

Src-mediated regulation of E-cadherin and EMT in pancreatic cancer

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1. ABSTRACT

The Src family of non receptor tyrosine kinases are integrators of divergent signal transduction pathways which regulate numerous cellular processes, including tumorigenicity and angiogenesis. In pancreatic adenocarcinoma, c-Src (Src) is frequently activated and results in increased tumor progression, invasion and metastasis. Dysfunction of the E-cadherin-mediated cell adhesion system plays an important role in tumor progression to invasive, metastatic carcinoma. Src has been shown to play a role in E-cadherin regulation and epithelial to mesenchymal transition (EMT). Increased Src activity promotes EMT while Src inhibition suppresses this process. Recent studies have focused on Src dependent regulation of E-cadherin and other tumor progression-related events such as EMT with the development of metastasis. Src has also been shown to be involved in chemoresistance of PDAC cells by promoting EMT. Although the molecular events associated with Src-dependent regulation of E-cadherin are becoming better defined, the cellular processes that trigger the onset of EMT remain unclear. Here we highlight recent work that advances our understanding of Src signaling as it relates to E-cadherin associated regulation and EMT in PDAC.

2. INTRODUCTION

Pancreatic cancer remains a major therapeutic challenge. Five-year survival remains around 5%, and has not changed over the past 30 years (1). Pancreatic ductal adenocarcinoma (PDAC) is associated with numerous genetic mutations and activated signal transduction proteins. Understanding the critical molecular events that promote PDAC carcinogenesis and how they contribute to its maintenance and progression will facilitate the development of effective targeted therapeutic modalities.

PDAC is associated with a high frequency of K-ras, p53, p16, and Smad4 mutations in conjunction with over expression of tyrosine kinase receptors and their ligands resulting in activation of numerous mitogenic signaling pathways (2, 3). The high frequency of mutations, inter-dependence of redundant signaling pathways and feedback loops remain significant challenges to treat PDAC. Analysis of resected human PDAC tumor specimens has led to the development of the histologic and genetic framework for initiation and progression of PDAC (4, 5). Preinvasive lesions termed pancreatic intraepithelial neoplasias (PanINs), manifest distinct nuclear and architectural changes as they progress with increased

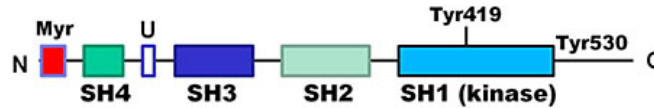


Figure 1. Src structure. Human Src is a non-receptor kinase comprised of a myristylation site (Myr), four unique Src homology (SH) domains and amino-terminal domain of unknown function - a SH4 domain involved in targeting Src to the plasmatic membrane, a region U that is specific of each Src family member, a SH3 and a SH2 domain involved in the interaction of Src with other intracellular proteins. The SH1 domain contains the kinase domain and a conserved tyrosine residue involved in autophosphorylation. Phosphorylation of the Tyr419 residue of the SH1 domain is required for maximum kinase activity. Placed immediately adjacent to the SH1 domain is a negative regulatory domain. After phosphorylation of the Tyr530 residue in the negative regulatory domain, Src becomes inactive. In the active configuration, Tyr530 is de-phosphorylated, and the SH2 and SH3 domains are released from the intra-molecular interactions and are available for binding.

grades of dysplasia from PanIN-1 to PanIN-2 to PanIN-3, or carcinoma *in situ* (4). Additionally, the rate of cellular proliferation increases with advancing stages of PanINs, ultimately resulting in invasive adenocarcinoma (4, 6, 7). Moreover, these progressive histologic changes have been correlated with progressive genetic mutations and signaling alterations which are integral in establishing the evolution and progression of PDAC (2, 3).

A hallmark of PDAC cells is their ability to invade and metastasize (8-11). Invasion and metastasis are complex processes, and their cellular, genetic and biochemical determinants are still largely unknown. During tumor progression, primary tumor cells invade adjacent tissues and intravasate into the surrounding microvasculature. This event is central to the development of metastasis, during which cells circulate to distant organs and form new tumor colonies (12).

