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Ascending the PEAK1 toward targeting TGFβ during cancer progression: Recent advances and future perspectives

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Abstract

Cancer is the second leading cause of death in the United States. Mortality in patients with solid, epithelial-derived tumors strongly correlates with disease stage and the systemic metastatic load. In such cancers, notable morphological and molecular changes have been attributed to cells as they pass through a continuum of epithelial-mesenchymal transition (EMT) states and many of these changes are essential for metastasis. While cancer metastasis is a complex cascade that is regulated by cell-autonomous and microenvironmental influences, it is well-accepted that understanding and controlling metastatic disease is a viable method for increasing patient survival. In the past 5 years, the novel non-receptor tyrosine kinase PEAK1 has surfaced as a central regulator of tumor progression and metastasis in the context of solid, epithelial cancers. Here, we review this literature with a special focus on our recent work demonstrating that PEAK1 mediates non-canonical pro-tumorigenic TGFβ signaling and is an intracellular control point between tumor cells and their extracellular microenvironment. We conclude with a brief discussion of potential applications derived from our current understanding of PEAK1 biology.

Keywords

TGFβ; PEAK1 kinase; EMT; Metastasis; Tumor Suppression; eIF5A; Ciclopirox Olamine (CPX); Cancer Biomarker

Introduction

Cancer is a major public health problem not only in the United States but also in many parts of the world. Currently, cancer is the second leading cause of death in the United States [1, 2]. Estimates demonstrate that lung and bronchus cancer cause the highest percentage of cancer-related deaths (28% in males and 26% in females) in the US. The second leading cancer-related deaths in the US are prostrate in men and breast cancer in women (9% and 15%, respectively). Colon, rectal and pancreatic cancers encompass the next tier of cancers

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Conflicting interests

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leading to mortality in the US [1, 2]. Major advances in cancer diagnosis and treatment over the past several decades suggest that cancer management is at the forefront of global scientific efforts [1, 2]. In some malignancies (e.g., breast cancer), these developments in screening, personalized therapies, biomarker identification and targeted therapy have improved disease prognosis [3]. However, other malignancies (e.g., pancreatic ductal adenocarcinoma, PDAC) remain extremely deadly. Such poor disease prognosis is usually attributable to challenges in early detection, early metastatic dissemination and/or therapeutic resistance [4]. When cancer cells acquire the ability to invade tissues and metastasize throughout the body, the chance of disease reoccurrence is significantly increased and thereby the patient prognosis for survival is reduced. Therefore, it is important to understand the molecular and cellular mechanisms that govern metastatic progression.

In human cancers, transforming growth factor beta (TGFβ) can act as either a tumor suppressor or pro-tumorigenic factor, which induces epithelial to mesenchymal transition (EMT) and metastasis [5]. Although EMT is fundamental and is strictly regulated during embryogenesis and tissue homeostasis [6], it is deregulated during the progression of epithelial cancers and correlates with the acquisition of metastatic behavior in cancer [7]. TGFβ has been previously reported to suppress tumor growth by inducing cytostasis, apoptosis, cell differentiation and immune responses [8, 9]. Many studies have also demonstrated that deregulation of both canonical and non-canonical TGFβ signaling pathways convert this protein hormone into a pro-progressive factor in epithelial tumors [10, 11].

We previously identified a novel non-receptor tyrosine kinase, PEAK1 (pseudopodium enriched atypical kinase 1, Sgk269) that is enriched in the pseudopodia of migrating cells [12]. Subsequently, we demonstrated that PEAK1 promotes tumor growth/metastasis and therapy resistance in pancreatic cancers through its regulation of the actin cytoskeleton and Src, KRas and ErbB2 signaling pathways [13]. Most recently, we demonstrated that PEAK1 is necessary and sufficient for TGFβ-induced migration, EMT, metastasis and proliferation in breast cancer [14]. In this regard, we reported that PEAK1 kinase mediates signaling cross talk between TGFβ receptors and the ITGB3/Src/Grb2/MAPK pathway and is essential for TGFβ-induced ZEB1 upregulation [15]. Herein, we review recent studies characterizing underlying mechanisms of TGFβ-induced metastasis and EMT in the context of PEAK1-mediated signaling in human cancer that emphasize further mechanistic studies that aim to identify novel therapeutic targets for blocking human cancer progression.

TGFβ signaling in cancer metastasis

The transforming growth factor beta (TGFβ) superfamily contains more than 30 secreted, extracellular ligands in human and other mammalian species [16] – many of these ligands are also conserved to lower vertebrates. Protein hormones in this superfamily include Activin [17], Nodal-related [18], TGFβ [19], Growth and Differentiation Factor (GDF) and Bone Morphogenetic Protein (BMP) [20] families. These ligands regulate a vast number of cellular processes such as tissue homeostasis, cell proliferation/differentiation, embryonic development, immune system responses, angiogenesis, wound or tissue damage repair and endocrine function [17, 18, 20–24]. As such, it is not surprising that disruption of the proper

function of ligands within this superfamily contributes substantially to multiple disease states including fibrosis and cancer [25–31].

Canonical signaling of TGFβ occurs via its interaction with two types of transmembrane receptors (type I and type II) that contain intrinsic serine/threonine kinase activities, called receptor serine kinases (RSKs) [23]. Following the characterization of the first vertebrate RSK [32], a dozen RSKs have now been identified in humans [23]. Type I RSKs are referred to as ALK1–7, for Activin Receptor-Like Kinases [33–38]. The general mechanism of activation for TGFβ ligand-receptor complexes involves TGFβ first binding to the type II receptor. This leads to binding and activation of the type I TβRI receptor (ALK5) to the ligand-type II receptor complex [39] – this mechanism was first established for TGFβ, but similar receptor activation mechanisms have been reported for other ligands in this superfamily [40–42]. Once activated in a ligand-dependent manner, intracellular Smad proteins are the targets of the type I serine/threonine receptors [43–46]. The TGFβ superfamily can be divided into Smad2/3-(e.g., Activin, Nodal and TGFβ) and Smad1/5/8-activating (e.g., BMPs and GDFs) ligands [47]. Upon phosphorylation of Smad proteins, they transport from the cytoplasm to the nucleus in complex with co-Smad proteins and directly interact with DNA and other transcriptional activators/repressors in a cell type and context-dependent manner. Ultimately, this leads to the activation or repression of target genes [7, 9, 23, 48].

