The Eph Receptor/Ephrin System: An Emerging Player in the Invasion Game

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Abstract
Eph receptor tyrosine kinases (Ephs) and their membrane-anchored ligands (ephrins) form a vital cell communication system capable of bi-directional signaling. This Eph receptor/ephrin system has classically been demonstrated to play a role in development. However, emerging evidence has revealed differential expression of Ephs and ephrins in numerous cancers. Recent studies suggest that this system influences invasive behaviour, promoting a more aggressive and metastatic phenotype. Hence, this mini-review summarizes the current understanding of the contribution of both Eph receptors and their ephrin ligands to invasiveness in cancer, as well as their use as potential therapeutic targets.

Eph Receptor/ Ephrin Signaling
Eph receptors (erythropoietin-producing human hepatocellular carcinoma) comprise the largest family of vertebrate receptor tyrosine kinases. In concert with their ephrin ligands (Eph family receptor interacting proteins), they form an essential cell-cell communication system capable of bi-directional signaling, where receptor signaling is designated “forward” and ephrin signaling is “reverse” (Fig.1; Kullander and Klein, 2002; Heroult et. al., 2006).

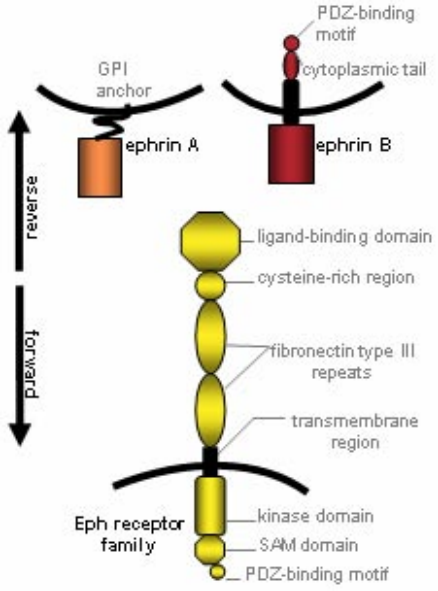

Fig. 1. Bi-directional signaling in the Eph receptor/ephrin communication system.

Eph receptors have been divided into an EphA subclass (8 members) and an EphB subclass (6 members) on the basis of sequence similarity and ligand affinity (Gale et. al., 1996). Ephrin ligands have also been divided into two subclasses: GPI-linked ephrin As (5 members) and transmembrane ephrin Bs (3 members). Although promiscuity has been observed, the ephrin A ligands preferentially bind to EphA receptors, while ephrin B ligands bind preferentially to EphB receptors (Heroult et. al., 2006).

The Eph receptor/ephrin system has been demonstrated to play a role in numerous biological processes. Generally, Ephs and ephrins are thought to act as graded molecular tags which translate the density of their cognate partner on opposing membranes into precisely graded cellular responses, resulting in cell-contact repulsion or cell-cell adhesion. Through this mechanism, the Eph receptor/ephrin system has been shown to direct the positioning, adhesion and migration of cells and cell layers during development (Wimmer-Kleikamp and Lackmann, 2005). This system has also been implicated in immune regulation (Wu and Luo, 2005), as well as in central nervous system injury and disease (Goldshmit et. al., 2006). Recently, a role for the Eph receptor/ephrin system has also emerged in cancer, especially in the area of invasive behaviour.

Eph Receptors and Ephrins in Cancer
Though the majority of research has studied the Eph/ephrin role in development, new evidence suggests strong involvement in tumourigenesis, including metastasis, angiogenesis, and invasion (Dodolet and Pasquale, 2000; Wimmer-Kleikamp and Lackmann, 2005). Upon identification of EphA1, the first member of the Eph family, breast, liver, lung and colon tumours showed overexpression, but no evidence of gene amplification nor mutation (Hirai, et. al., 1987; Dodolet and Pasquale, 2000; Surawska et. al., 2004). Genes for other Eph receptors and ephrins have since been recognized to be overexpressed or differentially expressed in numerous human cancers (for review, see Surawska et. al., 2004). Mounting evidence documents a strong correlation between the expression levels of many Eph/ephrin family members and increased invasiveness of a number of aggressive tumours, including breast cancer, colon carcinoma, malignant melanoma, kidney carcinoma, ovarian cancer, neuroblastomas, and prostate cancer (Wimmer-Kleikamp and Lackmann, 2005). It has also been suggested that elevated Eph/ephrin expression levels may be diagnostic for specific invasive, metastatic tumours and reduced patient survival rates (Saito et. al., 2004; Nakada et. al., 2006).

