**REVIEW**

**EGFR signaling pathway occupies an important position in cancer-related downstream signaling pathways of Pyk2**

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**Abstract**

Proline-rich tyrosine kinase 2 (Pyk2) is a member of focal adhesion kinase (FAK) non-receptor tyrosine kinase family and has been found to promote cancer cell survival, proliferation, migration, invasion, and metastasis. Pyk2 takes part in different carcinogenic signaling pathways to promote cancer progression, including epidermal growth factor receptor (EGFR) signaling pathway. EGFR signaling pathway is a traditional carcinogenic signaling pathway, which plays a critical role in tumorigenesis and tumor progression. FAK inhibitors have been reported to fail to get the ideal anti-cancer outcomes because of activation of EGFR signaling pathway. Better understanding of Pyk2 downstream targets and interconnectivity between Pyk2 and carcinogenic EGFR signaling pathway will help finding more effective targets for clinical anti-cancer combination therapies. Thus, the interconnectivity between Pyk2 and EGFR signaling pathway, which regulates tumor development and metastasis, needs to be elucidated. In this review, we summarized the downstream targets of Pyk2 in cancers, focused on the connection between Pyk2 and EGFR signaling pathway in different cancer types, and provided a new overview of the roles of Pyk2 in EGFR signaling pathway and cancer development.

**Keywords:** cancer; cell migration; intercellular communication; signal peptide/recognition particle

**Introduction**

Focal adhesion kinase (FAK), a kind of multi-domain non-receptor protein tyrosine kinase (PTK), controls cell survival, adhesion, and migration by transferring signals from integrins or growth-factor receptors to downstream kinases (Arold, 2011; Kleinschmidt and Schlaepfer, 2017). FAK is widely detectable in adult tissues and aberrant expression of FAK could be regarded as a promising factor to predict aggressive behavior and poor prognosis in patients with tumors (Ji et al., 2013; Li et al., 2015; Omura et al., 2016). FAK is overexpressed in many kinds of tumors and contributes to tumorigenicity and tumor development (Sood et al., 2004; Carelli et al., 2006; Yom et al., 2011; Tai et al., 2016). Proline-rich tyrosine kinase 2 (Pyk2) is a close parologue to FAK and possesses 46% sequence identity and 65% similarity related to FAK in structure (Du et al., 2001; Schaller, 2010). The effects on cellular events are not always the same between FAK and Pyk2. Pyk2 is only abundant in specific cell types such as macrophages, osteoclasts, and lymphocytes (Menegon et al., 1999; Allen et al., 2009; Beinke et al., 2010; Gao et al., 2015) and could be activated by multiple growth factors, neuropeptides, cytokines, hormones, and chemokines (Ivankovic-Dikic et al., 2000;...
Di Cioccio et al., 2004; Roelle et al., 2008; Cattaneo et al., 2009; Lane et al., 2016). In numerous researches in vivo and in vitro, overexpression of Pyk2 is found in different malignant tumors (Sun et al., 2007; Zhang et al., 2008; Hsiao et al., 2016) and it is implicated in multiple signal transduction cascades, which regulate cancer cell proliferation, apoptosis, and invasion (Okigaki et al., 2003; Sun et al., 2008; Wiese et al., 2015). Pyk2 promotes tumor progression and owes to a number of cancer-related functional domains in structure: N-terminal catalytic kinase domain, and C-terminal focal adhesion targeting (FAT) domain (Lipinski and Loftus, 2010). The FERM domain of Pyk2 could mediate both protein-protein and protein-membrane targeting interactions and plays a critical role in Pyk2-induced migration of tumor cells (Hirao et al., 1996; Hamada et al., 2000, 2003; Pearson et al., 2000; Loftus et al., 2009). Pyk2 contains central catalytic kinase domain that may be of potential use in the design of selective kinase inhibitors for cancer treatments (Han et al., 2009). The C-terminal domain of Pyk2 includes a FAT domain, which is implicated in the activation of carcinogenic mitogen-activated protein kinase (MAPK) signaling pathway (Blaukat et al., 1999; Kuang et al., 2013). In recent years, Pyk2 is found to be involved in epidermal growth factor receptor (EGFR) signaling pathway in cancer progression.