Non-canonical signaling mechanisms have also been identified for TGFβ and other superfamily ligands, involving a myriad of well-characterized Smad-independent signaling pathways including RhoGTPases, Wnt, MAPK, Src and PI3K/Akt [5, 49]. Notably, the majority of the non-canonical TGFβ signaling mechanisms that have been characterized to date are associated with dysregulated TGFβ responses and the deleterious effects of TGFβ that contribute substantially to human diseases [50, 51]. Current developments during the past two decades, attesting to the cellular/molecular complexity within tissues [52], have paved the way for researchers to identify novel factors within the heterogeneous extracellular environment that regulate TGFβ signaling responses. In many instances, these factors shift the signaling responses from canonical to non-canonical and are at the root of disease-specific TGFβ signaling mechanisms [5, 49, 53–55].

Context-dependent TGFβ signaling has paradoxical effects on various tissue types [9]. For example, Smad2/3 signaling in response to TGFβ can induce varied and/or opposite effects on epithelial-mesenchymal transition (EMT), mesenchymal-epithelial transition (MET), cellular proliferation, apoptosis and differentiation. Importantly, these responses often depend on cell type and context [56]. In regard to TGFβ‘s Smad2/3-dependent tumor suppressor function, TGFβ has been reported to block proliferation, induce terminal differentiation or apoptosis in multiple cell types [29]. While these TGFβ functions are critical for normal embryonic development, tissue maintenance and tumor suppression, dysregulation of these pathways have been identified and characterized as regulators of human cancer initiation and/or progression, including breast and pancreatic cancer [26, 29, 31, 57]. Dysregulated canonical and elevated non-canonical TGFβ signaling cause tumor cells to become refractory to the antiproliferative effects of the Smad2/3 pathway. Under these circumstances, TGFβ signaling promotes cell invasion/motility/proliferation/

survival and EMT in tumor cells as well as within the tumor microenvironment [30, 56, 58–60]. This shift in TGFβ outcome from tumor-suppressing to-promoting occurs in conjunction with quantitative and qualitative changes in the proteome, transcriptome and subcellular signaling landscapes within the tumor cells as well as in the associated stromal cells.

Role of TGFβ in promoting EMT

The role of TGFβ in promoting EMT during normal and pathophysiological processes has been extensively characterized [5, 8, 21, 22, 61–66]. EMT is a morphologic and phenotypic shift in cells that is associated with specific changes in gene expression, protein translation and post-translational modification. EMT is essential and strictly regulated during embryogenesis and tissue homeostasis [6, 67]; however, it is dysregulated during wound healing and the progression of epithelial cancers to promote fibrosis and metastasis, respectively [68]. During EMT, cells gradually lose their epithelial nature leading to decreased apical-basal polarity, ability to attach to the basement membrane and assembly of protein complexes that mediate tight cell-cell contacts. These changes are also associated with down regulation of epithelial genes (e.g., CDH1 or MUC1) and increased expression of mesenchymal genes (e.g., ZEB1 and FN1) - the resulting cells tend to migrate and invade more extensively and adopt a more spread, fibroblast-like morphology [67]. While it is well accepted that TGFβ signaling is modified to enable a pro-EMT outcome, the molecular mechanisms that govern TGFβ's ability to switch between its paradoxical growth suppressing and EMT promoting functions remain to be fully elucidated [9, 69]. Notably, TGFβ has been shown to cooperate with extracellular matrix (ECM) and growth factor pathways to promote EMT, migration, invasion and metastasis of breast cancer cells [54, 70–73]. In this regard, previous reports have demonstrated that specific ECM proteins which activate integrin beta 3 (ITGB3) shift TGFβ signaling away from the Smad2/3 pathway and toward the Src/TβRII/Grb2/MAPK pathway to promote EMT in normal and malignant epithelial cells [70, 71].

Biology and Mechanism of PEAK1 Kinase Function

Kinases play central roles in most cellular processes such as cell-cycle regulation, cell motility, tissue regeneration, differentiation and the development/progression of cancers. Therefore, understanding kinase functions and their mechanisms of action will illuminate new therapeutic strategies for combating cancer [74–76].

In order to examine, characterize and reveal the functions of known and novel kinases, the tyrosine phosphoproteome (pY) of subcellular pseudopodia in migrating cells was previously interrogated by immuno-precipitating pY proteins and identifying differentially enriched pY proteins in the pseudopodium via mass spectrometry-based proteomics [12]. Pseudopodia (or invadopodia during cancer cell invasion) are highly specialized, actin- and signaling molecule-rich structures protruding from the cell's body. Along with predicted molecular components of the pseudopodia, the initial findings revealed that PEAK1 kinase (Pseudopodium-Enriched Atypical Kinase, alternatively named KIAA2002 or SGK269) was tyrosine phosphorylated, enriched in the pseudopodium and associated with the actin cytoskeleton and BCAR1/Crk complex [12]. As a pseudopodium-enriched kinase, it was

further hypothesized that PEAK1 may promote cancer metastasis. Subsequently, a key role for PEAK1 was established in PDAC (an aggressive malignancy with no early detection biomarkers and few targeted therapies) – finding that PEAK1 was upregulated in metastatic lesions from patients and required for cell metastasis in a nu/nu orthotopic xenograft model. This body of work also highlighted the role of PEAK1 in therapy resistance – driving resistance to both gemcitabine (the common PDAC chemotherapeutic) and trastuzumab (Herceptin, Genentech) [13]. In agreement with our work, other phosphoproteomic screens have identified PEAK1 as a relevant kinase target in lung cancers and sarcomas [77, 78]. Additionally, other groups have reported that PEAK1 overexpression in non-malignant mammary epithelial cells induces EMT and can mediate EGF signaling by binding to Grb2/Shc1 complexes and activating Lyn kinase (a Src family member) [79, 80]. More recently, our collaborators reported a unique role for hypusination of the translation factor, eIF5A, in driving PEAK1 translation and PEAK1-dependent PDAC progression [81].

