STAT3 in Cell Cycle Arrest and Regulation

Subjects: Oncology
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There are seven STATs (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) that are intracellular proteins which function as signal messengers and transcription factors. They transmit signals from cytokines, growth factors, intracellular kinases, mutated oncoproteins, and other signaling pathways to the nucleus. STAT3 play critical roles within neoplastic cells, immune cells, and other stromal cells, such as cancer-associated fibroblasts (CAFs).

STAT3 | acquired drug resistance | kinase inhibitors | chemotherapy

1. STATs (Signal Transducer and Activators of Transcription)

There are seven STATs (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) that are intracellular proteins which function as signal messengers and transcription factors. They transmit signals from cytokines, growth factors, intracellular kinases, mutated oncoproteins, and other signaling pathways to the nucleus. Tyrosine phosphorylation cascade occurs after ligand binding by many extracellular molecules such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), interleukin-6 (IL-6), IL-5, oncostatin-M (OSM), granulocyte colony stimulating factor (GCSF), colony stimulating factor-1 receptor (CSF1R), leukemia inhibitory factor (LIF), c-kit, c-Met, insulin receptor, angiotensin-II receptor (AgtR2), interferons (IFNs), G-protein coupled receptors (GPCRs), and others. After such ligands bind the extracellular portion of their receptors, their intracellular portion attracts the Janus Kinase family (JAK1, JAK2, JAK3, and Tyk2) of proteins, which become phosphorylated. The JAK protein then phosphorylates STAT3 (pSTAT3) at tyrosine 705 and sometimes serine 727 to activate STAT3. Other intracellular kinases, which can directly activate STAT3 are Src and BCR–ABL, the mutant fusion protein in chronic myelogenous leukemia (CML) [1]. P-STAT3 then forms dimers, which translocate to the nucleus via chaperone proteins. There p-STAT3 dimers bind to specific nine base pair sequences in regulatory genomic regions to regulate transcription of specific genes. The signaling function of p-STAT3 is carefully regulated by inhibitory molecules such as protein inhibitors of activated STAT (PIAS), protein tyrosine phosphatases (PTPases), and suppressors of cytokine signaling (SOCS). Dysregulation of the normal physiologic balance of p-STAT3 and unphosphorylated STAT3 can occur due to upstream mutations or protein overexpression. This results in constitutive expression of p-STAT3 and continuous transcription of pro-oncogenic and anti-apoptotic genes, which promotes cancer growth, proliferation, cell cycle re-entry, angiogenesis, immunosuppression, and, metastasis when anticancer agents apply selective pressure might induce the development of acquired drug resistance (ADR).

2. The Role of STAT3 in Cell Cycle Arrest and Regulation

STAT3 play critical roles within neoplastic cells, immune cells, and other stromal cells, such as cancer-associated fibroblasts (CAFs). Once activated within tumor cells, phosphorylated STAT3 (p-STAT3) regulates the transcription of various immunosuppressive cytokines such as VEGF, IL-10, and TGF-β. p-STAT3 can promote tumor progression by increasing transcription of genes associated with stemness and epithelial to mesenchymal transition (EMT) [2]. Additionally, p-STAT3 is involved in two apoptotic processes, autophagy and anoikis, both contributors to ADR development.

