TYK2 in Cancer Metastases

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Genomic, transcriptomic and proteomic assays have led to identification of tyrosine kinase 2 (TYK2) mutations, fusion proteins and expression changes in a variety of hematological cancers, carcinomas and soft-tissue sarcomas. TYK2 is an approximately 134 kDa protein identified in 1990 as the first member of the Janus kinase (JAK) family, which includes non-receptor tyrosine kinases that mediate cytokine signaling. In humans, the TYK2 gene is found on chromosome 19, and is ubiquitously expressed at varying levels throughout the body.

tyrosine kinase-2 TYK2 cancer metastasis genomics proteomics transcriptomics JAK STAT

1. Introduction

Revolutionary advancements in bioinformatics techniques and computational data analysis within the last decade have transformed modern cancer diagnostics and therapeutics [1]. Innovations in next-generation sequencing (NGS) have allowed large-scale genomic and transcriptomic characterization, leading to the detection of novel genetic alterations in numerous types of cancer [1][2]. High throughput proteomics utilizing protein microarrays and mass spectrophotometry have similarly led to the discovery of proteins with aberrant expression or kinase activity in cancer development and progression [3].

While activating mutations in other members of the JAK family have long been known to be tumorigenic, it has only been in the last 10 years that a series of screening studies have shown the involvement of TYK2 as an oncogene driving cancer development and metastases [4]. Early proteomic analyses first reported the role of TYK2 as a biomarker in breast, cervical, colorectal and prostate cancers [5][6][7][8]. A dissociable antibody microarray (DAMA) staining screen of hundreds of proteins, a technique that combines immunostaining and protein microarrays, found that TYK2 protein levels were elevated in breast cancer compared to normal breast cell-lines [5]. Likewise, proteomics using two-dimensional (2D) gel electrophoresis followed by mass spectrometry showed increased TYK2 protein expression in squamous cervical cancer tissue [6]. Similarly, in colorectal cancer cells, high resolution mass spectrophotometry identified TYK2 as a phosphorylation target of hepatocyte growth factor (HGF), which stimulates proliferation in these cells [7]. Proteomic phosphotyrosine peptide enrichment and quantitative mass spectrometry identified several activated kinases, including TYK2 (Y 292) and its downstream target signal transducer and activator of transcription 3 (STAT3) (Y 705), in metastatic castration-resistant prostate cancer [8]. In addition, RNA sequencing (RNA-seq) of the transcriptome revealed that TYK2 and JAK3 mRNA levels were significantly increased in stomach adenocarcinoma, and both proteins were found to be prognostic biomarkers [9].

Genomic screens have also implicated *TYK2* as a pro-survival gene in soft-tissue sarcomas (Table 1). NGS identified activating *TYK2* mutations in malignant peripheral nerve sheath tumors (MPNST), an aggressive subtype of sarcomas associated with the Neurofibromatosis type 1 (NF1) cancer predisposition syndrome [10]. Subsequent genetic knockdown of *TYK2* in MPNST cell lines resulted in decreased tumor growth and increased cell death [11]. Additionally, genetic knockdown of *Tyk2* in murine MPNST cells resulted in decreased tumor burden in subcutaneous tumors and metastatic tumor models [11]. In line with these studies, genomic NGS profiling of over 100 patients with multiple types of advanced recurrent, metastatic or refractory sarcomas found that they harbored mutations in *TYK2*, *JAK1*, *JAK2*, and *JAK3* [12].

Similar to what is seen with other genes, the role of TYK2 in malignancy is complex and likely is cell type and context dependent. In some settings, TYK2 appears to play a role in suppressing tumor growth, and a few studies have reported lower TYK2 expression or loss-of-function (LOF) mutations associated with cancer development or progression [13][14][15][16]. In a proteomics screen for tyrosine kinase variants, multiple brain and hematopoietic cancer cell lines harbored an inactivating TYK2 splice variant, E971fsX67 [13]. Mice with knockout of Tyk2 were more susceptible to xenograft tumor growth and metastasis of breast cancer 4T1 cells, and Tyk -/- mice also developed leukemia and lymphoma at an increased rate, both likely due to defective tumor immunosurveillance [15][16]. Tumor immunosurveillance is the process of the host immune system identifying and destroying malignant or pre-cancerous cells [17]. Amplicon-based NGS revealed TYK2 variants with catalytic LOF in 25% of B-cell ALL (B-ALL) patients, as well as lower TYK2 gene expression overall in B-ALL [14]. These LOF TYK2 variants failed to phosphorylate STAT3 in cells in vitro , and further support the immunosurveillance role of TYK2 in cancer [14]. However, the intracellular mechanisms by which TYK2 deficiency within cancer cells may promote tumorigenesis in a cell autonomous manner under certain circumstances remains unclear.

