STAT3 and p53

Subjects: Others

Contributor: Do-Young Yoon

The tumor suppressor p53 is considered the “guardian of the genome” that can protect cells against cancer by inducing cell cycle arrest followed by cell death. However, STAT3 is constitutively activated in several human cancers and plays crucial roles in promoting cancer cell proliferation and survival. Hence, STAT3 and p53 have opposing roles in cellular pathway regulation, as activation of STAT3 upregulates the survival pathway, whereas p53 triggers the apoptotic pathway. Constitutive activation of STAT3 and gain or loss of p53 function due to mutations are the most frequent events in numerous cancer types. Several studies have reported the association of STAT3 and/or p53 mutations with drug resistance in cancer treatment. This review discusses the relationship between STAT3 and p53 status in cancer, the molecular mechanism underlying the negative regulation of p53 by STAT3, and vice versa. Moreover, it underlines prospective therapies targeting both STAT3 and p53 to enhance chemotherapeutic outcomes.

STAT3 wild-type p53 (wtp53) mutant p53 (mtp53) feedback regulation drug resistance cancer therapy

1. Introduction

Cancer is one of the leading causes of death worldwide, which was responsible for approximately 9.6 million cancer deaths in 2018 [1]. Targeted chemotherapy is a common method of cancer treatment in which the molecular pathways related to cancer growth or metastasis are blocked using targeted drugs. Molecularly targeted drugs are less toxic and more effective than conventional drugs because they are administered at lower doses than the higher tolerated dose of the latter [2]. However, both types of drugs suffer from problems associated with cellular resistance, which reduces their efficacy [3]. In addition, chemoresistance is often associated with transformation of tumors into more aggressive and/or metastatic forms.

Signal transduction and activator of transcription (STAT) 3 is a member of the STAT family, comprising seven transcription factors (STAT 1, 2, 3, 4, 5a, 5b, 6) [4]. It was discovered by two independent groups [5][6] and has been of particular interest due to its role in the regulation of cellular signaling, especially in cancers. STAT3 is constitutively active in several cancers such as breast, lung, ovarian, colorectal, cervical, gastric, and prostate cancers, and head and neck squamous cell carcinoma [7][8][9][10][11][12][13]. Despite the multifaceted function of STAT3 in cancer, growing evidence has revealed that constitutive activation of STAT3 contributes to cancer cell proliferation and that aberrant STAT3 activation is associated with tumor malignancy [14][15][16].

TP53 (tumor protein p53) is one of the most well-studied tumor suppressor genes. Owing to its pivotal role in protection against malignancies, wild-type p53 (wtp53) has long been called the “guardian of the genome” [17]. It is well known that p53 suppresses tumor formation and renders protection against DNA damage by inducing cell cycle arrest, DNA repair, or apoptosis [18]. Mutation of p53 is often observed in cancer, especially in late events in malignant progression [19][20].

Tumor cell proliferation and survival involve downregulation of wtp53 expression as well as increase in STAT3 activity. In contrast, wtp53 reduces STAT3 phosphorylation and DNA-binding activity in breast and prostate cancer cells [21][22]. In addition, another report revealed that STAT3 activity suppresses *TP53* expression [23]. Therefore, wtp53 and activated STAT3 negatively regulate each other. This adverse regulation can be explained by the opposing biological roles of both factors, as activated STAT3 functions as an oncogene [24], whereas wtp53 functions as a tumor suppressor [25]. Consequently, normal cells might have evolved mechanisms to adjust STAT3 and p53 expression for necessary cell proliferation conditions, whereas tumor cells might exploit such negative regulation for survival [23]. During the early stage of progression, tumors grow preferentially via STAT3-regulated signaling [26]. Although mutations of p53 have been reported to occur early and involve in tumor initiation, it appears that p53 mutations in certain cancers could be developed late and contribute significant roles in advanced stages of tumorigenesis [27]. Furthermore, the loss of wtp53 function along with the accumulation of mutated p53 (mtp53) can support STAT3-mediated tumor cell survival and expansion [28][29][30].

Several inhibitors targeting either STAT3 or p53 are under clinical trials, but their success has been limited because of resistance to targeted cancer therapy [31][32]. Resistance often occurs due to the complexity of cancer signaling pathways, making it difficult for single-target inhibitors to achieve satisfactory clinical outcomes; hence, a combinational therapy co-targeting STAT3 and p53 could overcome drug resistance. The present review provides our current understanding of two well-known targets for cancer therapy, STAT3 and p53, regarding the interaction between them as well as the potential underlying mechanisms. In addition, we have summarized the status of STAT3 and p53 in different cancer cell types and highlighted the potential therapies that target both factors to improve the efficacy of cancer prevention.