In an effort to identify a potential mechanism by which PEAK1 might drive EMT and metastasis in breast cancer, our group returned to the pseudopodial phosphoproteome [12]. Using Cytoscape, we generated a literature-based interactome in which PEAK1 (SGK269) is centrally located (Figure 1A). A closer look at the PEAK1-focused network revealed that Grb2 is the most common shared interactor between PEAK1 and the other subnetwork members (Figure 1B). We then evaluated the expression levels of these PEAK1/Grb2 co-interactors in breast cancer samples that express elevated levels of PEAK1 (Figure 1C) [82]. These data led us to previous work demonstrating that the ITGB3/Src/TβRII/Grb2/MAPK signaling cascade can mediate TGFβ-induced EMT and metastasis [49, 64, 69, 83]. Subsequently, we have demonstrated that PEAK1 kinase mediates signaling cross talk between TGFβ receptors and the ITGB3/Src/Grb2/MAPK pathway. In this regard, our results suggested that PEAK1 is essential for TGFβ-induced ZEB1 upregulation, proliferation, migration, EMT and metastasis in breast cancer [14, 15]. These findings are summarized in the Figure 2 schematic.

PEAK1 in the context of cancer biomarkers and targeted therapies

Reliable biomarkers can be used to differentiate patient diagnosis, predict cancer prognosis and determine the best therapeutic interventions. Notably, our findings have two primary clinical implications. First, we propose that the identification of subsets of breast cancer in which PEAK1 levels are elevated may indicate good candidates for anti-TGFβ therapy. Since TGFβ can function as a tumor suppressor, it is critical to ensure that therapeutic inhibition of TGFβ is not administered in a clinical context when it is eliciting anti-proliferative or pro-apoptotic effects [8, 9]. Second, we propose that direct or indirect targeting of PEAK1 may abrogate the pro-tumorigenic signaling functions of TGFβ. In this regard, and as referenced above, we were previously involved in a collaboration identifying the eukaryotic initiation factor 5A (eIF5A) as a novel regulator of PEAK1 translation. Notably, this work demonstrated that hypusination of eIF5A (a post-translational modification required for its activity) mediated increased PEAK1 protein levels and pathogenesis in pancreatic cancer [81]. eIF5A inhibition via pharmacological targeting of the enzymes deoxyhypusine synthase (DHPS) and deoxyhypusine hydroxylase (DOHH) that are required for hypusination/activation of eIF5A has also been previously demonstrated to

block progression of breast, pancreatic and hematologic malignancies [81, 84–88]. Thus, we suggest that pharmacological inhibition of eIF5A may be an important means toward blocking the pro-tumorigenic effects of TGFβ (Figure 3).

Future Perspectives

Despite the seminal discoveries that have been made over the past 30 years addressing the functions and mechanisms of action for TGFβ-induced signaling and EMT, significant hurdles remain toward which future research efforts must be directed [8, 9]. Our work to date and that of others suggests that future efforts should address the following two major challenges in the field: first, the identification and characterization of new non-transcriptional control mechanisms of TGFβ-induced EMT and/or cancer progression; and second, to qualitatively and quantitatively analyze important context-dependent spatiotemporal regulation of TGFβ response regulators. Importantly, these studies will shed light on the development of novel methods for modulating TGFβ and PEAK1 kinase signaling in order to improve cancer survival.

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References

1. Wild CP, Bucher JR, de Jong BW, Dillner J, von Gertten C, Groopman JD, et al. Translational cancer research: balancing prevention and treatment to combat cancer globally. Journal of the National Cancer Institute. 2015; 107:353. [PubMed: 25515230]
2. Vineis P, Wild CP. Global cancer patterns: causes and prevention. Lancet. 2014; 383:549–557. [PubMed: 24351322]
3. Joy AA, Ghosh M, Fernandes R, Clemons MJ. Systemic treatment approaches in her2-negative advanced breast cancer-guidance on the guidelines. Curr Oncol. 2015; 22:S29–42. [PubMed: 25848337]
4. Perera RM, Bardeesy N. Pancreatic Cancer Metabolism: Breaking It Down to Build It Back Up. Cancer Discov. 2015
5. Derynck R, Muthusamy BP, Saeteurn KY. Signaling pathway cooperation in TGF-beta-induced epithelial-mesenchymal transition. Curr Opin Cell Biol. 2014; 31:56–66. [PubMed: 25240174]
6. Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. Nat Rev Mol Cell Biol. 2014; 15:178–196. [PubMed: 24556840]
7. Padua D, Zhang XH, Wang Q, Nadal C, Gerald WL, Gomis RR, et al. TGFbeta primes breast tumors for lung metastasis seeding through angiopoietin-like 4. Cell. 2008; 133:66–77. [PubMed: 18394990]
8. Massague J. TGF-beta signaling in development and disease. FEBS Lett. 2012; 586:1833. [PubMed: 22651913]
9. Massague J. TGFbeta signalling in context. Nat Rev Mol Cell Biol. 2012; 13:616–630. [PubMed: 22992590]
10. Xu J, Lamouille S, Derynck R. TGF-beta-induced epithelial to mesenchymal transition. Cell Res. 2009; 19:156–172. [PubMed: 19153598]
11. Derynck R, Zhang YE. Smad-dependent and Smad-independent pathways in TGF-beta family signaling. Nature. 2003; 425:577–584. [PubMed: 14534577]

