoretically be regarded in targeted therapy methods.

STAT create a bridge between cytokine receptor stimulation and gene transcription in the nucleus. STAT are involved in many cellular activities and can be found in normal cells as well as in a variety of cells involved in development of disease and malignancies [3].

STAT family consists of seven known members, including STAT1 to STAT6 and STAT5. The latter has two types, namely STAT5a and STAT5b. The main differences between these members depend on their function, peptide size (ranging 750-850 amino acids), and structural properties [4].

According to their specific performance, STAT molecules can be divided into two major groups. The first group consists of STAT 1, 3, and 5, which can affect various tissues through a series of cytokines and signaling pathways such as IFN-γ and play a key role in apoptosis, cell cycle, and angiogenesis [5]. The next group includes STAT2, 4, and 6, which are activated by a limited number of cytokines and are involved in the developing T-cells and the gamma interferon signaling pathway [4].

Molecular structure of STAT

STAT molecules are made of genes from three chromosomes, namely chromosomes 2, 12, 17 that are involved in the creation of STAT. STAT 1 and 4 are coded by chromosome 2, STATs 2 and 6 are coded by chromosome 12, STAT3 is located on chromosome 17(17q21.2), and STAT5 is located on chromosome 17(17q11.2) [5].

STAT proteins have a similar structure, which has six conserved domains from N to C terminals (Figure 1) [6].

N-terminal domain (ND) contributes to protein-protein interactions and the expression of nuclear genes. This part is made up of 4 hydrophobic coiled alpha helices involved in hetero- and homo-dimers and hence stabilizes the DNA connection by creating tetramers. The Coiled-Coil Domain (CCD) of STAT helps activate the STAT protein through Tyr705 phosphorylation and nuclear transfer.

DNA Binding DNA (DBD) helps activate the target gene by recognizing the activating sequence of interferon-gamma. The γ-Interferon Activating Sequence (GAS) is the linker area responsible

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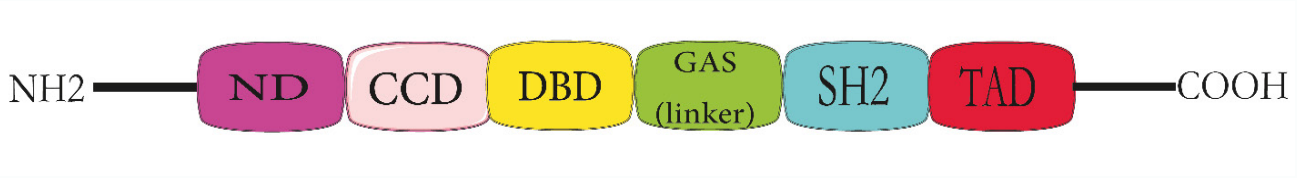

Figure 1: Structural organisation of STATs. Each box represents a functional region of the STAT protein structure. There are 6 functional areas from N-terminal to C-terminal including, the ND protein binding region, CCD phosphorylation zone, DBD, and SH2 connection area, TAD region supports phosphorylation and activation.

for connecting the SH2 region to DBD. The SH2 region contributes to communication between different regions with recipient's phosphotyrosine region. The Transcriptional Activation Domain (TAD) is part of C-terminal, which enables phosphorylation of STATs with its tyrosine and serine rich regions [3,7]. Structure of STAT dimer combinations can play a role in nuclear localization of protein, regulation of specific gene expression, DNA binding, and chromatin remodeling [8].

STAT proteins have a variety of structures at their carboxy-terminal, and STAT 1-4 have a repeated heptad leucine sequence at their amino-terminals [9].

STAT functions

Similar to other STAT family members, STAT1 can translate and transfer signals from the cytoplasmic membrane and cytoplasm to the nucleus. STAT1 can translate and transmit the message of various ligands such as IL-21, IL- 27, and IL-35. On the other hand, it is highly activated by any IFN type and creates homodimers [10].

Activation of STAT1 occurs in two different ways by phosphorylation in two sites. The first way, namely tyrosine 705 (Y705) phosphorylation, leads to the activation of message and its transfer to the nucleus. However, the second condition occurring after stimulation of IFNs in response to cellular stress, namely the Ser727, phosphorylates STAT1 and can play a variety of roles, including cell death, growth, and differentiation [11].

STAT1 acts as a tumor suppressor, and its innate mutations can cause hereditary disorders, including a variety of autoimmune diseases.STAT1 mutations were first observed in patients with fungal and bacterial diseases such as mycobacteria [12].

STAT1 can be involved in cell growth inhibition by suppressing CDK inhibitor and $p21^{Cip1}$ inhibitor genes [3].