Eph Receptors and Ephrins in Invasion
For the purpose of this review, invasion is defined as “penetration of tissue barriers, such as basement membrane and interstitial stroma, by cells” (Friedl and Wolf, 2003). It occurs during normal cell morphogenesis, wound healing, and in malignant cells. Numerous Eph receptors and ephrins have been noted to influence or correlate with invasive behaviour. Cytotrophoblast commitment to uterine invasion, for example, was noted

to be accompanied by upregulation of ephrin B1 and downregulation of EphB4 (Red-Horse et. al., 2005). Additionally, ephrin A5 expression was found to increase invasive behaviour, anchorage-independent growth, and morphological transformation of murine fibroblasts (Campbell et. al., 2006).The majority of research on Ephs and ephrins in invasion, however, has focused on their role in cancer (Table 1).

With respect to the EphA/ephrin A subsystem, Saito et. al. (2004) noted that expression level of EphA2 had a statistically significant relationship with liver metastasis, lymphatic vessel invasion, and clinical stage. Alford et. al. (2007) found that transglutaminase-cross-linked ephrin A1 and A5 bound to EphA receptors and promoted invasion and migration of HeLa cells. Moreover, Iida et. al. (2005) reported that the poor prognosis of patients with AFP-producing hepatocellular carcinoma was partially caused by ephrin A1 expression, which induced expression of genes related to tumour cell growth, angiogenesis, invasion, and metastasis.

With respect to involvement of the EphB/ephrin B subsystem in invasion, a greater depth of investigation has occurred, resulting in both observational and mechanistic insight. Nakada et. al. (2004) demonstrated that EphB2-transfected glioma cells showed increased invasive behaviour both *in vitro* and in an *ex vivo* rat brain slice. Furthermore, glioma invasion was promoted by activation of EphB2 or inhibited by blocking EphB2. This invasive behaviour was revealed to be controlled through an EphB2/R-Ras signaling pathway (Nakada et. al., 2005).

EphB4 was shown to confer survival and invasive properties in head and neck squamous cell carcinoma (Masood et. al., 2006). Moreover, Alam et. al. (2007) reported that histoscores and mRNA levels of EphB4 and ephrin B2 significantly increased with clinical stages, dedifferentiation, and myometrial invasion in uterine endometrial cancer. Similarly, Takai et. al. (2004) noted that ephrin B2 and EphB4 expression were significantly associated with the presence of clinical stage, histological grade, and invasion to >1/2 myometrium in endometrial carcinomas. Currently, controversy surrounds the role of EphB4 in invasiveness and potential prognosis in breast cancer, since this receptor has been reported to act both as a tumour suppressor and a tumour promoter (Noren et. al., 2006; Noren and Pasquale, 2007).

Aside from the observations described in endometrial carcinomas, ephrin B2 mRNA expression was further reported to be elevated in higher stage neoplasms and in patients with high-risk AMES in malignant thyroid cancer (Kebebew et. al., 2005). Ephrin B2 was also visualized in the invasive front of malignant melanoma (Meyer et. al., 2005).

In the case of the correlation of ephrin B1 and B3 expression with invasive properties in cancer, mechanistic insight has also been provided. For ephrin B1, tyrosine phosphorylation of this ligand promoted invasion of gastric scirrhous carcinoma cells both *in vitro* and *in vivo* (Tanaka et. al., 2007a). Through the

Table 1. Invasive involvement of Eph receptors and ephrin ligands in cancer.