Multiple lines of evidence support the importance of epithelial to mesenchymal transition (EMT) in promoting PDAC aggressiveness. Histological loss of cellular differentiation is a highly accurate predictor of poor outcome in PDAC (13, 14) and reduced expression of E-cadherin, a specific EMT marker, correlates with poor survival (15, 16) and invasion (17). In PDAC, E-cadherin-negative patients have been noted to have larger tumors, distant metastases and increased stage (18). Further evidence suggests that Src plays a critical role in promoting intracellular signaling pathways that lead to the induction of E-cadherin repressors and subsequent E-cadherin down regulation to allow tumor cell migration/invasion (19, 20). In this review, we will focus on Src regulation of E-cadherin expression and discuss options to target this process in human PDAC tumors.

3. SRC STRUCTURE

There are nine members of the Src family, including c-Src (Src), c-Yes, Fyn, Lyn, Lck, Hck, Blk, Fgr, and Yrk (21, 22). Src, c-Yes, and Fyn, however, display a more ubiquitous pattern of expression with particularly high levels in platelets, neurons, and epithelial tissues (23). The structure of Src is shown in Figure 1. It consists of a myristoylation site (Myr), amino (N)-terminal region, four unique Src homology domains (SH1, SH2, SH3 and SH4) and a carboxy (C)-terminal tail containing a negative regulatory tyrosine residue (24). A Myr site at the SH4

domain on the N-terminal tail is involved in translocating Src to the cell membrane. Adjacent to the SH4 domain is a region that is specific to each Src family member followed by a SH3 and a SH2 domain, both of which are involved in the interaction of Src with other intracellular proteins. The inactive conformation occurs when the phosphorylated C-terminal Tyr530 binds to the SH2 domain with SH3 bound to the kinase domain. The SH1 domain is involved in adenosine tri-phosphate (ATP) and substrate binding and shows tyrosine kinase activity, phosphorylation of which is required for maximum kinase activity (25). The SH3 domain binds amino acid sequences rich in proline residues. This domain is critical for intracellular localization of Src and the recruitment and binding of Src substrates (26). The SH3 domain stabilizes the inactive conformation by binding to the poly-proline motifs of the linker domain, and then positioning itself together with the SH2 domain on the back side of the catalytic domain (25). Together, the SH2 and SH3 domains cooperate in regulating Src catalytic activity. Phosphorylation of Src on Tyr530 is catalyzed by two known kinases, C-terminal Src kinase and the C-terminal Src kinase homologue kinase (27). Phosphorylation of the C-terminal tail by C-terminal Src kinase (Csk) results in a closed, less active protein conformation. Autophosphorylation of the kinase domain alters the conformation to increase the intrinsic kinase activity. This relative simplicity of regulation belies the fact that Src can be activated by a host of interacting proteins including growth factor receptors, integrins and G protein-coupled receptors (24). Upon signal stimuli, Src translocates from the cytosol to the membrane where it is activated by phosphorylation. Maintaining the intracellular localization of Src is therefore one of the key regulatory mechanisms that controls Src activation.

4. SRC FUNCTION IN PDAC

Once activated, Src is involved in the regulation of normal and oncogenic processes (26). Increased Src activity is caused by enhanced transcription or deregulation associated with over expression of upstream growth factor receptors such as epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), vascular endothelial growth factor (VEGF) receptor, ephrins, integrin, or focal adhesion kinase (FAK) (28-30). Over expression of these receptors, their ligands, or both, is common in many tumor types (31).