EGFR is a member of the EGF receptor tyrosine kinase family, which includes EGFR (ErbB1/HER1), HER2/neu (ErbB2), HER3 (ErbB3), and HER4 (ErbB4). EGFR is a transmembrane growth factor receptor and its downstream signaling pathways frequently contribute to tumor progression and metastasis (Ciardiello and Tortora, 2008; Kumar et al., 2016; Koukas et al., 2017; Singla et al., 2018). EGFR signaling mainly contains the RAS/MEK/ERK (extracellular regulated protein kinase), PI3K (phosphoinositide 3-kinase)/AKT and PLCγ/PKC (protein kinase C) cascades, moreover, the Src tyrosine kinase and Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway are also induced by EGFR activation (Brand et al., 2011). After ligand binding to EGFR, receptor auto-transphosphorylation triggers a series of signaling events, which result in the induction of cell proliferation, blockade of apoptosis, activation of invasion, and stimulation of neovascularization (Shepard et al., 2008). With ligand combining with EGFR, STAT3 is phosphorylated and promotes tumor cell invasion and poor prognosis of colorectal adenocarcinoma (Kusaba et al., 2006). Overexpression of EGFR antagonizes neoplastic con-rol of VEGF reduction and impairs anti-angiogenesis of neoalbaco-nol in cancer (Yu et al., 2017). EGFR-related downstream proteins, such as phosphatase and tensin homolog deleted on chromosome ten (PTEN), PI3K, and Akt, could have a significant impact on cell proliferation or apoptosis (Harle et al., 2015). EGFR can activate the RAS-MEK-ERK pathway and lead to cell proliferation and survival, which makes it a suitable target for cancer inhibition (Misale et al., 2014).

Pyk2 and EGFR signaling pathway are both proved to decide the fate of cancer. However, the exact role that Pyk2 plays in the EGFR signaling pathway still remains unclear. Traditionally, Pyk2 has been identified as a potential therapeutic target for human cancer treatment. Targeting Pyk2 could regulate its downstream signaling pathways and control the growth and metastasis of cancer cells. However, monotherapy of FAK has been found to fail to get the ideal anti-cancer outcomes because of the effects of compensatory signaling. Thus, as a member of the FAK family, Pyk2-related network of tumorigenesis and tumor progression needs to be elucidated and Pyk2-related carcinogenic signaling pathways should be paid more attention to. EGFR signaling has an important place and role in Pyk2 downstream signaling pathways, which will affect the growth and metastasis of cancer cells. In this review, we summarize the recent findings of endogenous mechanisms used by cells with respect to Pyk2-related regulation of cancer cell growth, proliferation, apoptosis, migration, invasion, metastasis, tumorigenesis, and tumor angiogenesis. We explore the interconnectivity between Pyk2 and EGFR signaling pathway in different cancer types, as well as aid in the identification of potential targets for cancer therapy. A systematic understanding of these mechanisms could contribute to the design of novel and more effective therapeutic interventions, which will block the aggressive growth of cancer cells.

**Anti-cancer effectiveness of FAK inhibitors could be arrested by compensatory EGFR-related signaling**

FAK is overexpressed in 80% of all solid tumors and FAK inhibitors have been considered as promising anti-cancer drugs (Weiner et al., 1993; Owens et al., 1995; Lark et al., 2003). However, anti-cancer clinical trials of FAK inhibitors show the limited single-agent efficacy (Gan et al., 2012; Infante et al., 2012) and compensatory signaling has been found to be responsible for this phenomenon. In the study performed by Marlowe et al., the results confirmed that the expression of receptor tyrosine kinases (RTKs) predicted patient response to FAK-kinase inhibitors. FAK-kinase inhibition induced RTK activation in RTK high cancer cells while the selective pressure of FAK-kinase inhibition was able to drive RTK low triple-negative breast cancer cells to express human epidermal growth factor receptor 2 (HER2). The inhibition of FAK induced compensatory increases of phosphorylated EGFR (pEGFR), pHER2, pAKT, and phosphorylated extracellular signal-regulated protein kinase (pERK). Moreover, FAK inhibition
Table 1  Downstream target sites of Pyk2 in human cancers. Pyk2 increases the activation of some downstream targets to reinforce human cancer progression and invasion.