STAT2 activation is also a function of IFN signals and can participate in STAT1/STAT2 heterodimer, which enhances the expression of genes associated with IFN stimuli. Studies on STAT1 and STAT2 genes of knock down mice have shown that these mice were not responsive to IFN and that they had a high susceptibility to infection. Nevertheless, the role of STAT2 protein in cancer has not been studied by itself; rather, it has been studied besides STAT4 that plays a role in Th1anti-tumor immune response [3].

IL-12 activates STAT4 by binding to its specific receptor on $CD4^{+}$Th-cells by phosphorylating tyrosine 693 and serine 721 in STAT4, transferring to the nucleus and binding to DNA. STAT4 improves the function of inflammatory cytokines such as IFN-γ in myeloid cells, activated monocytes, macrophages, and dendritic cells. Also, it can play an antiviral, anti-inflammatory, and fibrinogenesis role [13,14].

STAT5 is phosphorylated by Janus kinases at Tyr694 and Tyr699 and dimerized by the SH2 domain [15]. This dimer controls the function of IFN-γ by transferring to the nucleus and binding to DNA [16].

STAT6 modulates the immune responses and allergic inflammation *via* regulation of IL-4 and IL-13 gene expression in different cells [14,17].

STAT3

STAT3 is one of the most important signaling proteins involved in the transmission of messages from the membrane to the nucleus. Unlike STAT1, STAT3 has proven to cause cancer. This protein is fundamentally activated in 25% to 100% of malignancies. It contributes to the escape of cancer cells from the immune system and their resistance to chemotherapy and radiotherapy. Hence, STAT3 inhibition is considered a treatment target [18].

A study has shown that excessive STAT3 signaling plays an important role in chemotherapy resistance and that the inhibition of active STAT3 signaling causes drug resistance in tumor cells that become sensitive to toxic agents [19].

Under normal physiological conditions, the status of STAT3 phosphorylation in the cell depends on the response to extracellular stimuli, so that signal intensity and duration regulate that the response. Pathological conditions caused by abnormalities in signaling pathways as well as various factors such as excessive secretion of growth hormones and cytokines can lead to further phosphorylation of STAT3 [20].

Activation of STAT3

STAT3 signaling cascade provides many opportunities for manipulating its activity because every step in the process of activation could serve as a target. Thus, dominating the activation pathway could contribute to control of treatment response [3].

To activate STAT3, the ligand binds to the receptor and causes phosphorylation at Tyr705. It causes structural changes in the tail region and then binds to phosphotyrosine region of SH2 from the counterpart STAT and there by forms a dimer. By binding to the promoter region on DNA, this dimer causes gene expression, which promotes the development of cell cycle and cellular homeostasis.

STAT3 has no enzymatic activity and cannot be inhibited in this way. Instead, it always interacts with protein and binds to DNA, and this particular feature makes it ready for this process through small interfering molecules and inhibitors (Figure 2) [3,21].

STAT3 as an oncogene

Oncogenes are transformed genes that change the phenotype and structure of cells. They were first found in a viral genome, and it was subsequently found that oncogenes are active in many cells. STAT3 acts as an oncogene whose over activity in various malignancies

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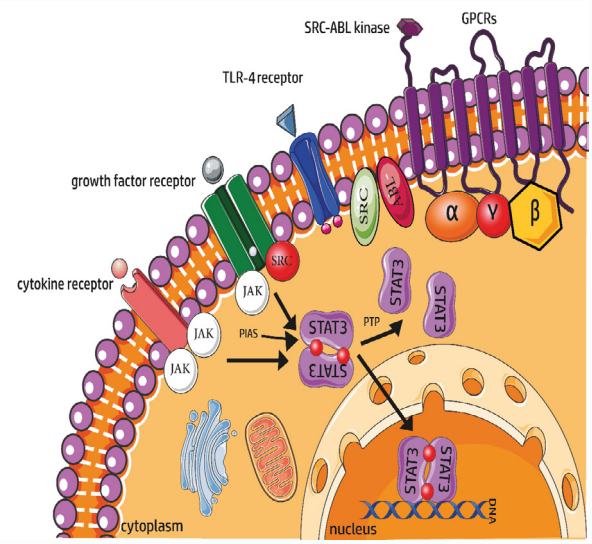

Figure 2: STAT 3 activation cascade. To activate STAT3, the ligand binds to the receptor, causing phosphorylation in Tyr705. The figure shows the types of ligands and receptors for STAT 3 cascade activation.

creates several solid and hematological tumors. This gene increases the growth and proliferation of cells with its excessive activity, inhibiting their apoptosis that leads to metastasis and angiogenesis [22].