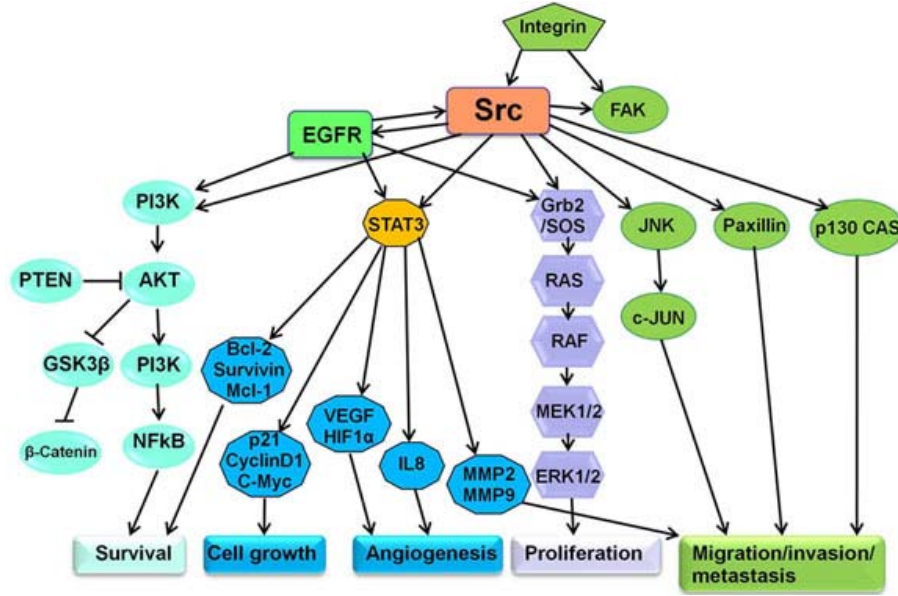


Figure 2. Src-mediated transduction pathways. Src plays a key role in multiple cellular signaling pathways implicated in cell growth, survival, migration, invasion, and angiogenesis. Some of these events require nuclear translocation of downstream mediators followed by gene transcription. Src-mediated complex signal transduction pathways may also contribute to tumor progression. CAS, Crk-associated substrate; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; IL-8, interleukin 8; JNK, Jun N-terminal kinase; MEK, mitogen-activated protein kinase, MAPK/ERK kinase; NFκB, nuclear factor κB; PI3K, phosphatidylinositol 3-kinase; SOS, son of sevenless; STAT3, signal transducer and activator of transcription 3; VEGF, vascular endothelial growth factor.

The major consequence of increased Src activity is to promote an invasive tumor phenotype characterized by breakdown of cell-cell adhesion, increased cell-matrix adhesion, and formation of focal adhesions (32, 33). Recent evidence suggests that Src activity, in concert with oncogenic Kras, plays a key role in the development of pancreatic tumors (34). Src channels phosphorylation signals through Ras/Raf/extracellular signal-regulated kinase (ERK) 1/2, phosphatidylinositol 3-kinase (PI3K)/AKT pathways and signal transducers and activators of transcription (STAT)3 signaling (35, 36) (Figure 2). Phosphorylation of FAK Tyr397 creates a binding site for Src, indicating that Src regulates cell adhesion (37). Paxillin is a substrate for the FAK-Src complex that functions as an adaptor molecule for various signaling and structural proteins associated with cell adhesion (38, 39). The mitogen-activated protein kinase (MAP kinase)/ERK cascade is a well-known target of FAK-Src signaling (40) and its activation can be facilitated by association with paxillin (41). Src can also be activated by dephosphorylation of tyrosine residue Tyr530 (Figure 1) and full Src activation requires the autophosphorylation of another tyrosine residue (Tyr419 in the human protein) present within the catalytic domain (42). Activation of STATs involves their tyrosine phosphorylation by either Janus associated kinase (JAK), receptor tyrosine kinase (RTK) s such as EGFR or non-receptor tyrosine kinases (NRTK) such as Src. Following phosphorylation, STATs dimerize and translocate to the nucleus where they regulate transcription of target genes (43, 44) (Figure 2).

Over expression of Src tyrosine kinase occurs in a ~70% of PDAC, resulting in increased EGFR activity during tumorigenesis and the development of a metastatic phenotype (45-48). Src kinase activity increases with progression from early PanIN through to late PanIN and invasive PDAC in a genetically engineered mouse model. Moreover, inhibition of Src kinase activity in this mouse model, inhibits the development of metastasis (11). Src also activates STAT3 signaling in PDAC (35, 49) and their linked activities act to control cell migration through the turnover of focal adhesions and the suppression of cell-cell contacts (50-52). Src dependent activation of STAT3 in turn contributes to the Myc mitogenic pathway (53). Furthermore, STAT3 also stimulates the production of VEGF and consequent angiogenesis, and may also have a role in invasion and metastasis (54, 55). Because serine phosphorylation is required for maximal activation of STAT3, a model has been postulated in which Src, in addition to mediating its tyrosine phosphorylation, also contributes to the activation of STAT3 by stimulating the serine/threonine kinase activity of p38 and JNK, both of which are known downstream effectors of Src (56).