A computational analysis found that the TYK2 rs34536443 variant (P1104A) conferred increased cancer risk, and this mutation was subsequently detected in several cancers, including MPNST, breast cancer, colon cancer, stomach cancer and AML [18][10][19]. Located within the activation loop of the highly conserved kinase domain, the P1104A mutation is predicted to cause activation of the catalytic domain [10][19]. Functional studies found that immune cells with the TYK2 P1104A variant exhibited impaired auto-phosphorylation in response to ATP or IFN-α [20]. Nevertheless, TYK2 P1104A transduced signaling of IFN-α/β, IL-6 and IL-10 to phosphorylate downstream STATs, suggesting that pairing with a catalytically competent JAK is sufficient for cytokine signaling [20]. In addition, the TYK2 P1104A variant corresponded to TYK2 overexpression in MPNST tumors [11]. Thus, the TYK2 P1104A variant may drive carcinogenesis through relative changes in the different TYK2-mediated cytokine signaling pathways and downstream STAT-induced gene transcription.

2. TYK2 Signaling: Intermediary of Cytokine Signaling and STATs

The JAK family of non-receptor tyrosine kinases is composed of TYK2 and JAK1-3 [21]. TYK2 and JAK1-3 associate with the type I and type II cytokine receptor superfamily, heterodimeric or multimeric receptors without intrinsic kinase activity [22]. TYK2 mediates signal transduction for many cytokines, including interferons (IFN) and

interleukins (IL), through association with five receptor chains: IFN-α/β receptor 1 (IFNAR1), IL-12 receptor-β1 (IL-12Rβ1), IL-10 receptor β (IL-10Rβ), IL-13 receptor α (IL-13Rα) and gp130 [23]. When an extracellular ligand binds to and activates its receptor, conformational changes in the transmembrane receptors bring JAKs close together, where they are activated by auto- or trans-phosphorylation and subsequently phosphorylate intracellular tyrosine residues on the receptors [24]. TYK2 heterodimerizes with JAK1 or JAK2, but not JAK3, depending on the cytokine and receptor complex [25]. Activated JAKs then recruit and phosphorylate signal transducers and activators of transcription (STAT), which has seven family members (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6) [26]. TYK2 specifically transduces activation of STAT1, STAT3 and STAT5A/B. Phosphorylated STATs then homo- or hetero-dimerize, allowing translocation to the nucleus where STAT dimers bind on the promoters of target genes to induce transcription.

In vertebrates, JAK1-3 and TYK2 are highly conserved proteins with seven homology domains (JH1-JH7). These form four structural domains: (1) the four-point-one, ezrin, radixin, moesin (FERM) homology domain (part of JH4 and JH5-JH7), (2) src-homology 2 (SH2) domain (JH3 and part of JH4), (3) pseudokinase (kinase-like) domain (JH2), and (4) kinase domain (JH1) [22][27]. The N-terminal FERM domain facilitates interaction of TYK2/JAK1-3 with the intracellular tails of receptors, while the adjacent SH2 domain is responsible for binding to receptors [28][29]. Various mutations to the catalytically inactive pseudokinase domain can result in either increased or decreased kinase activity [30]. Thus, the JH2 pseudokinase domain functions as a negative regulator of kinase activity in the absence of receptor activation, and conversely, to communicate the signal from the ligand-activated receptor to the JH1 kinase domain [31]. The catalytically active kinase domain on the C-terminal end of TYK2 contains two adjacent tyrosine residues (Y1054 and Y1055) in its activation loop that are auto-/trans-phosphorylated by ligand-binding induced conformational changes in its receptors [22][32]. TYK2 also contains several other phosphorylation sites located throughout all four domains, including tyrosine residues (Y292, Y433, Y827, Y884, and Y1145) and serine residues (S491, S499) [28][33]. Further post-translational modifications of TYK2 besides phosphorylation have not been widely studied.

The earliest studies on TYK2 signaling found it to be an intermediate in the IFNα and IFNβ pathways (Figure 2) [34]. Subsequently, TYK2 was shown to primarily be involved in the signaling of type I and type 2 IFNs [35][36]. The type I IFN family is a large group of mainly IFNα subtypes and IFNβ, as well as IFNε, IFNκ, IFNω, and IFNζ, and these cytokines are involved in anti-viral immunity and anti-cancer immunity [37][38][39][40]. The ubiquitously expressed type I IFNs bind to the IFNAR2 chain that is associated with JAK1, which then recruits the IFNAR1 chain associated with TYK2 [41]. Activated TYK2/JAK1 then typically phosphorylates a STAT1 and STAT2 dimer, and to a lesser extent STAT1 homodimers [42]. Other STATs (STAT3, STAT4, and STAT6) can also transduce type I IFN signaling in some conditions and cell-types [39]. The STAT1/STAT2 dimer complexes with the cofactor interferon regulatory factor 9 (IRF9) to bind to IFN-stimulated response elements (ISRE), while the STAT1/STAT1 homodimer binds to interferon-γ activated sequences (GAS) in promoter regions of IFN-targeted genes [40][41]. Type I IFNs stimulate transcription of over 1000 genes implicated in regulation of inflammatory and immune functions, including in cancer [40].