<table>
<thead>
<tr>
<th>Target sites</th>
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</tr>
</thead>
<tbody>
<tr>
<td>CREB</td>
<td>Neuroblastoma</td>
<td>SH-SYSY cell</td>
<td>Promoting the viability of tumor cells</td>
<td>Hirschler-Laszkiewicz et al. (2018)</td>
</tr>
<tr>
<td>ALDH1a1</td>
<td>Lung cancer</td>
<td>A549 cell, H460 cell</td>
<td>Enhancing cancer cell colony formation</td>
<td>Kuang et al. (2013)</td>
</tr>
<tr>
<td>ABCG2</td>
<td>Lung cancer</td>
<td>A549 cell, H460 cell</td>
<td>Augmenting cancer cell colony formation</td>
<td>Kuang et al. (2013)</td>
</tr>
<tr>
<td>Bmi-1</td>
<td>Lung cancer</td>
<td>A549 cell, H460 cell</td>
<td>Promoting cancer cell colony formation</td>
<td>Kuang et al. (2013)</td>
</tr>
<tr>
<td>HER3</td>
<td>Breast cancer</td>
<td>MDA-MB-468 cell, HCC38 cell, HCC1143 cell, BT-20 cell, HCC1937 cell</td>
<td>Augmenting cancer cell growth, survival, and proliferation</td>
<td>Verma et al. (2017)</td>
</tr>
<tr>
<td>Paxillin</td>
<td>Multiple myeloma</td>
<td>MM.1.S cell</td>
<td>Promoting cell-cycle progression, adhesion ability, and proliferation of tumor cells</td>
<td>Zhang et al. (2014)</td>
</tr>
<tr>
<td>Rac1</td>
<td>Gloma</td>
<td>T98G cell</td>
<td>Promoting tumor cell migration</td>
<td>Paulino et al. (2010)</td>
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<tr>
<td>N-Cadherin</td>
<td>Liver cancer</td>
<td>MHCC97L cell</td>
<td>Facilitating EMT, motility, and migration of cancer cells</td>
<td>Sun et al. (2011)</td>
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<tr>
<td>Hic-5</td>
<td>Liver cancer</td>
<td>Hep38 cell, MHCC97L cell</td>
<td>Promoting EMT, motility, and migration of cancer cells</td>
<td>Sun et al. (2011)</td>
</tr>
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<td>STAT5b</td>
<td>Liver cancer</td>
<td>MHCC97L cell</td>
<td>Promoting EMT, motility, and migration of cancer cells</td>
<td>Sun et al. (2011)</td>
</tr>
<tr>
<td>p130 Cas</td>
<td>Breast cancer</td>
<td>MDA-MB-468 cell, MDA-MB-231 cell, MDA-MB-43Scell, MDA-MB-453 cell, and MCF-7 cell</td>
<td>Enhancing migration and invasion of cancer cells</td>
<td>Vultur et al. (2008)</td>
</tr>
<tr>
<td>AMAP1</td>
<td>Breast cancer</td>
<td>MCF-7 cell</td>
<td>Promoting cancer cell adhesion, migration, and invasion</td>
<td>Li et al. (2018)</td>
</tr>
<tr>
<td>c-Met</td>
<td>Breast cancer</td>
<td>MDA-MB-468 cell, BT-549 cell</td>
<td>Promoting EMT, migration, invasion, and metastasis of breast cancer cells</td>
<td>Verma et al. (2015)</td>
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<tr>
<td>CD44</td>
<td>Breast cancer</td>
<td>MDA-MB-468 cell</td>
<td>Promoting EMT, migration, invasion, and metastasis of cancer cells</td>
<td>Verma et al. (2015)</td>
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<td>Zeb-1,2</td>
<td>Breast cancer</td>
<td>MDA-MB-468 cell, BT-549 cell</td>
<td>Promoting EMT, migration, invasion, and metastasis of cancer cells</td>
<td>Verma et al. (2015)</td>
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<td>Snail-1,2</td>
<td>Breast cancer</td>
<td>MDA-MB-468 cell, BT-549 cell</td>
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<td>Verma et al. (2015)</td>
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<tr>
<td>MMP</td>
<td>Breast cancer</td>
<td>BT-549 cell, MDA-MB-231 cell, 2D cell</td>
<td>Promoting EMT, motility, migration, invasion, and metastasis of cancer cells</td>
<td>Verma et al. (2015); Genna et al. (2018)</td>
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<tr>
<td>Arg</td>
<td>Breast cancer</td>
<td>MDA-MB-231 cell, 2D cell</td>
<td>Promoting cancer cell motility, migration, and invasion</td>
<td>Genna et al. (2018)</td>
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<tr>
<td>Cortactin</td>
<td>Breast cancer</td>
<td>MDA-MB-231 cell, 2D cell</td>
<td>Enhancing cancer cell motility, migration, and invasion</td>
<td>Genna et al. (2018)</td>
</tr>
<tr>
<td>EGFR</td>
<td>Breast cancer</td>
<td>MDA-MB-468 cell</td>
<td>Promoting EMT, migration, invasion, and metastasis of cancer cells</td>
<td>Verma et al. (2015)</td>
</tr>
<tr>
<td>Fibronectin</td>
<td>Liver cancer; breast cancer</td>
<td>MHCC97L cell; MDA-MB-468 cell</td>
<td>Enhancing EMT, motility and migration of liver cancer cells; promoting EMT, migration,</td>