Hypoxia, a common characteristic of the tumor microenvironment (57, 58), can favor invasive growth and malignant progression by stimulating the Src/STAT3/VEGF pathway which then promotes angiogenesis, a step necessary for the growth of both the primary tumor and distant metastases (22, 59, 60) (Figure 2). Src also mediates VEGF-induced permeability of endothelial cells, thereby facilitating tumor cell extravasation at distant sites allowing metastasis formation

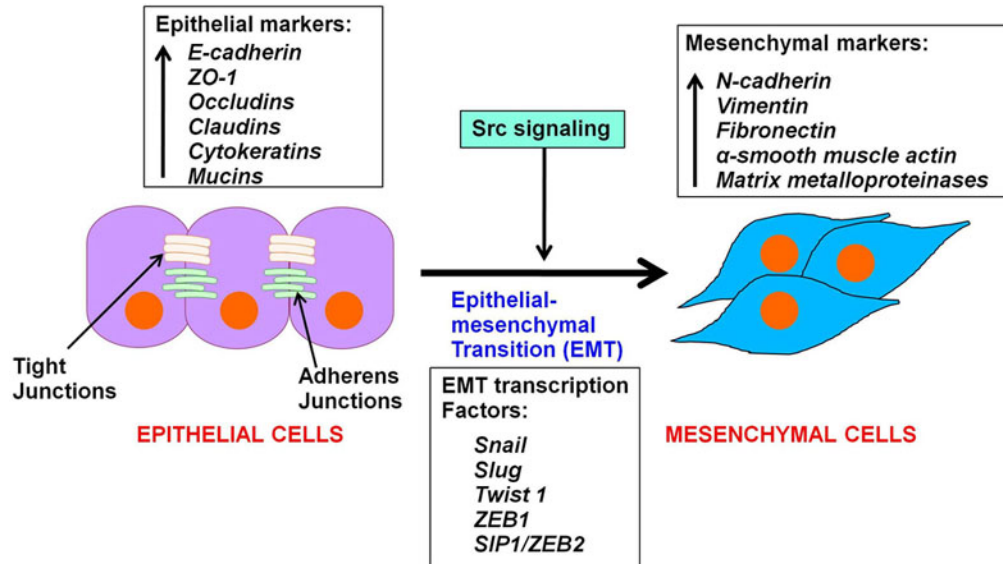


Figure 3. Epithelial to mesenchymal transition (EMT). Epithelial cells (left) are tightly interconnected by numerous cell-cell interactions. During EMT, these cells lose cell-cell junctions and the actin cytoskeleton is reorganized. Loss of expression of E-cadherin is the principal characteristic of EMT. E-cadherin repressors induce EMT by regulating expression of genes that suppress the epithelial character and promote the mesenchymal state (right) by gaining expression of mesenchymal markers vimentin, N-cadherin, fibronectin, α -smooth muscle actin, and matrix metalloproteinase's (MMP2, MMP3 and MMP9).

(61). Therefore, Src tyrosine kinase activity is important in the EMT that occurs in the early stages of invasion of carcinoma cells and is associated with angiogenesis and vascular permeability (62) (63) (Figure 3). The extensive presence of activated/over expressed Src in PDAC and its potential role in tumor development and progression makes Src an appealing target for PDAC (35, 45, 64).

5. E-CADHERIN AND EMT IN PDAC

E-cadherin is the major cadherin molecule expressed in epithelial cells and is often down-regulated in invasive tumors (65) (Figure 3). It is a single-span transmembrane glycoprotein that maintains intercellular contacts and cellular polarity in epithelial tissues. Loss of E-cadherin is associated with tumor invasiveness, metastatic dissemination, and poor prognosis in several solid tumors (66, 67). Restoring this system may enable suppression of the metastatic process. Down-regulation of E-cadherin is believed to induce EMT, which is characterized by dedifferentiation of neoplastic epithelial cells to a more motile, mesenchymal phenotype (68). Suppression of E-cadherin expression observed in human tumors can be caused by somatic mutations, chromosomal deletions, silencing of the CDH1 gene promoter, or proteolytic cleavage of E-cadherin (69, 70). Silencing of CDH1 can occur by DNA hypermethylation or by the action of transcription factors, such as Slug, Snail, or Twist1 (69-73). Recent evidence suggests that *in vivo* selection of highly metastatic PDAC cells show down-regulation of E-cadherin and induction of EMT and metastasis (74). Down-regulation of E-cadherin at the molecular level is mediated by transcriptional mechanisms involving a

histone deacetylase (HDAC) 1/HDAC2/Snail containing repressor complex (74).