12. Wang Y, Kelber JA, Tran Cao HS, Cantin GT, Lin R, Wang W, et al. Pseudopodium-enriched atypical kinase 1 regulates the cytoskeleton and cancer progression [corrected]. Proc Natl Acad Sci U S A. 2010; 107:10920–10925. [PubMed: 20534451]
13. Kelber JA, Reno T, Kaushal S, Metildi C, Wright T, Stoletov K, et al. KRas induces a Src/PEAK1/ErbB2 kinase amplification loop that drives metastatic growth and therapy resistance in pancreatic cancer. Cancer Res. 2012; 72:2554–2564. [PubMed: 22589274]
14. Agajanian M, Campeau A, Hoover M, Hou A, Brambilla D, Kim SL, et al. PEAK1 Acts as a Molecular Switch to Regulate Context-Dependent TGFbeta Responses in Breast Cancer. PLoS ONE. 2015; 10:e0135748. [PubMed: 26267863]
15. Agajanian M, Runa F, Kelber JA. Identification of a PEAK1/ZEB1 signaling axis during TGFbeta/fibronectin-induced EMT in breast cancer. Biochem Biophys Res Commun. 2015; 465:606–612. [PubMed: 26297948]
16. Vitt UA, Hsu SY, Hsueh AJ. Evolution and classification of cystine knot-containing hormones and related extracellular signaling molecules. Mol Endocrinol. 2001; 15:681–694. [PubMed: 11328851]
17. Vale, W., et al. Chemical and biological characterization of the inhibin family of protein hormones. In: Clark, JH., editor. Laurentian Hormone Conference, Vol. Academic Press, Inc; San Diego: 1998. p. 1-34.Recent Progress in Hormone Research
18. Massague J. TGF-beta signal transduction. Annu Rev Biochem. 1998; 67:753–791. [PubMed: 9759503]
19. Hogan BL. Bone morphogenetic proteins: multifunctional regulators of vertebrate development. Genes Dev. 1996; 10:1580–1594. [PubMed: 8682290]
20. Schier AF, Shen MM. Nodal signalling in vertebrate development. Nature. 2000; 403:385–389. [PubMed: 10667782]
21. Wu MY, Hill CS. Tgf-beta superfamily signaling in embryonic development and homeostasis. Dev Cell. 2009; 16:329–343. [PubMed: 19289080]
22. Flavell RA, Sanjabi S, Wrzesinski SH, Licona-Limon P. The polarization of immune cells in the tumour environment by TGFbeta. Nat Rev Immunol. 2010; 10:554–567. [PubMed: 20616810]
23. Massague J. How cells read TGF-beta signals. Nat Rev Mol Cell Biol. 2000; 1:169–178. [PubMed: 11252892]
24. Roberts, AB., Sporn, MB. The transforming growth factor-bs. In: Sporn, MB., Roberts, AB., editors. Handb Exp Pharmacol. Vol. 95/I. Springer-Verlag; Heidelberg: 1990. p. 419-472.
25. Kelber JA, Panopoulos AD, Shani G, Booker EC, Belmonte JC, Vale WW, et al. Blockade of Cripto binding to cell surface GRP78 inhibits oncogenic Cripto signaling via MAPK/PI3K and Smad2/3 pathways. Oncogene. 2009; 28:2324–2336. [PubMed: 19421146]
26. Bardeesy N, Cheng KH, Berger JH, Chu GC, Pahler J, Olson P, et al. Smad4 is dispensable for normal pancreas development yet critical in progression and tumor biology of pancreas cancer. Genes Dev. 2006; 20:3130–3146. [PubMed: 17114584]
27. Roberts AB, Wakefield LM. The two faces of transforming growth factor beta in carcinogenesis. Proc Natl Acad Sci U S A. 2003; 100:8621–8623. [PubMed: 12861075]
28. Pickup M, Novitskiy S, Moses HL. The roles of TGFbeta in the tumour microenvironment. Nat Rev Cancer. 2013; 13:788–799. [PubMed: 24132110]
29. Massague J, Blain SW, Lo RS. TGFbeta signaling in growth control, cancer, and heritable disorders. Cell. 2000; 103:295–309. [PubMed: 11057902]
30. Topczewska JM, Postovit LM, Margaryan NV, Sam A, Hess AR, Wheaton WW, et al. Embryonic and tumorigenic pathways converge via Nodal signaling: role in melanoma aggressiveness. Nat Med. 2006; 12:925–932. [PubMed: 16892036]
31. Chen YG, Lui HM, Lin SL, Lee JM, Ying SY. Regulation of cell proliferation, apoptosis, and carcinogenesis by activin. Exp Biol Med (Maywood). 2002; 227:75–87. [PubMed: 11815670]
32. Mathews LS, Vale WW. Expression cloning of an activin receptor, a predicted transmembrane serine kinase. Cell. 1991; 65:973–982. [PubMed: 1646080]
33. ten Dijke P, Ichijo H, Franzen P, Schulz P, Saras J, Toyoshima H, et al. Activin receptor-like kinases: a novel subclass of cell-surface receptors with predicted serine/threonine kinase activity. Oncogene. 1993; 8:2879–2887. [PubMed: 8397373]

