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Clinical relevance of Ephs and ephrins in cancer: lessons from breast, colorectal, and lung cancer profiling

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Abstract

Pre-clinical studies provide compelling evidence that members of the Eph family of receptor tyrosine kinases and their ephrin ligands promote tumor growth, invasion and metastasis, and neovascularization. Tumor suppressive roles have also been reported for the receptors, and ligand-dependent versus ligand-independent signaling has emerged as one key mechanism underlying tumor suppressive function as opposed to oncogenic effects. Determining how these observations relate to clinical outcome is a crucial step for translating the biological and mechanistic data into new molecularly targeted therapies. Expression profiling in human patient samples bridges this gap and provides valuable clinical relevance to laboratory observations. In addition to analyses performed using privately assembled patient tumor samples, publically available microarray datasets and tissue microarrays linked to clinical data have emerged as tractable tools for addressing the clinical relevance of specific molecules and families of related molecules. This review summarizes the clinical relevance of specific Eph and ephrin molecules in human breast, colorectal, and lung cancers.

Keywords

Eph; ephrin; cancer; patient; profiling; clinical relevance

Introduction

Tumorigenesis and malignant progression are complex processes that are regulated in part by activation of oncogenic signaling pathways and inhibition of tumor suppressor pathways [reviewed in [1–3]]. Oncogenic conversion, amplification, and/or overexpression of proto-oncogenes, such as those encoding receptor tyrosine kinases (RTKs), contribute to tumorigenesis [4]. Loss of tumor suppressor pathways that negatively regulate cell proliferation also contributes to tumorigenesis [5]. In addition, a third class of molecules displays dual roles in both tumor suppression and tumor promotion. The Eph family of RTKs belongs to this dual regulatory category. This large family is subdivided into class A and class B receptors based on sequence homology and binding affinity for two distinct types of membrane-anchored ephrin ligands. Originally characterized as axon guidance

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regulators, ephrins and Eph RTKs regulate physiologic and pathologic processes in development and disease [reviewed in {Brantley-Sieders, 2004 #7;Pasquale, 2010 #9].

The Eph family enhances tumor growth, invasion and metastasis, and neovascularization [reviewed in {Brantley-Sieders, 2004 #7;Pasquale, 2010 #9]. Indeed, data derived from laboratory research suggest that EphA2 and EphB4 function as oncogenes. Other studies, however, provide evidence that Eph receptors, including EphA2 and EphB4, inhibit tumor growth and progressson [reviewed in {Noren, 2007 #11}[6]]. These opposing functions appear to be influenced by tissue type, oncogenic context, and ligand-independent versus ligand-dependent signaling. Moreover, 'reverse' signaling that occurs downstream of membrane-tethered ephrin ligands upon receptor binding adds to the complexity of Eph and ephrin function [reviewed in [7]. Finally, the fact that this family is the largest RTK family in the genome, encompassing at least 14 receptors and 8 ligands that often display overlapping expression patterns in both tumor cells and the surrounding host stroma, also presents a potential barrier in designing molecularly targeted Eph therapies in human cancer [reviewed in {Pasquale, 2010 #9]].

Nonetheless, Eph receptors are very attractive therapeutic targets. They are expressed in a broad range of human cancer types in both tumor and its stromal microenvironment. In fact, several family members are known to simultaneously regulate tumor growth and neovascularization [reviewed in [6, 8]], enabling a single anti-Eph inhibitor to potentially disrupt at least two key processes in tumor progression. Translating the biological and mechanistic data from the laboratory into novel clinical therapeutic strategies will require a solid understanding of the expression patterns of individual Eph receptors, particularly in the context of relevant ligands, within molecularly defined tumor subsets. Identification of those patients who will receive the maximum therapeutic benefit can be achieved using expression profiling of large tumor datasets. In this review, we summarize expression profiles derived from a broad spectrum of human patient samples with an emphasis on how publically available datasets and samples linked to clinical outcome data have emerged as tractable tools for addressing the clinical relevance of Eph RTKs and ephrins to cancer. Due to space constraints, we limit our discussion to profiling efforts in human breast, colorectal, and lung cancers. Information and references for these data and a broader range of human epithelial malignancies are provided in Table 1 (Class A Eph family members) and in Table 2 (Class B Eph family members).