Ligand/ Receptor	Cell Line(s)/ Tissue(s)	Observation(s)	Reference(s)
ephrin A1	hepatocellular carcinoma; HeLa cells	poor prognosis of patients with AFP-producing hepatocellular carcinoma is partially caused by ephrin A1 expression, which induces expression of genes related to tumour cell growth, angiogenesis, invasion, and metastasis; transglutaminase-cross-linked ephrin A1 and A5 bind to A-type Eph receptors and promote invasion and migration of HeLa cells	Iida et. al., 2005; Alford et. al., 2007
ephrin A5	HeLa cells	transglutaminase-cross-linked ephrin A1 and A5 bind to A-type Eph receptors and promote invasion and migration of HeLa cells	Alford et. al., 2007
ephrin B1	gastric scirrhous carcinoma; pancreas cancer cell lines	tyrosine phosphorylation of ephrin B1 promotes invasion of cancer cells *in vitro* and *in vivo*; expression of ephrin B1 promotes the invasion of cancer cells in vivo, which requires the C-terminus of ephrin B1	Tanaka et. al., 2007a; Tanaka et. al., 2007b
ephrin B2	endometrial carcinoma; malignant thyroid neoplasms; malignant melanoma; uterine endometrial cancer	ephrin B2 and EphB4 expression are significantly associated with the presence of clinical stage, histological grade, and invasion to >1/2 myometrium; ephrin B2 mRNA expression is elevated in higher TNM stage neoplasms and in patients with high-risk AMES; prominent expression of ephrin B2 is noted in the invasive front of malignant melanoma; histoscores and mRNA levels of ephrinB2 and EphB4 significantly increase with clinical stages, dedifferentiation and myometrial invasion	Takai et. al., 2004; Kebebew et. al., 2005; Meyer et. al., 2005; Alam et. al., 2007
ephrin B3	invasive glioma cells; gliomas	ephrin B3 is expressed in invasive glioma cells; ephrin B3 expression, phosphorylation, and signaling through Rac1 are critically important to glioma invasion	Hoelzinger et. al., 2005; Nakada et. al., 2006
EphA2	colorectal cancer	expression level of EphA2 has a statistically significant relationship with liver metastasis, lymphatic vessel invasion and clinical stage	Saito et. al., 2004
EphB2	gliomas; glioma cells; colorectal cancer	U251 cells stably transfected with EphB2 show more pronounced invasive growth in an *ex vivo* rat brain slice and glioma cell invasion is promoted by activation of EphB2 or inhibited by blocking EphB2; EphB2/R-Ras signaling regulates glioma cell adhesion, growth, and invasion; reduced expression of EphB2 parallels invasion and metastasis in colorectal tumours	Nakada et. al., 2004; Nakada et. al., 2005; Guo et. al., 2006
EphB4	endometrial carcinoma; breast cancer; head and neck squamous cell carcinoma; uterine endometrial cancer	ephrin B2 and EphB4 expression are significantly associated with the presence of clinical stage, histological grade, and invasion to >1/2 myometrium; EphB4 activates an antioncogenic Abl-Crk pathway that inhibits breast cancer cell viability, proliferation, motility and invasion; histoscores and mRNA levels of ephrinB2 and EphB4 significantly increase with clinical stages, dedifferentiation and myometrial invasion; expression of EphB4 in HNSCC tumor cells confers survival and invasive properties	Takai et. al., 2004; Noren et. al., 2006; Masood et. al., 2006; Alam et. al., 2007
EphB6	breast cancer	downregulation of EphB6 correlates with the most invasive aggressive cell line and may serve as a prognostic indicator in breast cancer	Fox and Kandpal, 2004

use of multiple cell lines, including pancreatic cancer cells, it was demonstrated that the C-terminus of ephrin B1 was responsible for conferring the increased invasive properties through activation of matrix metalloproteinase-8 secretion (Tanaka et. al., 2007b). For ephrin B3, increased expression was noted specifically in invasive glioma cells (Hoelzinger et. al., 2005), and this elevated ephrin B3 expression accompanied by phosphorylation leading to signaling through Rac1 was identified as critically important to glioma invasion (Nakada et. al., 2006).

It has been proposed that Ephs operate during tumour progression through uncontrolled re-emergence of their developmental cell guidance capacity, promoting tumour metastasis, invasion and neo-angiogenesis (Wimmer-Kleikamp and Lackmann, 2005). Interestingly, some studies have noted a down-regulation of Eph receptor expression corresponding to an invasive phenotype in certain cancers. For example, Fox and Kandpal (2004) reported that decreased expression of EphB6, which was down-regulated in the most aggressive breast cancer cell line, was particularly important in invasiveness. Additionally, Guo et. al. (2006) observed that reduced expression of EphB2 paralleled invasion and metastasis in colorectal tumours. Moreover, Batlle et. al. (2005) also noted that loss of EphB2 in colorectal cancer correlated with degree of malignancy. Thus, researchers have chosen to focus on individual Ephs and ephrins in specific types of cancer when designing potential therapies, instead of working from a general model.

Therapeutic Implications

Based upon the observed differential expression of Eph receptors and their ephrin ligands in a wide variety of cancers, it is not surprising that components of this system have been flagged as potential therapeutic targets. One approach has been antibody targeting of Ephs identified as consistently upregulated in specific cancers, thus offering selective targeting of tumour cells while minimizing harm to healthy tissues. This method has been used to target EphA2 in breast cancer cells (Carles-Kinch et. al., 2002) and EphB2 in colorectal cancer (Mao et. al., 2004).