<td>Sun et al. (2011); Verma et al. (2015)</td>
</tr>
<tr>
<td>Target sites</td>
<td>Cancer types</td>
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<tr>
<td>Twist</td>
<td>Liver cancer; breast cancer</td>
<td>MHCC97L cell; MDA-MB-468 cell</td>
<td>Promoting EMT, motility, and migration of liver cancer cells; enhancing EMT, migration, invasion, and metastasis of breast cancer cells</td>
<td>Sun et al., 2011; Verma et al. (2015)</td>
</tr>
<tr>
<td>Vimentin</td>
<td>SCCHN; breast cancer</td>
<td>PCI-48 cell, PCI-37B cell; BT-549 cell, MDA-MB-468 cell</td>
<td>Enhancing EMT, migration, invasion, and metastasis of SCCHN cells; promoting breast cancer cell EMT, migration, invasion, and metastasis</td>
<td>Verma et al. (2015); Yue et al. (2015)</td>
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<tr>
<td>FAK</td>
<td>Prostate cancer</td>
<td>PC3 cell</td>
<td>Augmenting cancer cell motility, invasion, and metastasis</td>
<td>Iizumi et al. (2008)</td>
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<tr>
<td>MAPK</td>
<td>Prostate cancer</td>
<td>PC3 cell</td>
<td>Enhancing cancer cell motility, invasion, and metastasis</td>
<td>Iizumi et al. (2008)</td>
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<tr>
<td>p90RSK</td>
<td>Bladder cancer</td>
<td>5637 cell</td>
<td>Promoting motility, migration, and invasion of bladder cancer cells</td>
<td>Genua et al. (2012)</td>
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<tr>
<td>MEK1/2</td>
<td>Liver cancer</td>
<td>PLC cell</td>
<td>Promoting proliferation and invasiveness of cancer cells</td>
<td>Sun et al. (2008)</td>
</tr>
<tr>
<td>β-Catenin</td>
<td>Breast cancer; multiple myeloma</td>
<td>MDA-MB-468 cell; MM1S cell, RPMI8226 cell</td>
<td>Promoting EMT, migration, invasion, and metastasis of breast cancer cells; enhancing cell-cycle progression, adhesion ability, and proliferation of multiple myeloma cells; inhibiting multiple myeloma cell apoptosis</td>
<td>Zhang et al. (2014); Verma et al. (2015); Kamihara et al. (2016)</td>
</tr>
<tr>
<td>Src</td>
<td>Lung cancer; multiple myeloma; breast cancer; liver cancer</td>
<td>H69 cell, H510 cell; MM.1 S cell; MDA-MB-231 cell; PLC cell</td>
<td>Enhancing lung cancer cell proliferation; promoting cell-cycle progression, adhesion ability, and proliferation of multiple myeloma cells; promoting breast cancer cell motility, migration, and invasion; promoting proliferation and invasiveness of liver cancer cells</td>
<td>Roelle et al. (2008); Sun et al. (2008); Zhang et al. (2014); Lu et al. (2017); Genna et al. (2018)</td>
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<tr>
<td>AKT</td>
<td>Bladder cancer; prostate cancer; multiple myeloma; liver cancer</td>
<td>5637 cell; PC3 cell; MM.1S cell; PLC cell, Hep3B cell, MHCC97L cell, HL-7702 cell, SMMC-7721 cell, HepG2 cell</td>
<td>Promoting bladder cancer cell motility, migration, and invasion; augmenting prostate cancer cell motility, invasion, and metastasis; promoting cell-cycle progression, adhesion ability, and proliferation of multiple myeloma cells; promoting liver cancer cell survival, growth, invasion, promoting liver cancer angiogenesis, arresting liver cancer cell apoptosis</td>
<td>Iizumi et al. (2008); Geng et al. (2011); Genua et al. (2012); Cao et al. (2013); Zhang et al. (2014)</td>
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<td>S6K</td>
<td>Bladder cancer, prostate cancer, breast cancer</td>
<td>5637 cell, T24 cell; LNCaP cell, 22Rv1 cell; MDA-MB-468 cell, HCC38 cell, HCC1143 cell, BT-20 cell, HCC1937 cell</td>
<td>Promoting motility, migration, and invasion of bladder cancer cells; enhancing prostate cancer cell growth and proliferation; promoting breast cancer cell growth, survival, and proliferation, enhancing breast cancer growth</td>
<td>Genua et al. (2012); Hsiao et al. (2016); Verma et al. (2017)</td>
</tr>
<tr>
<td>STAT3</td>
<td>SCCHN; multiple myeloma;</td>
<td>PCI-48 cell, PCI-37B cell; RPMI8226 cell,</td>
<td>Promoting migration and invasion of SCCHN cells;</td>
<td>Liu et al. (2014); Verma et al. (2015); Meads (Continues)</td>
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</table>
The biological roles of downstream targets of Pyk2 (Continued)