1.1 Eph expression profiles in human breast cancer

EphA2 and EphB4 are the two Eph RTK family members that have been most extensively studied in breast cancer [reviewed in [9]]. Ogawa et al. first reported expression of EphA2 and its primary ligand, ephrin-A1, in both tumor epithelium and associated vascular endothelium in human breast cancers, [10], and EphA2 overexpression in human breast cancer relative to benign human breast epithelium was also reported by Zelinksi et al. [11], and may be associated with estrogen receptor (ER) expression [12]. Subsequent studies reported that increased *ephA2* mRNA expression levels, which are relatively low in normal human breast tissue, correlated with poor patient prognosis in two independent breast cancer microarray datasets [13, 14]. These data are consistent with cell culture, biochemical, and genetic laboratory studies that support the oncogenic function of EphA2 in human breast cancer [reviewed in [9]]. In addition, EphA2 appears to play a role in both intrinsic and acquired resistance to trastuzumab (Herceptin), a monoclonal anti-HER2 antibody used as a first line of treatment for HER2 amplified breast cancer [15]. These data are consistent with laboratory studies showing a physical and functional interaction with ErbB/EGFR RTKs [16–19]. Indeed, elevated *ephA2* mRNA expression correlated significantly with decreased overall and recurrence-free survival in HER2-positive patients in a microarray dataset [15],

providing clinically relevant evidence to support this association. These data suggest that expression profiling for *ephA2* and/or other resistance-associated gene products in resistant versus sensitive patient samples could be used to identify patients who may benefit from EphA2-targeted therapies. In addition, expression profiling in host endothelium may also provide valuable diagnostic information. A recent study reported that EphA2-positive human breast tumor endothelium correlated with diminished expression of Slit2, a tumor suppressive angiocrine signal. Negative regulation of endothelial Slit2 by EphA2 in murine endothelial cells enables increased tumor growth [20]. These data support a novel role for endothelial EphA2 in regulation of tumor growth and motility independent of its angiogenic function, suggesting additional therapeutic benefits for EphA2 inhibition in human breast cancer.

Elevated mRNA and protein expression of EphB4 and EphB2 have also been reported in human breast cancer [21, 22]. While elevated EphB2 expression was associated with poorer overall and disease-free survival, EphB4 protein expression increased with grade and stage but showed no clear association with survival. Indeed, stronger EphB2 and EphB4 staining was observed in normal breast glandular epithelium than in malignant tumor epithelium [22]. An independent profiling study reported similar trends, with higher expression in normal breast tissue and low histologic grade tumors relative to invasive human breast carcinomas [23]. These expression data illustrate the often paradoxical findings regarding Eph RTKs in tumor promotion versus tumor suppression [8]. For example, laboratory studies demonstrated that systemic delivery of ephrin-B2-Fc inhibits the growth of MDA-MB-435 tumor xenografts [24]. EphB4 forward signaling activates the Abl/Crk pathway, inhibiting tumor cell growth and motility in breast cancer cells [24]. In contrast, a more recent expression analysis of multiple large patient datasets correlated elevated *ephB4* mRNA expression with reduced overall and recurrence-free survival (Brantley-Sieders et al., in preparation). Together, these data suggest that further analysis of EphB4 expression, in both tumor parenchyma and the surrounding stroma, should be performed using large sets of human patient samples carefully stratified by stage and grade, as well as by molecular subtype and treatment regimen. Particular attention should be paid to expression profiles in tumor endothelium, given the role of B class receptors like EphB4 in angiogenesis and tumor neovascularization [8], as well as vessel maturation and vascular integrity [25].

EphA5 was recently identified as a putative tumor suppressor through expression profiling, as mRNA expression was significantly downregulated in human breast cancer samples relative to normal human breast tissue, likely due to aberrant promoter methylation [26]. While several laboratory studies present evidence supporting EphB6 promoter methylation and tumor suppressor function [27–31], our analysis of mRNA expression in patient datasets revealed a significant association between elevated *ephB6* and poorer overall and recurrence-free survival in breast cancer (Brantley-Sieders et al., in preparation). In addition, we also observed negative associations between survival/recurrence and elevated mRNA expression of *ephA2*, *ephA4*, *ephA7*, and *ephB4* (Brantley-Sieders et al., in preparation). These observations are consistent with laboratory data for some Eph family members (e.g. EphA2, EphA7), but not others (e.g. EphA4, EphB4, EphB6), in human breast cancer cell lines [27], suggesting that cell line models must be carefully selected and multiple cell lines should be used so that they accurately recapitulate trends in human disease. At least one explanation for these conflicting data may reside in ligand-independent versus dependent signaling. For example, though we found no clear positive or negative correlations between expression of ephrin ligands and clinical outcome, we did observe an inverse correlation between EphA2 and ephrin-A1 protein expression in a significant number of invasive ductal carcinoma samples in lymph node relative to normal breast and ductal carcinomas confined to the breast, which co-express both (Brantley-Sieders et al., in preparation). This observation is consistent with profiling studies in breast cancer cell lines [16] and with the