Autophagy, a cellular degradation process, is another regulatory mechanism that plays a major role in maintaining homeostasis, and its dysfunction has been implicated in cancer progression and ADR. The signaling pathways that control inducible autophagy and cell death are closely associated and incorporated into the tumor regulatory network of autophagy related proteins, ultimately affecting the fate of tumor cells [3]. The crosstalk between autophagy and other stress response pathways including STAT3, determines the survival or death of a cell. Nuclear STAT3 regulates autophagy in various forms. For instance, STAT3 inhibits autophagy by activating BCL2 or increases it by upregulating and stabilizing HIF1A under hypoxia; however, it has been determined that cytoplasmatic STAT3 regulates autophagy in a more direct way [4]. Autophagy initially prevents cancer progression but under stressful situations improves the survival of cancer cells [5] contributing to ADR and therapy failure. p-STAT3 has been found to be associated with aberrant autophagy activity in many oncological studies [6]. The anti-autophagy action is partly due to STAT3-mediated inhibition of the BEBN1/PIKC3 complex, resulting in reduced Beclin-1 activity. There is a link between ADR to chemotherapeutics, sometimes described as chemoresistance, and autophagy. The autophagic process vary depending on the tumor stage. In some cases, high dosage chemotherapy may induce protective autophagy that leads to ADR. Some proteins such as mTOR, Beclin-1, miRNA, and autophagy-related genes play a role during treatment of some cancers such as osteosarcoma. The use of autophagy inhibitors in combination with chemotherapeutics is being studied as a new treatment of cancer that might avoid chemoresistance [7]. STAT3 inhibition increases autophagy by increasing transcription of key activators of autophagy. [8]. The importance of autophagy in tumor immunity and ADR is now recognized and has been reported that optimal induction or inhibition of autophagy may induce effective treatments when combined with immunotherapy [9].

Anoikis, another type of apoptosis, is triggered by loss of cell adhesion [10]. It might be activated during tumorigenesis to clear off extracellular matrix (ECM) and detached cells. Cancer cells that develop the ability to survive are called anoikis-resistant cells. These cells become very aggressive and drug resistant, developing the capacity to invade and migrate to metastatic sites. Several features have been identified as responsible for modulating anoikis resistance, one of which is STAT3. STAT3-related anoikis-resistance has been reported in cancer cells of human pancreatic cancer, melanoma, cholangiocarinoma, esophageal squamous cell carcinoma, squamous cell carcinoma, nasopharyngeal carcinoma, and lung carcinoma [11][12][13][14][15]. These cancer cells were reported to have enhanced cell migration, invasion capability and high metastatic potential, and inhibition of STAT3 led to sensitization of all those anoikis-resistant cells [16].

Nicotinamide N-methyltransferase (NNMT) participates in the development of ADR. NNMT, a cytoplasmic enzyme that methylates nicotinamide, is regulated by STAT3 and has been shown to be overexpressed in solid tumors.

Furthermore, STAT3 activation intensifies the expression of NNMT and stimulates its activity [17]. NNMT has been identified as an oncogene in intrahepatic cholangiocarcinoma [18]. NNMT is upregulated in cutaneous squamous cell carcinoma, induces cellular invasion via EMT-related gene expression [19] and plays critical roles in the incidence and development of various cancers [20].

Evidence that NNMT plays an important role in cancer can be seen by the fact that NNMT knockdown reduces tumorigenesis and chemoresistance and that Yuanhuadine, a natural inhibitor of NNM, reverses EGFR inhibitors ADR [21]. Chemoresistance or ADR to adriamycin and paclitaxel in breast cancer has been also reported by Wang et al., 2019. This group found that reversal of NNMT related ADR can be accomplished by using the SIRT1 inhibitor, EX527 or using siRNA therapy. SIRT1 also represses the activation of STAT3 and NF-κB proteins via deacetylation [22].

The major function of the tumor suppressor p53 is to induce transient cell cycle arrest, cellular senescence, and apoptosis, a significant barrier to the development of tumors; however, p-STAT3 can inhibit these repressive functions of p53 [23]. This crosstalk between STAT3 and p53 also contributes to the development of ADR and the loss of the pharmacologic effects of anticancer agents [24]. STAT3 inhibition upregulates the expression of p53 and increases cellular apoptotic activity, thereby reversing ADR. Another important signaling pathway for growth and proliferation is the RAS/mitogen activated pathway kinase (MAPK). The crosstalk between STAT3 and p53/RAS signaling regulates metastasis and cisplatin resistance in ovarian cancer through the Slug/MAPK/PI3K/AKT-mediated regulation of EMT and autophagy [25]. Therefore, RAS and STAT3 activation promote ovarian cancer growth, metastasis, and cisplatin resistance. Dual inhibition of STAT3 and KRAS, achieved by nano-antibody SBT-100, would be an ideal treatment for this type of cancer to overcome ADR in ovarian and many other types of cancer [26].

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