The level of cadherin expression, rather than the level of catenins seems to be the rate-limiting step for E-cadherin complex formation and cell adhesion, emphasizing the importance of accurate regulation of E-cadherin expression (75, 76). E-cadherin inactivation may be involved in the process of dedifferentiation in PDAC as the absence of E-cadherin expression distinguishes undifferentiated PDAC from the more commonly observed differentiated PDAC. In a recent report, patients with differentiated PDAC, had membranous E-cadherin labeling, while undifferentiated foci in 20 of 21 cancers completely lacked E-cadherin expression (77).

EMT is a process in which cells lose epithelial characteristics and gain mesenchymal properties. These cells are characterized by an increased potential to invade surrounding tissues and disseminate to distant sites (68, 78, 79). Loss of E-cadherin is the characteristic associated with these phenotypic changes and is hallmark of EMT (72). We have screened expression of EMT markers in PDAC cell lines. BxPC3 cells have high levels of E-cadherin and β -catenin expression, but reduced expression of mesenchymal markers (N-cadherin and vimentin) while MIApaca2 and PANC1 cells have increased expression of mesenchymal markers and low expression of E-cadherin and β -catenin. BxPC3 tumor xenograft tissues treated with dasatinib, a Src family kinase (SFK) inhibitor show high expression of E-cadherin when compared to vehicle treated control mice tissues (unpublished data). Consistent with this, BxPC3 is highly sensitive to gemcitabine and Src and EGFR inhibition while MiaPaca2 and PANC1 are more

resistant to these therapies (49). However, the role of E-cadherin and Src, and their regulation at transcriptional level, screening Snail, Slug, and Twist or zinc-finger transcription factor (ZEB) 1/2 (71), need further study *in vivo*, after overexpressing and knocking out the respective genes in order to define their interplay and role in EMT.

EMT is considered a prerequisite to metastasis for most carcinomas, allowing cancer cells to disassociate from the primary tumor and enhancing cell motility. Mouse models of PDAC recapitulate this relationship (74). Studies of human PDAC tumors have revealed abnormal reduction or loss of E-cadherin expression in 42%–60% of specimens and a significant correlation with dedifferentiation, lymph node, and distant organ metastasis (80, 81). Promoter hypermethylation is perhaps a more attractive mechanism for E-cadherin inactivation because loss of heterozygosity at 16q (the E-cadherin locus) is a rare event in PDAC (82). Not surprisingly, this hypermethylation is normally regulated, in part by Src family members during development, differentiation, and homeostasis.

6. SRC REGULATES E-CADHERIN EXPRESSION AND EMT IN PDAC

Src has been shown to increase invasiveness of human cancer cells. This increase in cellular invasion is a result of a variety of events including altered activity of adhesion proteins, integrins and cadherins and altered secretion of proteinases into the extracellular matrix (83–85). SFKs also affect cadherin-mediated cell-cell adhesion by phosphorylation of catenins and link signal transduction cascades to the regulation of cell adhesion (86–88). In fibroblasts, binding of integrins to their ligands leads to formation of focal adhesion plaques and activation of focal adhesion kinase, which, in turn, recruits and activates Src kinase (89). Furthermore, activation of SFKs is required to disrupt cadherin-dependent cell-cell contacts (90). Several studies have shown that Src-mediated phosphorylation of VE-cadherin, a cell adhesion molecule that is essential for vascular cell-to-cell junctional integrity, directly leads to increased vascular permeability, thus facilitating intravasation and extravasation of migratory tumor cells (91, 92).

In PDAC cell lines, over expression of activated Src has been reported to stimulate proliferation, migration and down regulation of E-cadherin (93). We have shown that increased Src expression and activity correlates with PDAC progression and advanced malignancy (35). Tumors with high Src expression have low E-cadherin expression while normal pancreatic ductal cells have low Src expression and high E-cadherin expression (unpublished data). TGF- β is a well known promoter of EMT, however, the role of Src in this process is still a matter of debate. Recently, Ungefroren *et al.* showed that TGF- β 1-induced EMT is sensitive to Src inhibition in PDAC cells, however, Src regulated TGF- β 1 mediated cell motility but not EMT (94).