**Table 1**

<table>
<thead>
<tr>
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<th>Cancer types</th>
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</tr>
</thead>
<tbody>
<tr>
<td>ERK</td>
<td>Bladder cancer</td>
<td>T4; T2; MDA MB 231, MDA MB 468, Caki cell</td>
<td>Zrihan-Licht et al. (2000); Picascia et al. (2002); van der Horst et al. (2005); Yuan et al. (2007); Behmoaram et al. (2008); Sun et al. (2008); Genua et al. (2012); Verma et al. (2015)</td>
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<td>ERK</td>
<td>Breast cancer</td>
<td>NCIH929 cell, OPM2 cell; MDA MB 468 cell, HCC38 cell, BT 20 cell, HCC1937 cell</td>
<td>Golden et al. (2016); Verma et al. (2017)</td>
</tr>
<tr>
<td>ERK</td>
<td>Glioma</td>
<td>SF767 cell</td>
<td>Golden et al. (2015)</td>
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<tr>
<td>GSK3β</td>
<td>Intestinal cancer</td>
<td>SW480 cell</td>
<td>Gao et al. (2015)</td>
</tr>
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</table>

Pyk2 promotes different cancer progression by modulating distinct downstream target sites

In multiple kinds of cancer types, Pyk2 mediates its downstream target genes and controls a variety of signaling pathways that are involved in human cancer cell growth, proliferation, apoptosis, migration, invasion, and metastasis, as well as tumorogenesis and tumor angiogenesis (Tables 1 and 2). EGFR signaling occupies an important position among these signaling pathways.

Pyk2 regulates downstream targets and promotes cancer cell growth and proliferation