laboratory observations that ephrin-A1 ligand inhibits tumor cell growth and invasion [16, 32, 33]. Thus, future profiling efforts should include the full spectrum of relevant ephrin-ligands as well as Eph RTKs in order to elucidate potential differences in clinical outcome associated with the presence or absence of ligand. Moreover, soluble, monomeric ephrin-A1 has been detected in human breast cancer line supernatants [34, 35]. Soluble ligand can impose alternate biological outcomes compared to membrane-tethered ligands [35–37]. Therefore, assessing the localization (membrane versus soluble) of these ligands in situ may provide insight into the behavior of receptors detected in human cancers.

Together, these profiling efforts identified several A and B class Eph RTKs that may serve as tractable targets for human breast malignancies. Further analysis of how ligand expression profiles track with RTK expression will help elucidate the function of these receptors in specific malignancies. In addition, protein expression profiling, particularly studies geared toward detection of soluble ligands and post-translational modifications (e.g. serine/threonine versus tyrosine phosphorylation) of Eph RTKs and ephrin-B ligands, will no doubt shed light on the complex function of these molecules in cancer.

1.2 Eph expression profiles in human colorectal cancer

In addition to roles in normal gastrointestinal homeostasis and cell sorting in the gut, several B class Eph RTKs have been implicated in colorectal cancer [reviewed in [38, 39]]. Using commercial cDNA arrays coupled with immunoblot and immunohistochemical methods, Stephenson et al. reported elevated EphB4 expression in 82% of colon cancer tissues relative to matched normal tissue from the same patients, with protein expression localizing to tumor epithelium [40]. Martiny-Baron et al. reported elevated mRNA expression of *ephB4* in human colon carcinomas relative to adjacent normal tissue controls [41]. Expression of *ephB2*, *ephB3*, and *ephB4* mRNA was reported in human colon cancer tissue, along with B class ligand *ephrin-B2*. Interestingly, these tumors, as well as a panel of colorectal cancer (CRC) cell lines, were negative for *ephB1*, *ephrin-B1*, and *ephrin-B3* [41, 42]. While these early studies suggested that several EphB family members play a role in human CRC, the relative number of patient samples analyzed was low [n=15 to 60; [40–42]] and the samples were not stratified by stage, grade, or level of invasiveness.

Although increased EphB RTK expression was detected in colorectal tumors, subsequent expression analyses coupled with genetically engineered mouse models suggest tumor suppressive functions for EphB receptors. Reduction or loss of EphB2 and EphB4 expression correlated with the shift from adenoma to invasive carcinoma in a panel of 108 human CRC samples, and loss of *ephB3* mRNA was also observed in a smaller panel of tumors [43]. Similar results were reported in independent EphB2 [44] and EphB3 [45] profiling studies for human CRC. Reduced expression of EphB1 was also reported in poorly-differentiated, invasive CRCs [46] and in invasive gastric carcinomas [47]. In normal gut epithelium, the Wnt/β-catenin/TCF pathway regulates expression of EphB receptors in the Paneth/progenitor cell domain within the lower regions of crypts in a counter gradient to ephrin-B ligands that are expressed in differentiating cells higher in the crypt and in the villus. Thus, loss of EphB receptor expression may disrupt the normal cues that restrict tumor cell movement and enable unrestricted repopulation of the epithelial compartment as tumor progression proceeds [reviewed in [38]]. Indeed, a positive correlation between EphB2 expression and better overall and recurrence-free survival in human CRC patients has been identified in three independent studies [48–50]. Similar trends were reported for EphB4 expression in human CRC patient samples [51]. Moreover, EphB4 may have prognostic value for risk of relapse in human CRC [52]. Together, these data suggest that EphB receptors function as tumor suppressors in human CRC.

Relative to B class receptors and ligands, EphA RTKs have not been investigated extensively in human CRC. EphA1, EphA7, and EphA8 are reported to be downregulated in human CRC [53–56], and reduced EphA1 expression correlated with poor overall survival [53, 55]. These data suggest that, like their B class counterparts, these A class receptors may function as tumor suppressors in human CRC. Elevated EphA2 expression, however, correlated with liver/lymph node metastasis, lymphatic vessel infiltration, and clinical stage, as opposed to E-cadherin [57], and a similar trend was also reported for EphA2 [58, 59] and E-cadherin [59] in gastric cancer. EphA2 and ephrin-A1 expression were also correlated with MVD in human CRC samples [60], suggesting they might regulate neovascularization as well as tumorigenesis. These clinical observations are consistent with data derived from cell culture and animal studies [61–63]. Elevated EphA4 expression was reported for CRCs in the presence of liver metastasis, whereas lower EphB2 levels correlated with liver metastasis [64].