2. Role of STAT3 Signaling in Cancer

2.1. Activation and Regulation of STAT3

STAT3 is maintained as an inactive homodimer in the cytoplasm of nonstimulated cells. It forms a stable dimer to translocate into the nucleus of stimulated cells and acts as a transcription factor for numerous targeted genes. Activation of STAT3 is induced by various cytokines (interleukin (IL)-6, type I interferons) and growth factors (epidermal growth factor (EGF), platelet-derived growth factor (PDGF)) through receptors (EGFR, PDGFR) and Janus kinase (JAK) signaling pathway [33][34][35][36][37][38], or through oncogenic proteins (Ras, protein kinase C (PKC)) [39][40][41]. It is stringently controlled by several negative regulators, including phosphatases (Src homology region 2 (SHP2), phosphatase and tensin homolog (PTEN), CD45) [42][43][44], suppressor of cytokine signaling

proteins (SOCS), mainly SOCS3 [45], and protein inhibitors of activated STAT (PIAS) proteins, particularly PIAS3 [46].

STAT3 can be activated by two major mechanisms: nuclear activation upon tyrosine phosphorylation (Tyr705) and mitochondrial activation (mitoSTAT3) upon serine phosphorylation (Ser727) [47]. The phosphorylation of STAT3 at Tyr705 is primarily regulated by JAK2, IL-6, and EGF, whereas phosphorylation at Ser727 is commonly regulated by PKC, mitogen-activated protein kinases (MAPKs), and cyclin-dependent kinase (CDK) [39][48]. Phosphorylation of STAT3 at Tyr705 site has been studied extensively as it leads to nuclear translocation, DNA binding activities, and transcription of target genes [48]. It has been shown that mitoSTAT3 along with phosphorylated Ser727 can promote tumor growth and metastasis [47]. Phosphorylation of STAT3 at Ser727 supports or represses the transcriptional activity of STAT3 in the presence of phosphorylated Tyr705 [49]. The actual effects of Ser727 phosphorylation remain somewhat controversial.

2.2. Function as an Oncogene

STAT3, like other STAT proteins, was initially characterized for its role in cytokine signaling and was then classified as an oncogene for the following reasons. First, it is constitutively active in several tumor samples and is correlated with high metastatic threat and poor survival consequences [8][11][13][38][50]. Aberrant persistent STAT3 activity has been observed in various hematological and solid cancers [24]. Noticeably, constitutive STAT3 activity is frequently found in triple negative breast cancers, and in more than 40% of all breast cancers [51]. In normal cells, STAT3 is activated for a temporary duration from a few minutes to several hours [49]. The oncogenic role of STAT3 in gliomas is consistent with the observation that STAT3 activation is rarely detected in normal brain tissue [52]. Second, STAT3 acts as a transcription factor that activates several downstream target genes that are involved in multiple steps of metastasis, including invasion, cell survival, self-renewal, angiogenesis, and tumor-cell immune evasion [53]. It also localizes in the mitochondria and supports gene regulation [47]. Third, STAT3 is directly associated with oncogenic signaling and responses to specific oncogenic kinases, such as SRC, ABL, FPS, and JAK2 [54][55]. STAT3 can activate transcription in the absence of tyrosine phosphorylation by interacting with nuclear factor-κB (NF-κB) subunits to induce specific cancer genes [54]. STAT3 has been reported as a part of the JAK2/STAT3/STAT5/PD-L1 axis which can drive immune escape in myeloproliferative neoplasms [55]. Fourth, blocking STAT3 activity decreases cellular transformation in SRC-transformed cell lines [56]. Mutated STAT3 construct (STAT3C), which constitutively forms dimers in normal mouse fibroblasts, forms tumors when transplanted into nude mice. This STAT3C construct was found to drive tumor formation in a variety of cell types by upregulating important oncogenic and angiogenic factors such as matrix metalloproteinase MMP-9, vascular endothelial growth factor (VEGF). Although some evidence raised the question about the multifaceted function of STAT3 as it exerted a normal role in immunosuppressive cells [57], growth inhibitory effect in prostate cancer cells [58], and tumor suppressing functions in some cases [59], most observations demonstrated the major role of constitutively active STAT3 in tumorigenesis.