In hepatocellular carcinoma (HCC), Pyk2 overexpression increases MEK1/2 (mitogen-activated protein kinase 1/2) phosphorylation, promotes the activation of c-Src and ERK1/2, induces cancer cell proliferation (Sun et al., 2008). ERK is an important downstream target of Pyk2, which promotes cancer progression. Pyk2 contributes to ERK1/2 activation and enhances ErbB-induced cell proliferation and breast cancer growth (Behmoaram et al., 2008). Pyk2 facilitates prostatic cancer cell proliferation by upregulating ERK1/2 phosphorylation (Picascia et al., 2002). Pyk2 depletion could inhibit the activation of S6K (S6-kinase), STAT3, and HER3 while FAK depletion influences Akt activation in triple-negative breast cancer (TNBC). Pyk2-NDRG1 (N-myc downstream regulated 1 gene)-NEDD4 (neural precursor cell-expressed developmentally down-regulated gene 4) axis is proved to be a key regulator of HER3 degradation. Precluding Pyk2 could lead to the inhibition of TNBC cell growth, survival, and proliferation (Verma et al., 2017). Pyk2 activates ribosomal S6K1, regulates androgen receptor (AR) function, and enhances prostate cancer cell growth and survival (Hsiao et al., 2016). Cyclic-AMP response element-binding protein (CREB) is a nuclear transcription factor and regulates transcriptional responses to all kinds of growth factors and stress signals in cells (Shaywitz and Greenberg, 1999; Wang et al., 2016).
Pyk2 downregulation is proved to decrease CREB phosphorylation and expression and inhibits the viability of neuroblastoma (Hirschler-Laszkiewicz et al., 2018). Src is also a downstream target of Pyk2 in cancer development. Pyk2 promotes neuropeptide-mediated Src kinase phosphorylation and neuropeptide-stimulated survival and proliferation of small-cell lung cancer (SCLC) cells while FAK activity isn’t affected by neuropeptides in SCLC cells (Roelle et al., 2008). Pyk2 could induce the expression of cancer stem cell marker ALDH1a1, ABCG2, and Bmi-1 and is proved to be associated with the colony formation of lung cancer cells (Kuang et al., 2013). In multiple myeloma (MM), Pyk2 plays a tumor-promoting role and facilitates cell adhesion ability, cell-cycle progression, and cell proliferation by activating Wnt/β-catenin signaling. Inhibition of Pyk2 will result in the decrease of β-catenin and p-Akt. Moreover, Pyk2 overexpression is found to increase the phosphorylation of Src and Paxillin in MM cells (Zhang et al., 2014). Pyk2 shows a more malignant phenotype and promotes MM cell growth and proliferation by enhancing JAK1/STAT3 signaling (Meads et al., 2016).

Pyk2 is important for cancer cell growth and proliferation.

The roles of Pyk2-modulated downstream targets in inhibiting cancer cell apoptosis

Overexpression of Pyk2 increases downstream AKT phosphorylation, arrests HCC cell necrosis and apoptosis, and contributes to cancer resistance to cisplatin (Geng et al., 2011). Iron chelator deferasirox (DFX) could inhibit Pyk2 expression, subsequently arrest β-catenin expression, and induce MM cell apoptosis. However, FAK is not correlated with DFX-induced MM cell apoptosis (Kamihara et al., 2016).

Pyk2 enhances cancer cell migration, invasion, and metastasis by regulating different downstream targets

In the study of cancer cell migration, invasion, and metastasis, epithelial-mesenchymal transition (EMT) has become an increasingly serious concern. EMT is the process that epithelial cells transit to invasive mesenchymal cells with epithelial genes downregulation and mesenchymal genes upregulation (Zeisberg and Neilson, 2009). Pyk2 promotes EMT by downregulating epithelial gene cytokeratin and E-cadherin and upregulating mesenchymal gene Twist, N-cadherin, fibronectin, hydrogen peroxide inducible clone-5 (Hic-5) and STAT5b, thus contributing to HCC cell motility and migration (Sun et al., 2011). In squamous cell carcinoma of the head and neck (SCCHN), E-cadherin and vimentin are proved to be downstream target molecules of chemokine receptor 7 (CCR7)-Pyk2, which may participate in the modulation of EMT, migration, and invasion of cancer cells (Yue et al., 2015). Inhibition of Pyk2 is reported to block the phosphorylation

Table 2: Downstream target sites of Pyk2 in human cancers. Pyk2 promotes the progression of different cancers by inhibiting some downstream targets.

<table>
<thead>
<tr>
<th>Target sites</th>
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<tbody>
<tr>
<td>Cytokeratin</td>
<td>Liver cancer; breast cancer</td>
<td>Hep3b cell, MHiC/LC7 cell, PCI-4B cell, PCI-37B7 cell, BT-549 cell, MDA-MB-231 cell, HCC38 cell, HCC1143 cell, BT-20 cell, HCC1937 cell</td>
<td>Inhibiting EMT, motility, and migration of cancer cells</td>
<td>Sun et al. (2011); Verma et al. (2015); Yue et al. (2015)</td>
</tr>
<tr>
<td>E-cadherin</td>
<td>SCCHN; breast cancer; liver cancer</td>
<td>BT-549 cell, MDA-MB-231 cell, HCC38 cell, HCC1143 cell, PCI-4B cell, PCI-37B7 cell, BT-549 cell, MDA-MB-231 cell, HCC38 cell, HCC1143 cell</td>
<td>Inhibiting cancer cell growth, survival, and proliferation, attenuating EMT</td>
<td>Sun et al. (2011)</td>
</tr>
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<td>ZO-1</td>
<td>Breast cancer</td>
<td>BT-549 cell, HCC38 cell, HCC1143 cell, BT-20 cell, HCC1937 cell</td>
<td>Inhibiting cancer cell growth, survival, and proliferation, attenuating EMT</td>
<td>Verma et al. (2015)</td>
</tr>
<tr>
<td>NDRG1</td>
<td>Breast cancer</td>
<td>MDA-MB-231 cell, BT-549 cell, HCC38 cell, HCC1143 cell, BT-20 cell, HCC1937 cell</td>
<td>Inhibiting cancer cell growth, survival, and proliferation, attenuating EMT</td>
<td>Verma et al. (2017)</td>
</tr>
</tbody>
</table>