As with breast carcinoma, several Eph RTKs display expression profiles suggesting complex roles in CRC tumor progression. An emerging theme from analysis of clinical specimens and laboratory models is that Eph RTKs differentially regulate tumor growth versus tumor suppression in a stage-dependent manner. Thus, expression must be scored in the context of stage and grade. In addition, future profiling efforts should be geared toward looking at RTK expression in the context of ligand. In the case of CRC, this may be particularly important in determining the invasive potential of individual tumors, as localization of ligand relative to receptor may restrict invasion until receptor expression is lost, similar to what has been observed in development and normal gut homeostasis [reviewed in [38, 65]].

1.3 Eph expression profiles in human lung cancers

Recent studies suggest that Eph RTKs, particularly of the A class, play important roles in tumor progression or tumor suppression, depending on the individual family member. Initial presentation with high levels of EphA2 expression in non-small cell lung cancer (NSCLC) patients correlates with a history of smoking and is prognostic for metastasis, particularly brain metastasis, whereas low levels in the primary tumor correlate positively with disease-free survival or contralateral lung metastasis [66–68]. Subsequent studies demonstrated that *ephA2* is part of a gene signature in NSCLC patients harboring somatic mutations in EGFR [69], an interesting parallel to the interaction between EphA2 and EGFR family members in breast cancer [reviewed in [9]]. EphA2 is also mutated in human NSCLC, as reported by Faoro et al. who demonstrated that an activating mutation G391R in EphA2 confers constitutive activation and activated signaling pathways that promote invasion [70]. *Ephrin-A3* is also reportedly upregulated in human lung cancer [56]. In addition to changes in receptor levels, somatic mutations have been found in nearly all Eph receptors. Notably, 11 somatic mutations in EphA3 receptor were identified in 5–10% of lung cancer, placing EphA3 among 27 most frequently mutated genes in human lung adenocarcinoma [[52, 71–73]; Zhuang et al., submitted]. However, as these mutations are scattered throughout the receptor, and it is unclear whether they are "driver" or biologically neutral "passenger" genetic mutations. Elucidating the effects of these mutations will greatly improve our understanding of how Eph receptor functions in cancer. Indeed, insight into the function of individual domains, particularly putative and confirmed phosphotyrosine residues, will no doubt be provided by studies such as those conducted by Shi et al. [74]. We did observe, however, that overexpression of wild-type EphA3, but not several variants harboring mutations found in human cancers, significantly inhibited tumor cell survival in culture and in xenograft models, suggesting that they do play an important, possibly tumor suppressive role, in NSCLC (Zhuang et al., submitted).

Class B family members have also been detected in human lung cancer. EphB3 overexpression in human NSCLC samples correlated with tumor size, differentiation, and metastasis, in agreement with laboratory studies showing tumor promoting effects in culture and in mouse models [75]. Recent phosphoproteomic profiling analysis suggests that interplay between ephrin-B3 silencing in NSCLC lines and stabilization of EphA2 by phosphorylation Akt target Ser-897 may promote stability of EphA2 to support tumor cell survival [76]. It would be of great interest to determine if these observations are relevant to human disease, as they suggest that cross-talk between class A and class B Eph family molecules may also play a critical role in tumor progression.

Conclusions

In summary, Eph RTKs are altered in several types of human cancers and many represent promising targets for novel, molecularly targeted therapies, particularly in breast, colon, and lung carcinomas. While the studies discussed here demonstrate the relevance of Eph RTKs and their ligands to human malignancies, several questions remain. In spite of the wealth of information regarding expression profiles in human cancer, gaps remain in our knowledge for some family members, as well as for the spectrum of tumor progression (e.g. stage and grade). Given the complexity of signaling regulated by this RTK family, as well as extensive cross-talk with other RTK families involved in cancer, future efforts should be aimed at understanding how Eph receptor expression and function is modulated in the context of relevant cancer pathways.