STAT3 and cancer

STAT3 is over expressed in many human cancers and plays a key role in tumorigenesis, angiogenesis, and cancer cell metastasis. Inhibition or control of STAT3-related gene expression can control the progression of cancer cells with minimum side effects on healthy cells [23].

Cancer cells in which STAT3 is over expressed affect the immune cells and inhibit their activities and lead to continued growth of cancer cells [24].

Angiogenesis occurs as a result of the activation of Vascular Endothelial Growth Factor (VEGF) in cancer cells that causes tumor growth and metastasis.STAT3 is a direct transcriptional activator of VEGF that stimulates angiogenesis [25-27].

Cancer metastasis occurs after transmission of cancer cells to tissues around the tumor and then by angiogenesis and penetration into blood circulation leading to their transfer to more distant tissues. Protein tyrosine kinases, oncogenes, and viruses can activate STAT3 to transform malignant cells [28].

Cellular context affects STAT3 signaling, which controls tumor growth and suppression. Tumor size and the rate of metastasis are inversely related to STAT3 expression, reduced aerobic glycolysis and energy metabolism in cancer cells *via* suppression of tumor expression through increasing STAT3 expression [29].

Sosonkina N et al. [30] showed that the thyroid gland over expresses STAT3 for normal function.STAT3 phosphorylation at Tyr705 of thyroid epithelium occurs in both the cytoplasm and nucleus.

STAT3 expression levels have different patterns in various types of thyroid disease.STAT3 expression is restricted to epithelial cells in tissue samples of patients with Hashimoto's disease [31].

Breast cancer cells have higherSTAT3 expression that leads to tumor growth by inhibiting apoptosis-related genes such as C-Myc, BCL-2, and CCND1 [32].

Different interleukins can modify STAT3 expression. For example, IL-35inhibits conventional T-cells that activate STAT3, and; STAT1and IL-8 promote breast cancer progression by activating STAT3.In contrast, IL-17 reduces STAT3 expression [33-35].

Activation of STAT3 by phosphorylation at Tyr705 site causes human cancers with epithelial origin such as Head and Neck Squamous Cell Carcinoma (HNSCC) with a poor prognosis and metastasis [36,37].

Studies in ovarian cancer cell lines have shown that STAT3 is phosphorylated and activated, leading to a poorer prognosis of disease with metastasis [38,39].

Ovarian cancer resistance to paclitaxel can be attributed to STAT3 over activity, which can be reduced by inhibiting the resistance of this cancer to treatment [40].

STAT3 inhibition in leukemia

Leukemia refers to the clonal malignancy of hematopoietic cells caused by changes in stem cells. These changes include increasing cell proliferation, as well as changing or blocked differentiation. Changes in the number of blood cells lead to other symptoms such as infection and multiple bleeding. Chemotherapy is used to treat leukemia, but it is a highly cytotoxic approach. Also, there is a high probability of recurrence after the treatment courses [41].

The mortality rate is so high due to leukemia that 26,000 cases are diagnosed in the United States every year. Therefore, finding the right way to treat the disease can be difficult but highly efficient [42].

Potentially, excessive autocrine and paracrine activity of STAT3 pathways by growth factors and cytokines leads to leukemia. By inhibiting this pathway with antibodies and other molecules, we can create more effective treatment methods than chemotherapy. Studies on mice have shown that STAT3 inhibition is associated with low toxicity [22].

The first studies to detect STAT3 hyperactivity in leukemia were performed on samples from ALL and AML patients. In these studies, phosphorylation status was examined by electrophoretic mobility shift assays. As a result, STAT1, 3, and 5 activities were observed in AML patients and the activity of STAT1 and 5 was seen in ALL patients [43].

Inhibiting the STAT3 pathway leads to an increase in apoptosis of cancer cells and is not as toxic as chemotherapy for the remaining healthy cells. It is completely specific and does not create resistance. Direct inhibition of STAT3 pathway with the help of various inhibitors is less effective than indirect inhibition, i.e., inhibition of the pathways activating STAT3 [44].

STAT1 signaling pathway is a practical pathway that can have anti-tumor effects, which is related to STAT3 in some signaling pathways. It is better to be careful not to affect this pathway when controlling the STAT3 [6].

Regulation of STAT3 (phosphorylation and dephosphorylation)

Activation and function of STAT3 depend on its phosphorylation. STAT3becomes phosphorylated at Tyr705 and Ser727 by 1) Tyrosine

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Kinase Receptors (RTK) such as EGFR, PDGFR, Fibroblast Growth Factor (FGFR), Insulin-Like Growth Factor Receptor (IGFR); 2) Receptor associated kinases such as JAK; 3) Non-receptor kinases such as src and abl [2].