34. Ebner R, Chen R-H, Shum L, Lawler S, Zioncheck TF, Lee A, et al. Cloning of type I TGF-β receptor and its effect on TGF-β binding to the type II receptor. Science. 1993; 260:1344–1348. [PubMed: 8388127]
35. Tsuchida K, Mathews LS, Vale WW. Cloning and characterization of a transmembrane serine kinase that acts as an activin type I receptor. Proc. Natl. Acad. Sci. USA. 1993; 90:11242–11246. [PubMed: 8248234]
36. Bassing CH, Yingling JM, Howe DJ, Wang T, He WW, Gustafson ML, et al. A transforming growth factor-β type I receptor that signals to activate gene expression. Science. 1994; 263:87–89. [PubMed: 8272871]
37. ten Dijke P, Yamashita H, Ichijo H, Franzen P, Laiho M, Miyazono K, et al. Characterization of type I receptors for transforming growth factor- beta and activin. Science. 1994; 264:101–104. [PubMed: 8140412]
38. Tsuchida K, Sawchenko PE, Nishikawa SI, Vale WW. Molecular cloning of a novel type I receptor serine/threonine kinase for the TGFβ superfamily from rat brain. Molecular and Cellular Neuroscience. 1996; 7:467–478. [PubMed: 8875430]
39. Wrana J, Attisano L, Carcamo J, Zentella A, Doody J, Laiho M, et al. Mechanism of activation of the TGF-β receptor. Nature. 1992; 370:341–347.
40. Attisano L, Wrana JL, Montalvo E, Massague J. Activation of signalling by the activin receptor complex. Mol Cell Biol. 1996; 16:1066–1073. [PubMed: 8622651]
41. Lebrun J-J, Vale WW. Activin and inhibin have antagonistic effects on ligand-dependent heterodimerization of the type I and type II activin receptors and human erythroid differentiation. Mol Cell Biol. 1997; 17:1682–1691. [PubMed: 9032295]
42. Kelber JA, Shani G, Booker EC, Vale WW, Gray PC. Cripto is a noncompetitive activin antagonist that forms analogous signaling complexes with activin and nodal. J Biol Chem. 2008; 283:4490–4500. [PubMed: 18089557]
43. Heldin CH, Miyazono K, ten Dijke P. TGF-beta signalling from cell membrane to nucleus through SMAD proteins. Nature. 1997; 390:465–471. [PubMed: 9393997]
44. Macias SM, Abdollah S, Hoodless PA, Pirone R, Attisano L, Wrana JL. MADR2 is a substrate of the TGFbeta receptor and its phosphorylation is required for nuclear accumulation and signaling. Cell. 1996; 87:1215–1224. [PubMed: 8980228]
45. Zhang Y, Feng X, We R, Derynck R. Receptor-associated Mad homologues synergize as effectors of the TGF-beta response. Nature. 1996; 383:168–172. [PubMed: 8774881]
46. Kretzschmar M, Liu F, Hata A, Doody J, Massague J. The TGF-beta family mediator Smad1 is phosphorylated directly and activated functionally by the BMP receptor kinase. Genes Dev. 1997; 11:984–995. [PubMed: 9136927]
47. Wrana JL, Attisano L. The Smad pathway. Cytokine Growth Factor Rev. 2000; 11:5–13. [PubMed: 10708948]
48. Schmierer B, Hill CS. TGFbeta-SMAD signal transduction: molecular specificity and functional flexibility. Nat Rev Mol Cell Biol. 2007; 8:970–982. [PubMed: 18000526]
49. Parvani JG, Taylor MA, Schiemann WP. Noncanonical TGF-beta signaling during mammary tumorigenesis. J Mammary Gland Biol Neoplasia. 2011; 16:127–146. [PubMed: 21448580]
50. Massague J. TGFbeta in Cancer. Cell. 2008; 134:215–230. [PubMed: 18662538]
51. Massague J, Gomis RR. The logic of TGFbeta signaling. FEBS Lett. 2006; 580:2811–2820. [PubMed: 16678165]
52. Donati G, Watt FM. Stem cell heterogeneity and plasticity in epithelia. Cell Stem Cell. 2015; 16:465–476. [PubMed: 25957902]
53. Wendt MK, Smith JA, Schiemann WP. Transforming growth factor-beta-induced epithelial-mesenchymal transition facilitates epidermal growth factor-dependent breast cancer progression. Oncogene. 2010; 29:6485–6498. [PubMed: 20802523]
54. Wendt MK, Smith JA, Schiemann WP. p130Cas is required for mammary tumor growth and transforming growth factor-beta-mediated metastasis through regulation of Smad2/3 activity. J Biol Chem. 2009; 284:34145–34156. [PubMed: 19822523]
55. Chow A, Arteaga CL, Wang SE. When tumor suppressor TGFbeta meets the HER2 (ERBB2) oncogene. J Mammary Gland Biol Neoplasia. 2011; 16:81–88. [PubMed: 21590373]