IL-10 family members are essential anti-inflammatory cytokines with immunosuppressive actions that promote epithelial homeostasis and barrier function in response to infection or inflammatory conditions, while IL-10 deficiency is involved in autoimmune disorders [43]. However, IL-10 has opposing immune stimulatory actions depending on cell type and circumstance [44]. The IL-10 family of cytokines include IL-10, IL-22, IL-26 and IFNλs, which bind to their specific JAK1-associated receptor chains and to the TYK2-associated IL-10R2 chain (IL-10Rβ), leading to phosphorylation of STAT3 homodimers, with a minor component through STAT1 and STAT5 [22][45].

Other cytokines that signal through TYK2 include those that bind to the gp130 receptor subunit, e.g., IL-6, IL-11, IL-27, oncostatin M (OSM), cardiotrophin-1 (CT-1), and leukemia inhibitory factor (LIF). However, TYK2 is redundant with other JAKs in these pathways. A full list of cytokines and receptors reported to signal through TYK2 have been reviewed previously [17][22].

3. Pro-survival Actions of TYK2 in Cancer

TYK2 has emerged as a pro-survival factor in many types of cancer through stimulation of proliferation and protection from cell death [46]. In various cancers, TYK2 overexpression or GOF mutations lead to STAT1 or STAT3 activation and upregulation of anti-apoptotic proteins, including B-cell CLL/lymphoma-2 (BCL-2) and myeloid cell leukaemia-1 (MCL-1) [11][47]. Recent reports investigated the pro-survival mechanisms of TYK2 signaling using pharmacologic or genetic inhibition of TYK2 or STAT3 in various cancer cell lines and mouse tumor models [11][47][48][49]. In human ALCL cells, inhibition of TYK2 by small molecule inhibitors or genetic depletion decreased proliferation and induced apoptosis with concomitant reductions in STAT1/STAT3 activation, MCL-1, IL-22 and IL-10 [47]. Correspondingly, loss of *Tyk2* in an NPM-ALK lymphoma mouse model delayed tumor growth and prolonged overall survival [47]. Likewise, TYK2 is highly expressed in MPNST compared to lower expression in benign precursor plexiform neurofibroma tumors [11]. TYK2 deficiency reduces MPNST tumor growth through decreased proliferation and increased apoptosis mediated via lower phosphorylated STAT3 (p-STAT3) and BCL-2 with a concomitant increase in caspase 3 cleavage [11]. In esophageal cancer, *TYK2* is also overexpressed, and associated with later stages of disease and shorter patient survival [48]. The flavonoid cirsiliol blocks TYK2-STAT3 induced cell proliferation and patient-derived xenograft (PDX) esophageal cancer tumor growth, likely through decreased C-MYC, BCL-2 and MCL-1 protein levels [48]. Fibroblast growth factor-2 (FGF-2) activates TYK2 to stimulate proliferation and protect osteosarcoma cells from chemotherapeutic drugs *in vitro* [49]. In B-cell lymphoma cells, binding of the CD86 ligand to cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) results in recruitment and phosphorylation of TYK2, which activates STAT3 to drive transcription of genes promoting tumor growth and survival [50]. Similarly, IL-10 activation of TYK2 or GOF mutations in *TYK2* promote survival of T-ALL cells through phosphorylation of STAT1, but not STAT3, and upregulation of BCL-2 [51]. In head and neck cancer cells, inhibition of STAT3 leads to cell cycle arrest and apoptosis through pro-apoptotic PARP cleavage and decreases in anti-apoptotic BCL-xL and survivin [52].

4. Conclusions and Perspectives

Personalized, or precision, medicine has increasingly become a valuable tool in clinical diagnostics to evaluate potential therapeutic options for individual cancer patients [53]. Based on genetic mutations, gene expression or protein level changes in patient tumors for known oncogenes or tumor suppressors, personalized medicine can aid in prognostication, as well as predict responses to anti-cancer agents [54]. Given the identification of TYK2 as a potential biomarker for numerous types of cancer, evaluation of patient tumors for TYK2 mutations or expression levels may help determine patient prognosis. In addition, with the development of multiple pharmacologic inhibitors of TYK2 and JAKs, those tumors that are TYK2-positive may be viable candidates for TYKinib/JAKinib targeted therapies. Future pre-clinical studies should be geared at evaluating therapeutic interventions with TYK2 inhibitors as single agents, or in combination therapy to pave the way for biomarker-driven clinical trials.

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