In this way, STAT3 activation can create a dimer and cause gene expression. STAT3 controls the expression of genes associated with proliferation and survival, including c-Myc, Bcl-xL, and MCL-1 [45].

STAT3 phosphorylation reaches its peak 15 minutes to 1 hour after exposure to cytokine. Afterward, with its dephosphorylation, a negative control is performed in two modes: Suppressor of Cytokine Signaling (SOCS) that transcribes STAT3 in the transcription stage, and Protein Inhibitors of Activated STATs (PIAS) which stops in the stage of DNA binding to STAT3 [2].

Inhibitors

STAT3 has vital biological functions that can cause problems in both deletion and over-activation cases. At first, the protein was thought to be activated only *via* IL-6signal; however, it was subsequently found that many other cytokines and growth factors can activate STAT3 [46].

Studies have shown that cancer cells are more dependent on the activity of STAT than healthy cells; therefore, the inhibition of STAT3 and 5 leads to higher apoptosis in these cells while healthy cells can survive at very low levels of STAT3 and 5 signaling and can grow through alternative growth mechanisms. As a result, targeting and inhibiting this protein and its components has recently received much attention for the treatment of various diseases [6].

The signaling pathway often begins with peptide hormones and connects to three different types of receptors, including kinase receptors and protein G receptors.

To transducer the message from membrane to nucleus, STAT3 is first phosphorylated that causes protein-protein reactions.

STAT3 is phosphorylated at Tyr705, and this phosphorylation helps to create monomers or hetero-dimers to be connected to the tail from SH2 domain [47].

The goal of STAT3 pathway inhibitors is to study artificial molecules that can directly target STAT3 molecule or different functional parts of protein such as SH2 region of DNA binding region. Some of these molecules can prevent STAT3 from creating a dimer. Others inhibit the transmission of messages from membrane to nucleus, and some of them affect the downstream pathways and genes. Ideally, the best molecules are those that are no longer affected by STAT molecules and their upstream pathways directly affect the STAT molecule [48].

Peptides and peptidomimetics

As mentioned above, STAT3 requires phosphorylation to transfer the message from plasma membrane to the nucleus and forma homodimers or heterodimer. Peptides can directly target the STAT3 signaling pathway by connecting to SH2 region and deforming this region. It prevents the formation of a dimer and does not allow the monomer to be converted to a dimer. Synthesized peptides have a phosphorylated PY sequence so that they can bind to SH2 region to prevent the formation of dimmers [10]. Turkson et al. [6] were the first researchers to use pro-pTyr-Leu-Lys-Thr-Lys-derived phosphopeptides for inhibiting this pathway. Theoretically, this approach can be effective; however, it is not a good idea to target STAT3 specifically as SH2 domains are the same in different signaling molecules of various signaling pathways.

STAT3 can remain in the signaling pathway by binding its SH2 region to phosphotyrosines of the residual of some proteins, including gp130, Lysosomal Inhibitor Factor Receptor (LIFR), epidermal growth factor receptor, IL-10R, and G-CSF receptor. In order to inhibit this part of STAT3 signaling pathway due to its cell permeability as well as low metabolic and pharmacokinetic properties, Ren et al. [49] created peptidomimetics from peptides,namely molecules with improved properties to create a scaffolding with XpYL as the main structure [10].

Phosphopeptides are molecules derived from STAT3 Tyr705 that can bind to and inhibit phosphotyrosine ligands [11].

Another inhibitor is PDP, a phosphor-do-decapeptide that contains Y1068 in its EGFR sequence and can bind to non-phosphorylated STAT3 to inhibit its DNA binding site [50].

Non-peptidic small molecule inhibitors

Due to pharmacokinetic limitations, instability of peptides in the body and low membrane permeability of them, a series of new molecules called small molecules were designed in peptidomics to inhibit this pathway. These molecules are among the largest group of inhibitors and have high permeability. Small molecules are inside the cell and that is why these molecules are so attractive to study [3,51].

Like peptides, these small molecules target the pTyr-SH2 region to inhibit STAT and prevent the formation of STAT3-STAT3 dimers [52].

The STA-21 molecule is a small molecule that is synthesized naturally. This molecule was identified as an antibiotic released when a species of *Streptomyces rimosus* bacterium was examined and cultured.STA-21 is an analog of tetrangomycin and can structurally inhibit STAT3 at different doses, so that at a dose of 20 μM, it can inhibit the DNA binding region, and at a dose of 20 μM - 30 μM, it expresses STAT3-related genes and inhibits the growth of cells [51,53].