EMT, epithelial-mesenchymal transition; NDRG1, N-myc downstream regulated 1 gene; SCCHN, squamous cell carcinoma of the head and neck.
of STAT3 induced by chemokine (C-C motif) ligand 19 (CCL19), thus arresting SCCHN cell EMT, migration, invasion, and metastasis (Liu et al., 2014). In breast cancer, Pyk2 is found to promote cancer cell migration, invasion, and metastasis by regulating distinct downstream targets. EGF activates Pyk2, regulates functions of downstream Twist-1,2, CD44, Snail-1,2, matrix metalloproteinase-10 (MMP-10), β-catenin, fibronectin, vimentin, E-cadherin, ZO-1, and Zeb-1,2, promotes EMT, migration, invasion, and metastasis of breast cancer cells. However, FAK cannot be activated by EGF. Under EGF stimulation, Pyk2, STAT3, and c-Met interact with each other and form positive feedback, which contributes to prolonging EMT-associated signals and cancer metastasis (Verma et al., 2015). Pyk2 has higher affinity with cortactin than FAK. Pyk2 colocalizes with cortactin to invadopodia of breast cancer cells and regulates EGF-induced cortactin phosphorylation through Src-mediated Abl-related gene (Arg) activation, leading to actin polymerization and breast cancer cell invasion. In addition, Pyk2-depleted cells show a decreased MMP secretion and extracellular matrix degradation (Genna et al., 2018). The abundance of breast cancer stem cell (BCSC) has proved to be essential for breast cancer recurrence and metastasis. Pyk2/Src/STAT3 signaling pathway is activated by the rise of glutathione S-transferase omega 1 (GSTO1)-induced cytosolic calcium and leads to BCSC enrichment (Lu et al., 2017). Pyk2 acts downstream of ErbB-2 and can be phosphorylated by heregulin (HRG). Phosphorylated Pyk2 activates ERK and plays a key role in breast cancer cell invasion (Zrihan-Licht et al., 2000). Src/FAK/Pyk2/p130 Cas (crk-associated substrate) is another effective pathway, which is reported to be associated with cell migration and invasion of breast cancer (Vultur et al., 2008). Through phosphorylating GTPase-activating protein AMAP1, Pyk2 plays a critical role in CCL18-induced cell adhesion, migration, and invasion in breast cancer (Li et al., 2018). ERK is an important downstream target, which contributes to different cancer cell migration, invasion, and metastasis. Overexpression of Pyk2 facilitates HCC cell invasiveness by upregulating the phosphorylation of c-Src, ERK1/2, and MEK1/2 (Sun et al., 2008). Through activating Pyk2, elevated ErbB-2 could increase the ERK/MAPK activity and enhance cell adhesive ability and metastasis in human prostate cancer (PCA), while FAK isn’t correlated with PCA cell adhesive ability (Yuan et al., 2007). As a member of Ras homolog gene family, RhoC promotes PCA cell invasion and metastasis via sequentially phosphorylating Pyk2, FAK, MAPK and AKT (Iizumi et al., 2008). Under the effects of Heregulin/HER3-stimulated signaling pathway, phosphorylated Pyk2 activates the MAPK pathway and facilitates glioma cell invasion (van der Horst et al., 2005). In urothelial carcinoma, FAK depletion doesn’t affect (insulin-like growth factor 1 [IGF-1]-
ediated cell invasion while Pyk2 is strongly activated by IGF-1 and promotes IGF-IR-dependent motility and invasion. Knockdown of Pyk2 is found to inhibit downstream IGF-1-dependent activation of Akt, ERK1/2, p90RSK, as well as ribosomal protein S6K (Genua et al., 2012). Depletion of Pyk2 inhibits tumor necrosis factor receptor superfamily member 19 (TNFRSF19/TROY)-mediated glioma cell migration by suppressing TROY-induced Rac1 activity. Pyk2 lies downstream of TROY and plays an important role in TROY-induced glioma cell migration (Paulino et al., 2010).