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Table 1

Expression profiles for Eph A class RTKs and ligands in human epithelial malignancies

Eph A Class Family Member	Cancer Type	↑/↓ Relative to Normal Tissue	References
EphA1	Ovarian	↑	[77]
	Colon, Gliobastoma	↓ (↑associated with necrosis)	[53, 55, 56, 78]
	Gastric	↑	[79, 80]
	Pancreatic	↑(associated with tumor size)	[81]
	Hepatocellular	↑(associated with angiogenesis)	[82, 83]
EphA2	Breast, Lung, Gastric, Colon, Kidney;	↑ (tumor and endothelium)	[10–12, 14, 84]
	Breast	↑	(Brantley-Sieders et al., in preparation)
	Breast	↑ (HER2+ samples)	[15]
	Lung (NSCLC)	↑(correlates with smoking history, brain metastasis, EGFR somatic mutation); mutation G391R associated with invasion	[66–70]
	Ovarian	↑(correlates with MVD)	[77, 85]
	Colon	↑(correlates with MVD)	[57, 60]
	Gastric	↑	[58, 59, 86]
	Esophageal	↑	[87, 88]
	Gliobastoma	↑(PS897-EphA2)	[89–91]
	Pancreatic	↑(associated with patient age)	[81, 92]
	Hepatocellular	↑	[93]
	Prostate	↑	[94]
	Urinary Bladder	↑	[95]
EphA3	Lung (NSCLC)	↓(and/or mutated)	[[71, 72, 96, 97]; Zhuang et al., submitted]
	Hepatocellular	mutated	[98]
	Glioblastoma	mutated	[99]
	Melanoma	mutated	[99]
EphA4	Breast	↑	(Brantley-Sieders et al., in preparation)
	Colon	↑(correlates with liver metastases)	[64]
	Glioblastoma	↑	[100]
	Pancreatic	↑(associated with proliferation)	[81, 101]
EphA5	Breast	↓	[26]
	Pancreatic	↑(associated with prognosis)	[81]
EphA6	Colon	↓	[56]
	Kidney	↓	[56]
EphA7	Breast	↑	(Brantley-Sieders et al., in preparation)
	Colon	↓	[54]
	Glioblastoma	↑	[102]
	Pancreatic	↑(associated with prognosis)	[81]
	Prostate	↓(promoter hypermethylation)	[103]
EphA8	Colon, Glioblastotma	↓	[56]

Eph A Class Family Member	Cancer Type	↑/↓ Relative to Normal Tissue	References
Ephrin-A1	Breast, Lung, Gastric, Colon, Kidney Ovarian Gastric Esophageal Melanoma Urinary Bladder Glioblastoma	↑(tumor and endothelium) ↑ ↑ ↑ ↑ ↑ ↓	[10] [77] [58, 86] [87] [104] [95] [91]
Ephrin-A2	Hepatocellular	↑	[105]
Ephrin-A3	Lung	↑	[56]
Ephrin-A5	Ovarian Glioblastoma	↑ ↓	[77] [106]

Table 2

Expression profiles for Eph B class RTKs and ligands in human epithelial malignancies.

Eph B Class Family Member	Cancer Type	↑/↓ Relative to Normal Tissue	References
EphB1	Colon Gastric	↓(transition to invasive cancer) ↓(transition to invasive cancer)	[46] [47]
EphB2	Breast Colon Gastric Glioblastoma Neuroblastoma Hepatocellular	↑ ↑/↓(transition from adenoma to carcinoma) ↓ ↑tyrosine phosphorylation ↑(higher levels in low stage) ↑	[22] [42]/[43, 44, 48, 49] [50] [107] [108] [56]
EphB3	Colon Lung (NSCLC)	↑/↓ (transition from adenoma to carcinoma)* ↑	[42]/[43, 45] [75]
EphB4	Breast Ovarian Cervix Endometrium Colon Prostate	↓/↑ ↑ ↑(correlates with MVD) ↑ ↑/↓(transition from adenoma to carcinoma) ↑	[21–23]/(Brantley-Sieders et al., in preparation) [73] [109, 110] [111, 112] [40–42]/[43, 51] [113]
EphB6	Breast Glioma Neuroblastoma Melanoma	↓/↑ ↑variant protein ↑(higher levels in low stage) ↓	[27–31] /(Brantley-Sieders et al., in preparation) [114, 115] [116–118] [119]
Ephrin-B1	Ovarian Glioblastoma Hepatocellular	↑ ↑total and tyrosine phosphorylated ↑associated with tumor angiogenesis	[120] [121] [122]
Ephrin-B2	Ovarian Cervix Endometrium Colon Esophageal Glioblastoma Melanoma	↑ ↑(correlates with MVD) ↑ ↑ ↑ ↑total and tyrosine phosphorylated ↑	[73, 120] [109, 110] [111, 112] [41, 42] [123] [121] [124]
Ephrin-B3	Ovarian Glioblastoma Neuroblastoma	↑ ↑/increased tyrosine phosphorylation ↑(higher levels in low stage)	[120] [125]/[126] [116–118]