56. Pardali K, Moustakas A. Actions of TGF-beta as tumor suppressor and pro-metastatic factor in human cancer. Biochemica and Biophysica Acta. 2007; 1775:21–62.
57. Fleisch MC, Maxwell CA, Barcellos-Hoff MH. The pleiotropic roles of transforming growth factor beta in homeostasis and carcinogenesis of endocrine organs. Endocr Relat Cancer. 2006; 13:379–400. [PubMed: 16728569]
58. Akhurst RJ, Derynck R. TGF-beta signaling in cancer--a double-edged sword. Trends Cell Biol. 2001; 11:S44–51. [PubMed: 11684442]
59. Derynck R, Akhurst RJ, Balmain A. TGF-beta signaling in tumor suppression and cancer progression. Nat Genet. 2001; 29:117–129. [PubMed: 11586292]
60. Wakefield LM, Roberts AB. TGF-beta signaling: positive and negative effects on tumorigenesis. Curr Opin Genet Dev. 2002; 12:22–29. [PubMed: 11790550]
61. Katsuno Y, Lamouille S, Derynck R. TGF-beta signaling and epithelial-mesenchymal transition in cancer progression. Current Opinion in Oncology. 2013; 25:76–84. [PubMed: 23197193]
62. Saitoh M. Epithelial-mesenchymal transition is regulated at post-transcriptional levels by transforming growth factor-beta signaling during tumor progression. Cancer Sci. 2015; 106:481–488. [PubMed: 25664423]
63. Tojo M, Hamashima Y, Hanyu A, Kajimoto T, Saitoh M, Miyazono K, et al. The ALK-5 inhibitor A-83-01 inhibits Smad signaling and epithelial-to-mesenchymal transition by transforming growth factor-beta. Cancer Sci. 2005; 96:791–800. [PubMed: 16271073]
64. Morrison CD, Parvani JG, Schiemann WP. The relevance of the TGF-beta Paradox to EMT-MET programs. Cancer Lett. 2013; 341:30–40. [PubMed: 23474494]
65. Rockey DC, Bell PD, Hill JA. Fibrosis--A Common Pathway to Organ Injury and Failure. New England Journal of Medicine. 2015; 373:96.
66. Drabsch Y, ten Dijke P. TGF-beta signalling and its role in cancer progression and metastasis. Cancer Metastasis Rev. 2012; 31:553–568. [PubMed: 22714591]
67. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. J Clin Invest. 2009; 119:1420–1428. [PubMed: 19487818]
68. Thiery JP, Lim CT. Tumor dissemination: an EMT affair. Cancer Cell. 2013; 23:272–273. [PubMed: 23518345]
69. Wendt MK, Tian M, Schiemann WP. Deconstructing the mechanisms and consequences of TGF-beta-induced EMT during cancer progression. Cell Tissue Research. 2012; 347:85–101. [PubMed: 21691718]
70. Galliher-Beckley AJ, Schiemann WP. Grb2 binding to Tyr284 in TbetaR-II is essential for mammary tumor growth and metastasis stimulated by TGF-beta. Carcinogenesis. 2008; 29:244–251. [PubMed: 18174260]
71. Galliher AJ, Schiemann WP. Src phosphorylates Tyr284 in TGF-beta type II receptor and regulates TGF-beta stimulation of p38 MAPK during breast cancer cell proliferation and invasion. Cancer Res. 2007; 67:3752–3758. [PubMed: 17440088]
72. Wendt MK, Schiemann WP. Therapeutic targeting of the focal adhesion complex prevents oncogenic TGF-beta signaling and metastasis. Breast Cancer Res. 2009; 11:R68. [PubMed: 19740433]
73. Taylor MA, Davuluri G, Parvani JG, Schiemann BJ, Wendt MK, Plow EF, et al. Upregulated WAVE3 expression is essential for TGF-beta-mediated EMT and metastasis of triple-negative breast cancer cells. Breast Cancer Res Treat. 2013; 142:341–353. [PubMed: 24197660]
74. Manning G, Whyte DB, Martinez R, Hunter T, Sudarsanam S. The protein kinase complement of the human genome. Science. 2002; 298:1912–1934. [PubMed: 12471243]
75. Manning G, Plowman GD, Hunter T, Sudarsanam S. Evolution of protein kinase signaling from yeast to man. Trends Biochem Sci. 2002; 27:514–520. [PubMed: 12368087]
76. Liu W, Kovacevic Z, Peng Z, Jin R, Wang P, Yue F, et al. The molecular effect of metastasis suppressors on Src signaling and tumorigenesis: new therapeutic targets. Oncotarget. 2015; 6:35522–41. [PubMed: 26431493]
77. Rikova K, Guo A, Zeng Q, Possemato A, Yu J, Haack H, et al. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. Cell. 2007; 131:1190–203. [PubMed: 18083107]

78. Bai Y, Li J, Fang B, Edwards A, Zhang G, Bui M, et al. Phosphoproteomics identifies driver tyrosine kinases in sarcoma cell lines and tumors. Cancer Res. 2012; 72:2501–11. [PubMed: 22461510]

79. Croucher DR, Hochgrafe F, Zhang L, Liu L, Lyons RJ, Rickwood D, et al. Involvement of Lyn and the atypical kinase SgK269/PEAK1 in a basal breast cancer signaling pathway. Cancer Res. 2013; 73:1969–1980. [PubMed: 23378338]

80. Zheng Y, Zhang C, Croucher DR, Soliman MA, St-Denis N, Pasculescu A, et al. Temporal regulation of EGF signalling networks by the scaffold protein Shc1. Nature. 2013; 499:166–171. [PubMed: 23846654]

81. Fujimura K, Wright T, Strnadel J, Kaushal S, Metildi C, Lowy AM, et al. A hypusine-eIF5A-PEAK1 switch regulates the pathogenesis of pancreatic cancer. Cancer Res. 2014

82. Uhlen M, Oksvold P, Fagerberg L, Lundberg E, Jonasson K, Forsberg M, et al. Towards a knowledge-based Human Protein Atlas. Nat Biotechnol. 2010; 28:1248–1250. [PubMed: 21139605]

83. Balanis N, Wendt MK, Schiemann BJ, Wang Z, Schiemann WP, Carlin CR. Epithelial to mesenchymal transition promotes breast cancer progression via a fibronectin-dependent STAT3 signaling pathway. J Biol Chem. 2013; 288:17954–17967. [PubMed: 23653350]

84. Xu GD, Shi XB, Sun LB, Zhou QY, Zheng DW, Shi HS, et al. Down-regulation of eIF5A-2 prevents epithelial-mesenchymal transition in non-small-cell lung cancer cells. J Zhejiang Univ Sci B. 2013; 14:460–467. [PubMed: 23733422]

85. Ding L, Gao LJ, Gu PQ, Guo SY, Cai YQ, Zhou XT. The role of eIF5A in epidermal growth factor-induced proliferation of corneal epithelial cell association with PI3-k/Akt activation. Mol Vis. 2011; 17:16–22. [PubMed: 21224998]

86. Li AL, Li HY, Jin BF, Ye QN, Zhou T, Yu XD, et al. A novel eIF5A complex functions as a regulator of p53 and p53-dependent apoptosis. J Biol Chem. 2004; 279:49251–49258. [PubMed: 15371445]

87. Zhou H, Shen T, Luo Y, Liu L, Chen W, Xu B, et al. The antitumor activity of the fungicide ciclopirox. Int J Cancer. 2010; 127:2467–2477. [PubMed: 20225320]