Src binds to E-cadherin, causing disruption of cell–cell interaction, enabling cancer cells to detach from

their original site (95). Specific collagens are able to promote metastatic behavior by down-regulation of E-cadherin gene expression in a Src-kinase-dependent manner. E-cadherin down regulation in response to collagen can be suppressed by treatment with SFK inhibitors including PP1 and herbimycin A (93). In addition, inhibition of Src by small interfering RNA (siRNA) or the pharmacologic agent dasatinib halts the development of PDAC metastases (47). E-cadherin has been shown to be down regulated at the cell membrane when Src Y527F is over expressed (96). Furthermore, PP2, a Src kinase inhibitor, promotes downregulation of E-cadherin mRNA (97) and also reverses the disruption of E-cadherin signaling (98).

E-cadherin is connected to β -actin via β -catenin and FAK, which are also bound to integrins (98, 99). Integrins are a family of cell-surface receptors that interact with the extracellular matrix to maintain cell shape, cell motility and the cell cycle through signal transduction. Src binds to integrins to activate these molecules and thus facilitates the adhesion of cancer cells to the extracellular matrix at another site (95). Over expression of the Src inhibitor Csk blocks the myosin light chain kinase–myosin pathway that regulates integrin and cadherin signaling and cell–cell interactions (50). Several FAK inhibitors have been patented as inhibitors of Src-induced cytoskeletal changes for use in cancer treatment, however none have been evaluated in a clinical trial. E-cadherin is also down regulated when Src is over expressed and Src inhibition with PP2 and SKI-606, another SFK inhibitor, reverse this loss (96, 100). Restoration of E-cadherin in PDAC cell lines results in increased apoptosis and decreased cell growth (101). Down regulation of E-cadherin has been demonstrated in almost every cancer as a negative prognostic indicator and is linked to metastatic disease. Decreased E-cadherin and increased vimentin expression, specific EMT markers, correlate with poor survival (15, 16) and invasion (17). Up regulation of vimentin, a mesenchymal cell marker, is a hallmark of EMT that is Src regulated (102). Therefore, Src activation is emerging as a promoter of the phenotypic characteristic of EMT in cancer cells.

7. TRANSCRIPTION FACTORS TO REPRESS E-CADHERIN EXPRESSION IN PDAC

Regulation of E-cadherin expression in PDAC remains poorly understood. Recently, it was demonstrated that repression of E-cadherin transcription is dependent on HDAC activity in a variety of murine and human models of PDAC (74). The transcription factors Snail, Slug, and Twist or ZEB 1/2 play a central role for repression of the CDH1 gene and induction of EMT (71) (Figure 3). These transcription factors down-regulate the expression of E-cadherin via interaction with two 5'-CACCTG (E-box) sequences of the E-cadherin promoter (103, 104). In fact, these transcriptional repressors, which are involved in EMT during development, are also induced in response to EMT stimuli to repress E-cadherin expression during tumor progression (71). Snail has a detrimental impact on human PDAC cells by triggering EMT and enhancing their

invasive and metastatic capabilities *in vivo* (105). Recently, Von Burstin *et al.* demonstrated, in a genetically defined endogenous mouse model of PDAC, that up-regulation of Snail occurs in highly metastatic PDAC cell lines upon induction of EMT (74). High to moderate Snail expression has been observed in 78% of PDAC specimens, Slug expression in 50%, while Twist1 expression was seen in only 3% of PDAC (106). Moreover, patients with a low Snail expression score revealed a high E-cadherin expression score. Therefore, Snail appears to be a highly relevant mediator of E-cadherin repression in PDAC (106). Expression of Snail in PDAC also promotes metastasis and chemoresistance (107).

ZEB1 is one of the target genes of Snail (108). Repression of E-cadherin expression may also occur through ZEB1 by binding to E-boxes in its promoter region. ZEB1 also regulates expression of microRNAs specific for genes relevant in metastasis and migration of cancer stem cells (109). Previous studies have emphasized the expression of SIP1/ZEB2 in PDAC cells (110).

Prevalence of E-cadherin expression loss is greater than the combined prevalence of genetic (110) and DNA methylation-induced inactivation of E-cadherin (111) or expression of SIP1, suggesting that there are additional mechanisms for E-cadherin silencing in PDAC. Up-regulation of the known E-cadherin repressor Twist1 has been studied in tumor metastasis, and a role for this factor cannot be excluded (72). However, whether increased Twist1 expression is a cause or a consequence of reduced E-cadherin awaits further investigation (73). Although the expression pattern of EMT-related molecules, such as Snail, Slug, Twist, ZEB (15, 106) have been widely studied, their specific role in EMT remains to be fully elucidated in PDAC.