2.3. Targeting STAT3 for Cancer Therapies

Several strategies have been established to inhibit STAT3 signaling, including: (i) downregulating the upstream regulators, (ii) targeting the STAT3 SH2 domain, (iii) blocking the STAT3 DNA-binding domain, (iv) inhibiting the STAT3 N-terminal domain, (v) suppressing the STAT3 mRNA, and (vi) targeting the STAT3 endogenous negative regulators [60]. Direct inhibitors target the SH2 domain (Stattic, S3I-201 and derivatives, OPB-31121, OPB-51602), the DNA-binding domain (Decoy oligonucleotides [ODNs]), the N-terminal domain (ST3-HA2A), or the STAT3 mRNA (AZD9150) to regulate STAT3 activation [61][62][63][64][65][66][67]. Indirect inhibitors target the upstream regulators of the STAT3 signaling pathway (IL-6, RTK, JAK, SRC, BCR-ABL), such as siltuximab, sunitinib, sorafenib, ruxolitinib, bosutinib, or the endogenous STAT3-negative regulators (AdCN305-cppSOCS3 targeting SOCS3) [68][69][70][71][72][73]. The current promising direct STAT3 inhibitors which have entered clinical trials include STAT3 antisense-based AZD9150 (Phase I in hepatocellular carcinoma metastatic, Phase II in advanced cancers), OPB-31121 (Phase I in advanced cancers, phase I/II in hepatocellular carcinoma), OPB-51602 (Phase I in advanced cancers, hematologic malignancies), OPB-111077 (Phase I in solid tumors, leukemia), STAT3 decoy (Early phase I in head and neck cancer).

Feedback activation of STAT3 plays an important role in mediating drug resistance to various conventional chemotherapies and molecularly targeted therapies [32]. The long term activation of tyrosine kinases in malignant tumors can lead to constitutive activation of STAT3, which may not only provide advantages of growth and accumulation of tumor cells, but also confers resistance to conventional therapies that rely on apoptotic machinery to get rid of tumor cells [21]. The downstream outcomes of STAT3 activation supporting tumorigenesis consist of deregulation of cell cycle progression and protection against apoptosis [21]. For example, persistent activation of STAT3 can resist apoptosis in human myeloma cells [74], fibroblasts [75], breast cancer [76], and gastric cancer [13].

As stated above, once activated by phosphorylation at Tyr705, STAT3 forms a dimer and translocates into the nucleus. Hence, drugs targeting the dimeric form of STAT3 are expected to be useful for tumors that rely on STAT3 activation. The SH2 domain is necessary for STAT3 dimer formation and phosphorylation which are recruited to tyrosine-phosphorylated receptor complexes; thus, targeting the SH2 domain is a prospective approach. Some SH2 domain inhibitors have been used in preclinical research (S3I-201 and derivatives) or entered clinical trials (OPB-31121, OPB-51602) for hematologic cancer treatment [77]. However, STAT3 interacts with NF-κB subunits in the absence of Tyr705 phosphorylation or is modified at other sites such as Ser727 to activate transcription [49][78]. It has been reported that nuclear translocation and DNA binding of STAT3 can occur independently of their P-Y status [77]. These observations indicate that SH2 domain-targeting inhibitors may not be adequate to abolish STAT3 oncogenic functions totally, which may become the limitation of these compounds. Therefore, it is obvious that a drug targeting the dimer and its Tyr705 phosphorylation would probably be ineffective if a tumor does not depend solely on the dimeric STAT3 and Tyr705 site for modification.

In brief, several small molecules and inhibitors have been developed and have shown effects in cancer treatment in preclinical research; however, a small number of them could enter clinical trials due to the lack of efficacy issues.

3. The Contribution of p53 in Cancer

3.1. Role of wtp53

The p53 protein functions as a nuclear transcription factor in the form of a homotetramer and contributes to normal cellular processes. It is activated in response to stress conditions such as DNA damage, oncogenic stress, replicative stress, and hypoxia [25][79]. Activation of p53 is regulated through three basic steps: stabilization of p53, DNA binding to a specific sequence, and transcriptional initiation of target genes. Three major functions of p53 include growth arrest, DNA repair, and cell death (apoptosis and senescence). When there is DNA damage in the cell, the growth arrest stops the progression of the cell cycle, preventing replication of damaged DNA, and activating the transcription of proteins involved in DNA repair. If the DNA cannot be repaired, apoptosis or senescence would be the last step to avoid proliferation of cells containing abnormal DNA. Multiple p53-mediated downstream target genes have been implicated in apoptosis (*PUMA*, *NOXA*, *BAX*, *APAF1*, *FAS*), cell cycle arrest (*CDK1a*, *GADD45*, *14-3-3*), senescence (*PML*, *PAI-1*, *E2F7*), DNA damage repair (*POLK*, *MGMT*, *FANCC*, *ERCC5*, *XPC*, *DDB2*, *GADD45α*, *MSH2*, *POLH*), and DNA metabolism (*GLUT1/3/4*, *TIGAR*, *SLC7A11*) [25]. Metabolic dysfunction also triggers p53 expression, and it was reported that p53 could regulate metabolism by inducing ferroptosis, an iron-dependent regulated form of cell death, or autophagy cell death [25]. Furthermore, p53 is involved in other cellular processes, including cell differentiation and stem cell renewal [79]. p53 is essential for regulating DNA repair and cell division; hence, it has been described as the “guardian of the genome” [18].