Another approach is to use antagonistic peptides that display selective binding. This method has been used in the case of EphB2 (Chrencik et. al., 2007) and EphA2 (Koolpe et. al., 2002). Recently, Yamaguchi et. al. (2007) engineered a vaccine using dendritic cells pulsed with EphA2-derived peptides that resulted in long-term antitumour immunity against a rechallenge with MC38 tumour cells in a murine colon cancer model.

Function-blocking soluble Eph receptors have also been used to interfere with tumour growth and properties. As with the peptide approach, this method has been demonstrated for both the EphA and EphB subclasses (Brantley et. al., 2002; Martiny-Baron et. al., 2004; Kertesz et. al., 2006; Yang et. al., 2006). A recent encouraging result was reported by Dobrzanski et. al. (2004) who found that administration of EphA2/Fc profoundly inhibited the growth of primary tumours and the development of peritoneal, lymphatic, and hepatic metastases in a murine pancreatic ductal adenocarcinoma model. Interestingly, this approach was also employed from a ligand perspective by introducing soluble ephrin A1-Fc to suppress growth of EphA2-expressing gastric cancer cells (Nakamura et. al., 2005).

Eph/ephrin-influenced cytoskeletal signal transduction pathways dealing with cell motility, tumour invasiveness and metastatic potential have also been investigated as therapeutic targets. Such flagged components have included FAK, CRK, Rho, paxillin, Cbl, and Grb4 (Surawska et. al., 2004). Further understanding of the Eph/ephrin system will bring forth more candidate targets.

Summary

Due to the emergence of the Eph receptor/ephrin system as a contributor to cellular invasive behaviour, it is likely that this system will remain a high priority in oncology for the development of new therapies and treatments. For example, a currently underutilized approach is the use of RNA interference, the sequence-specific gene silencing induced by double-stranded RNA (Campbell and Choy, 2005). Numerous studies have utilized RNA interference to explore the effect of an Eph or ephrin knock-down *in vitro*, but have yet to engineer a successful *in vivo* method for the treatment of cancer.

Further studies in the manipulation of the Eph receptor/ephrin system will aid in engineering cancer therapies and in elucidating the complexity and additional functional implications of the system.

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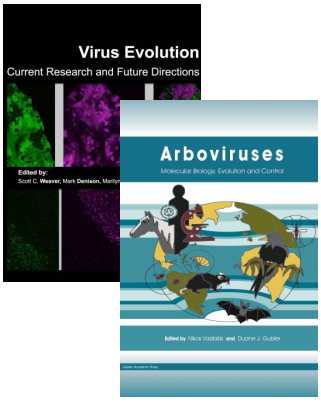

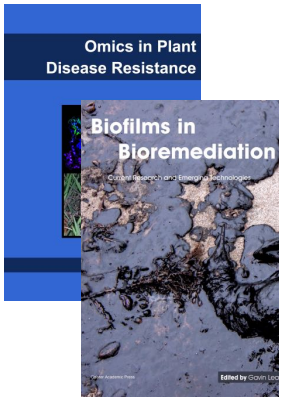

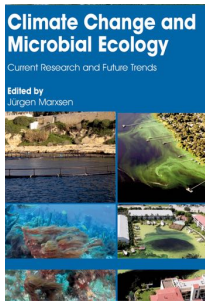

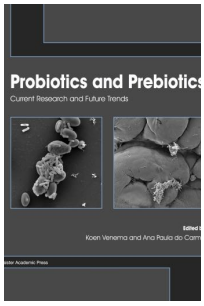

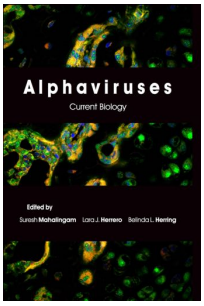

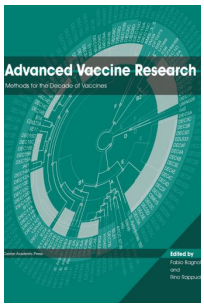

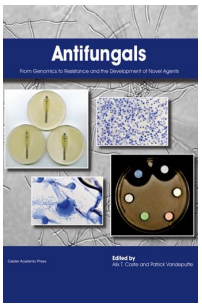

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