Stattic (Stat three inhibitory c compound) is another small non-peptide inhibitory molecule. With the chemical structure of nitro-benzo[b] thiophene-1,1-dioxide-6, it can target the SH2 region of STAT3 molecule and inhibit its dimerization and message transmission. However, it has no inhibitory effect on STAT1 [51].

Stattic is a drug that depends on temperature and dose. It has different functions at various temperatures and doses. Its activity is low at lower temperatures and its activity increases with the increase in temperature. Stattic has a low activity at 22°C, a moderate activity at 30°C, and its inhibitory potential is significantly increased at 37°C [54].

Stattic can selectively inhibit STAT3 at different doses. In IC_{50}=5.1 μM, it can inhibit the STAT3 phosphopeptide (PY) region and in IC_{50}=20 μM, Stattic inhibits the signal transmission pathway triggered by IL-6 [52,53].

Curcumin is another small molecule that inhibits STAT3 pathway. It is a natural compound that is also known as diferuloylmethane, i.e. a polyphenol. This drug can affect different cell pathways, and it is involved in cell apoptosis, proliferation and survival, metastasis, and angiogenesis. This molecule affects the growth factors, cytokines, and enzymes to express genes [55].

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The function of curcumin depends on the type of isomer. This compound has two isomers, including enol, and beta-diketone. Enol isoform links the enolic and phenolic groups with three ionizable protons and makes this drug unique [56].

Curcumin is a quite safe drug in terms of toxicity even in high doses. It can be used in the treatment of various conditions, including inflammatory diseases. This compound is also used as a supportive agent in chemotherapy [57]. Curcumin is derived from the rhizome of *Curcuma longa*,_which is known as turmeric in East of India. This yellow compound is in powder form and has different solubility degrees, so that it is insoluble in water and ether solutions but organic solvents such as acetone, dimethyl sulfoxide, and methanol can solve curcumin [55].

Curcumin can inhibit the IL6-dependent STAT3 activation in STAT3 and STAT5a-5b pathways ofK562 cell line and has no inhibitory effect on STAT1.

Chronic myeloid leukemia (K562) is identified by JAK2 and BCR-ABL, both of which are inhibited by curcumin. So, this drug can be used alone or in combination with other chemotherapy drugs [58].

Oligonucleotides

Decoy oligonucleotides are synthesized to inhibit the expression of certain genes and can also have therapeutic uses. The first application of oligonucleotides for treatment of cytomegalovirus retinopathy was achieved in 1999 [59].

Structurally, oligonucleotides are in the form of two strands. In each part, there are about 10-20 base pairs that are synthesized as a cis-element. The oligonucleotides are inhibited in a competitive manner, so that they first enter the cell and bind to the transcription factors of DNA binding region to prevent DNA binding to that region and inhibit transcription [6].

STAT3 can be inhibited in this way, so that oligonucleotides can prevent and inhibit the binding of STAT3 to DNA after entering the cell and binding to DBD region but have no effect on other genes [59,60].

The decoy-ON therapeutic potential to neutralize the transcription factor has also been tested in clinical trials. The application of decoy-on as a tool to examine the role of transcription was first explained by Bielinska et al. [61]. However, the most serious disadvantage of decoy-ON is its sensitivity to nuclease activity. Phosphorylate decoy-ON that is resistant to nuclease activity has been used to overcome this problem [3].

Another advantage of using a modified decoy-ON is that it can be more effectively assembled in cells than a standard decoration and control gene expression in a particular way. As mentioned earlier, decoy-ON has led to a revolutionary change in the treatment of cancer, inflammatory and cardiovascular diseases, cystic fibrosis, and so forth that are caused by the high expression of the gene, and its low toxicity compared to other drugs is an advantage. However, the use of decoy-on limits its effectiveness due to low targeting ability and lack of an efficient delivery system.

The exact mechanism of decoy-ON uptake by the cell has not been confirmed. Nevertheless, there is evidence suggesting that both pinocytosis and endocytosis can be mediated by the receptor. Intracellular delivery can be improved by a variety of concepts, including liposomal capsule bait oligonucleotides and flavored oligonucleotide lipoxin complexes that are confined to nanoparticles or cholesterol compounds [3].

Conclusion

STAT signaling pathway is one of the most important pathways for transmitting extracellular signals to the cell nucleus, which, when overactive, can cause a variety of cancers. Different types of inhibitors have been designed for this pathway, and STAT3 and STAT5 pathway inhibitors are being further investigated to pave the way for clinical trials. Also, because STAT3 pathway is inhibited in mature cells, it has fewer side effects and may have a promising therapeutic future.

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