88. Weir SJ, Patton L, Castle K, Rajewski L, Kasper J, Schimmer AD. The repositioning of the anti-fungal agent ciclopirox olamine as a novel therapeutic agent for the treatment of haematologic malignancy. J Clin Pharm Ther. 2011; 36:128–134. [PubMed: 21366640]

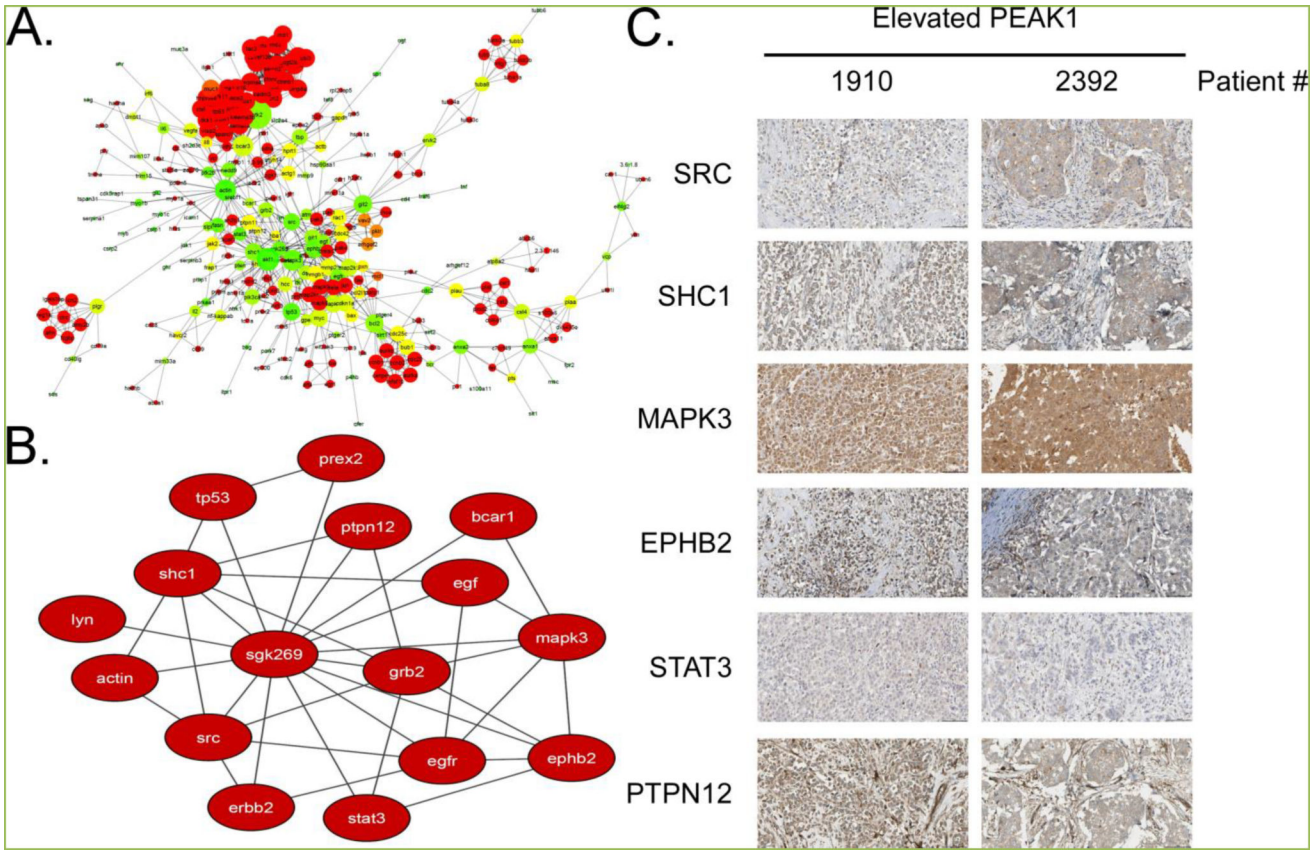

Figure 1.

Panel A: Cytoscape-derived literature-based interactome of phosphotyrosine proteins and common interactors derived from the cell pseudopodium of migrating cells. Panel B: PEAK1-focused subnetwork from the larger interactome in panel A. Panel C: IHC data from the Human Protein Atlas.