8. TARGETING SRC IN PDAC

Several new molecularly targeted agents for Src are in clinical development have the potential to prevent disease progression and a large number of clinical trials to test their efficacy are ongoing (24). However, whether Src functions primarily to promote tumor progression or metastasis or contributes to proliferation of the tumor at the primary site remains unclear in PDAC. In addition, whether specific SFK members play overlapping or distinct roles in tumor growth has not been studied. We have shown that Src inhibition prevents PDAC tumorigenicity *in vitro* and *in vivo* (35) and also identified a novel role for Src in the regulation of E-cadherin internalization and cell-cell adhesion (112).

As tumors progress, dedifferentiate and metastasize, an increase in Src activation is frequently observed and the more metastatic phenotype is often linked to EMT (113). Src activation may also lead to chemoresistance by promoting EMT (113). Abrogating Src signaling has been shown to restore sensitivity to gemcitabine both *in vivo* and *in vitro* (114-116). Duxbury *et al.* (114) developed a gemcitabine-resistant human PDAC cell line that restored sensitivity to gemcitabine with PP2

inhibition. Furthermore, increasing gemcitabine resistance in a panel of PDAC cell lines was associated with higher Src expression. Furthermore, Src siRNA PDAC cell lines increased sensitivity to gemcitabine (115). However, modulating Src activity did not change PDAC sensitivity to 5-fluorouracil (115).

The Gallick group created gemcitabine-resistant PDAC cell lines which undergo an EMT-like process in which the cells have lost E-cadherin expression, express vimentin, and are more invasive and migratory (113). It is unclear whether these gemcitabine resistant PDAC cells exposed chronically to Src inhibitors show EMT changes. Phase 1 clinical trials are currently ongoing with the Src inhibitor dasatinib in combination with chemotherapy in PDAC tumors (24, 49). However, it remains difficult to assess the efficacy of these agents in relation to EMT in the clinical setting, and an increased understanding of how such agents work at different stages of the metastatic cascade will be important in guiding their clinical use.

9. CONCLUSIONS

The extensive presence of activated/over expressed Src in PDAC and its potential role in tumor development and progression makes Src an appealing target for PDAC drug discovery. Cells resistant to gemcitabine undergo an EMT-like process in which the cells have lost E-cadherin expression, express increased amount of EMT markers, and are more invasive. Although it remains difficult to assess the efficacy of anti-invasive and anti-metastatic agents in the clinical setting, it appears that the inhibition of Src may have significant potential in treating PDAC and other cancers. Contributions of Src to the biology of PDAC is likely due to both elevated kinase activity and increased availability of the functional domains for intermolecular interactions (21). Although potential biomarkers of resistance to Src inhibition have been identified (35), their role on E-cadherin regulation and EMT needs further evaluation. Evaluation of EMT markers in these tissues is ongoing. If drug combinations with Src inhibitors can enhance E-cadherin expression, as recently shown (113), identifying EMT related biomarkers to assess target inhibition, anti-invasive efficacy and predicted treatment response will be crucial for future clinical trials. Understanding how E-cadherin expression can be enhanced in PDAC may lead to development of novel chemotherapeutic strategies for tumors with high Src expression and the emerging link between these phenotypes may have profound therapeutic implications.

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Abbreviations: PDAC, Pancreatic ductal adenocarcinoma, c-Src, Src, EMT, Epithelial to mesenchymal transition, PanINs, Pancreatic intraepithelial neoplasias, ATP, Adenosine tri-phosphate, Csk, C-terminal Src kinase, EGFR, Epidermal growth factor receptor, HER2, Human epidermal growth factor receptor2, PDGFR, Platelet-derived growth factor receptor, FGRF, Fibroblast growth factor receptor, VEGF, Vascular endothelial growth factor, FAK, Focal adhesion kinase, ERK, Extracellular signal-regulated kinase, PI3K, Phosphatidylinositol 3-kinase, STAT, Signal transducers and activators of transcription, MAPK, mitogen-activated protein kinase, JAK, Janus associated kinase, RTK, Receptor tyrosine kinase, NRTK, Non-receptor tyrosine kinases, HDAC, Histone deacetylase, siRNA, Small interfering RNA, ZEB, Zinc-finger transcription factor, Src, Src family kinase

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