3.2. Negative Regulation of wtp53

wtp53 is inactivated by negative regulators such as E3-ubiquitin ligases (mouse double minute 2 [MDM2], C-terminus of HSC70-interacting protein [CHIP], tripartite motif-containing 24 [TRIM24]), and asparaginase endopeptidase [31]. Under normal conditions, the protein level of p53 is low because of the feedback regulation between p53 and MDM2, an E3 ubiquitin-protein ligase [79]. MDM2 is the most recognized p53 inactivator. Cellular stress disrupts MDM2 binding to p53 by phosphorylation of both proteins and stimulates p53 acetylation, leading to p53 accumulation and activation [79]. p53 activates the MDM2 gene, and subsequently, the MDM2 protein directly binds to and triggers the degradation of p53 using the ubiquitin system. The constitutive expression of MDM2 is sufficient for maintaining a normal level of p53 protein. Thus, the feedback loop p53–MDM2 is critical for regulating p53 activity to protect cells against DNA damage induced by stress [31][80]. Another notable homolog of MDM2 is MDM4, which acts like MDM2 to inhibit p53 transcriptional activity. The different mechanism of MDM4 compared to MDM2 is due to the lack of intrinsic E3 ubiquitin activity; however, it can bind to MDM2 and trigger ubiquitylation of p53 [31].

3.3. p53 Mutations in Cancer—From Loss of Function to Gain of Function

Mutations in *TP53* are often present in nearly 50% of all human cancers [81]. Missense mutation, where a single amino acid is substituted within the DNA binding domain of *TP53*, especially at six hot-spot codons (R175, G245, R248, R249, R273, R282), is the most frequently found type of mutation (approximately 80–90%). Other mutations, including insertion, deletion, and nonsense, occur in a small number [31].

The common types of mutations affecting *p53* function are loss of function (LOF) and gain of function (GOF). The p53 LOF mutation was first proposed by Alfred G. Knudson in 1971 [82]. More than 90% of cancers with p53 mutations present loss of both functional alleles [31]. The most common cause of p53 LOF is a missense mutation in one allele that leads to the inactivation of *TP53*. Based on the loss of p53 functionality, damaged cells may transfer their mutations, without being repaired, to the next generation. The accumulation of deregulated p53 often leads to the formation of tumors.

GOF is described as the ability of mtp53 to be exerted in the absence of wtp53 co-expression [83]. This function includes the capacity to promote cell proliferation, invasion, and metastasis; inhibit apoptosis; and induce resistance to cancer treatments [31]. Notably, the GOF mutation is usually a hot-spot mutation and occurs at a higher frequency than expected [84]. Knock-in allele of some common p53 mutations within hot-spot codons, using a mouse model, demonstrated the GOF phenotype, which supported tumor development and metastasis [85]. A proposed mechanism by which mtp53 exerts GOF is the binding and modulation of the function of other transcriptional regulators such as p63, p73, NF-X, and NF-Y [83]. Another mechanism is the upregulation of chromatin regulatory enzymes such as MLL1, MLL2, and MOZ, which increase histone methylation and acetylation, subsequently promoting cancer cell growth [86].

Recently, p53 mutations were defined as separation of function (SOF) mutations [84]. SOF mutations produce stable proteins with loss of certain biochemical properties, but do not disrupt the other wild-type allele activities [84]. It has been shown that several *TP53* truncating mutations occur at the boundary of exon 6/exon 7, which induce cell proliferation and metastatic features in cancer cells. Particularly, these p53-exon-6 truncated proteins have molecular characteristics similar to those of the p53 alternative splice isoforms, and partially localize to the mitochondria to interact with cyclophilin D (CypD), a regulator of the mitochondrial permeability transition pore (MPTP) [84][87]. SOF mutations occur especially at hot-spot locations, and the total frequency is limited [84].