Pyk2 promotes tumorigenesis and tumor angiogenesis by regulating downstream signaling pathways

Pyk2 and FAK are overexpressed in intestinal cancer. Elevated Pyk2/FAK is found to function redundantly in the activation of Wnt/β-catenin pathway by phosphorylating GSK3β and enhances intestinal tumorigenesis (Gao et al., 2015). In HCC, Pyk2 activates PI3K/AKT pathway to increase vascular endothelial growth factor (VEGF) expression, which is associated with tumor angiogenesis (Cao et al., 2013).

Concluding remarks

Pyk2 represents a potential high-value target for therapeutic discovery efforts due to its critical position within signaling pathways, which regulate cancer progression and invasion. Systematical understanding of downstream targets of Pyk2 is necessary to find more effective ways to control human cancer progression. Pyk2 promotes distinct cancers progression by regulating different downstream signaling pathways, and EGFR signaling pathway is found to be involved in Pyk2-regulated downstream signaling pathways in liver cancer, breast cancer, lung cancer, MM, prostate cancer, bladder cancer, SCCHN, and glioma. Pyk2 could regulate AKT, STAT3, ERK, MEK1/2, Src, HER3, MAPK, EGFR, and STAT5b in EGFR signaling in different cancer types. Moreover, EGFR signaling is reported to be responsible for the single-agent limitation of FAK inhibitors. As a member of FAK family, the relationship between Pyk2 and EGFR signaling pathway requires more attention in cancer development.

Nowadays, targeting a single receptor using monotherapy often relapses due to the utilization of autonomous parallel-redundant signaling (Fan and Guan, 2011). There are usually downstream molecules, which enable EGFR-independent activation to compensate the inhibition of intracellular signaling cascades (Normanno et al., 2009). Approaches to the therapeutic discovery of small molecules, which prevent protein-protein interactions between key signaling effectors, represent a promising area of anti-cancer therapy. Combination therapies using two or more drugs usually lead to better anti-cancer effects. For example, dual inhibition of
FAK and Src enhanced the rate of detachment and apoptosis of colon cancer cells than FAK inhibition alone or Src inhibition alone (Golubovskaya et al., 2003). The combination of FAK/Pyk2 tyrosine kinase inhibitor (PF-562,271) and sunitinib could inhibit different aspects of angiogenesis and tumor aggressiveness and it might have better anti-cancer effect than a relevant single agent in HCC (Bagi et al., 2009). Pyk2 acts as the crossroad of multiple carcinogenic signaling pathways and Pyk2 is involved in the modulation of EGFR signaling pathway, which facilitates cancer cell proliferation, survival, migration, invasion, metastasis, and chemo-resistance. In some cases, Pyk2 could regulate malignant biological behavior of tumor when FAK doesn’t work (Roelle et al., 2008; Kamihara et al., 2016). Thus, Pyk2 could be considered as an important target in cancer treatment. Significant progress in the exploration of Pyk2-regulated mechanisms during cancer formation and progression will provide a robust list of potential targets for therapeutic intervention. The combination treatments of Pyk2 inhibitors with molecules that target carcinogenic EGFR signaling pathway may help acquiring better clinical outcomes of anti-cancer treatment. Some catalytic inhibitors of the FAK, such as PF-562,271, can also inhibit Pyk2 activity (Bagi et al., 2008). Dual inhibition of FAK and Pyk2 can be more promising in cancer treatment. However, it may be easier to lead to limitation of therapy due to the possibility of activation of complementary EGFR signaling. As there is no relevant study reporting mechanisms of Pyk2 resistance yet, combination treatments of Pyk2 inhibitors and EGFR signaling inhibitors may be a better choice than the combination of FAK inhibitors and EGFR signaling inhibitors in some cases. Moreover, the combined inhibition of Pyk2 and EGFR signaling may be a rescue therapy when the combination treatments of FAK inhibitors and EGFR signaling inhibitors fail to get the ideal effects in cancer treatment.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

Compliance with Ethical Standards

This article does not contain any studies with human participants or animals performed by any of the authors.

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Relationship between Pyk2 and EGFR signaling

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