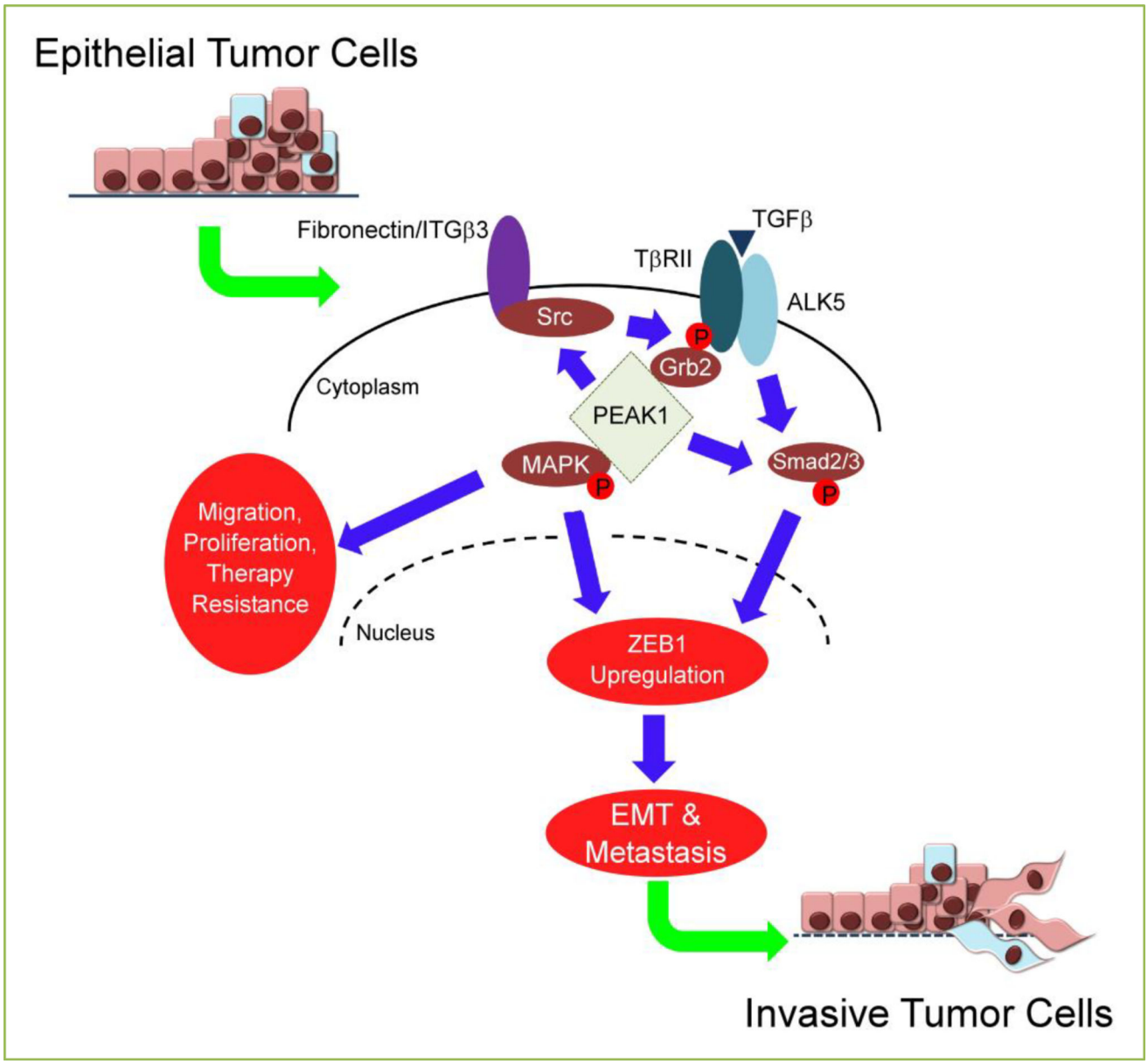

Figure 2. PEAK1 can bind and facilitate the recruitment of Src kinase to integrins and TβRII/Grb2 complexes to promote non-canonical TGFβ-induced MAPK signaling in the presence of extracellular matrix proteins that activate ITGB3

Additionally, PEAK1 can promote Smad2/3 activation in the presence of fibronectin while potentiating TGFβ-induced Smad2/3 signaling in the absence of ECM protein. Finally, PEAK1 is required for ZEB1 upregulation downstream of TGFβ. The net result is that PEAK1 converts TGFβ signaling from an anti-proliferative growth factor to a pro-tumorigenic one, leading to EMT and metastasis.

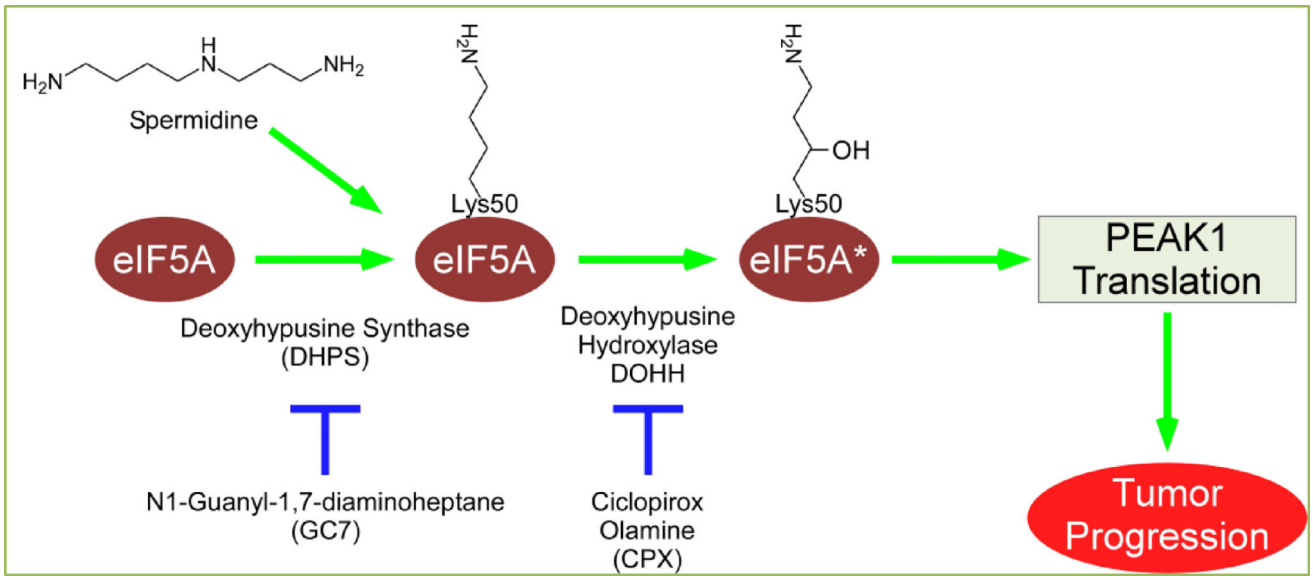

Figure 3. Schematic of eIF5A hypusination and eIF5A-dependent PEAK1 translation and tumor progression

Briefly, deoxyhypusine synthase (DHPS) catalyzes the addition of spermidine to lysine 50 on eIF5a. Subsequently, deoxyhypusine hydroxylase (DOHH) hydroxylates the spermidine-modification. Once activated via this hypusination mechanism, eIF5A drives PEAK1 translation and tumor progression. Both GC7 and CPX have been reported to inhibit eIF5A hypusination/activation, PEAK1 translation and tumorigenesis.