Mtp53 is more stable than wtp53 because it does not activate the expression of its negative regulator, MDM2, nor is it degraded by MDM2. In addition, mtp53 interacts with chaperones (heat shock protein (HSP)90, HSP70) to form a stable association that supports cancer cell survival under stress-induced conditions, and blockage of this mechanism elicits mtp53 degradation [88]. Therefore, in cancer cells, mtp53 may accumulate more extensively than wtp53 and exert its dominant negative effect against the wild-type function [89]. It has been shown that wtp53 and mtp53 are co-expressed at an equivalent level in vitro and in vivo [89]. Notably, the mtp53 allele is not generally carried in human nontransformed tissues and is found in patients with the rare disorder Li-Fraumeni Syndrome (LFS) [90]. Moreover, LFS patients would have one allele harboring wtp53 in untransformed tissues, whereas the majority of tumors upon transforming events maintain only the mutant allele [90]. This raises a question regarding the relationship between different *TP53* mutations and LFS patients. One explanation could be that during evolution or at an early stage of tumor generation, mtp53 is derived from one mutated allele co-existing with wtp53 from the other allele until the wild-type allele is totally lost by loss of heterozygosity (LOH), which results in the existence of only one mtp53 allele [90]. LFS patients hold different germline mutations in *TP53*; thus, they are susceptible to cancer development [84]. Consistent with this notion, LFS patients with the LOF *TP53* mutation would

have tumors later in life, whereas the GOF *TP53* mutation group tends to acquire cancers in their inherited generation [91].

3.4. Mutant p53 and Cancer Therapy Resistance

Current strategies targeting p53 in cancer include two types: one targets wtp53 by blocking the degeneration of wtp53 or prolonging its cellular life and disrupting the interaction between wtp53 and its negative regulators MDM2/MDM4; the other targets mtp53 by destabilization of highly accumulated GOF p53 mutants and reactivation of mtp53 via recovery of the wild-type conformation and activity [31][92][93]. Other approaches that indirectly target mtp53 focus on the mtp53-specific downstream signaling pathways, the retaining G2 checkpoint on which a tumor depends, and the mtp53 interactors related to cancer progression [81].

Cancers harboring mtp53 are commonly characterized by serious metastasis and genomic instability; mtp53 is considered a “guardian of the cancer cell” [88]. A variety of p53 mutations produce different oncogenic activities to support tumor development. Generally, mtp53 core activities are recognized as the mirror basal function of the wtp53 counterpart and the adaptive ability to perform oncogenic function. p53 mutations have been linked to chemoresistance in breast, ovarian, lung, gastric, and colorectal cancers [94]. It is not only LOF but also GOF mutation forms that contribute to drug resistance.

The mtp53 confers resistance to different MDM2 inhibitors, as these compounds mainly target wtp53 [95]. Another reason might be that MDM2 inhibitors cannot bind to MDM4, which is an MDM2 homolog with similarities in the N-terminal p53-binding domains; thus, most of the available MDM2 inhibitors lack activity against MDM4 [96]. For example, Nutlin-3a can activate wtp53 in cancer cells overexpressing MDM2 but not in cells overexpressing MDM4 [97]. Another problem with MDM2/MDM4 inhibitors is the unexpected increase in the expression levels of non-MDM2/MDM4 E3 ubiquitin ligases that may degrade wtp53 [98]. These MDM2 inhibitors would be effective mostly in wtp53 tumors because it is possible that p53 pathway restoration disrupts survival pathways and causes cancer cell death, although they also exert hematological toxicity as side effects during clinical trials [99][100]. Therefore, MDM2 antagonists might need to be better developed or used in combination with another method to increase specificity and reduce side effects.

Drug absorption and DNA repair changes are also possible mechanisms causing drug resistance in p53-based cancer therapy. For example, mtp53 stimulates the expression of ABCB1, an ABC transporter, and mediates drug efflux from cells in an ATP-dependent manner, conferring multidrug resistance [94]. Furthermore, p53 mutants disrupt critical DNA damage response pathways by interfering with binding of the MRE11–RAD50–NBS1 complex to the site of DNA damage, resulting in *ataxia telangiectasia mutated* (*ATM*) inactivation and genetic instability [101]. Notably, mtp53 recruits poly(ADP-ribose) polymerase 1 (PARP1), MCM4, and proliferating cell nuclear antigen (PCNA) to change chromatin structure and thus negatively regulates DNA repair while still allowing DNA replication to increase in breast cancer cells [102]. From these observations, it can be inferred that the indirect p53 inhibition approach could not satisfy drug treatment outcomes; hence, there is a need for a combination method that directly targets mtp53 as well as cancer-specific activation mechanisms.

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