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EDITORIAL

EPH-EPHRIN in human gastrointestinal cancers

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Abstract

Ever since its discovery two decades ago, the erythropoietin-producing hepatoma (EPH)-EPHRIN system has been shown to play multifaceted roles in human gastroenterological cancer as well as neurodevelopment. Overexpression, amplification and point mutations have been found in many human cancers and many investigators have shown correlations between these up-regulations and tumor angiogenesis. Thus, the genes in this family are considered to be potential targets of cancer therapy. On the other hand, the down-regulation of some members as a result of epigenetic changes has also been reported in some cancers. Furthermore, the correlation between altered expressions and clinical prognosis seems to be inconclusive. A huge amount of protein-protein interaction studies on the EPH-EPHRIN system have provided a basic scheme for signal transductions, especially bi-directional signaling involving EPH-ERPHRIN molecules at the cell membrane. This information also provides a manipulative strategy for harnessing the actions of these molecules. In this review, we summarize the known alterations of EPH-EPHRIN genes in human tumors of the esophagus, stomach, colorectum, liver and pancreas and present the perspective that the EPH-EPHRIN system could be a potential target of cancer therapy.

Key words: Erythropoietin-producing hepatoma; EPH-EPHRIN; Gastric cancer; Colorectal cancer; Methylation; Secreted form

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INTRODUCTION

Erythropoietin-producing hepatoma (EPH) amplified

sequence is an acronym for erythropoietin-producing hepatocellular carcinoma[1] from which the first member of the EPH family was isolated. The involvement of one gene in this family in human gastric cancer was reported in 1994[2] prior to the designation of this gene as EPHB2 according to a unified nomenclature system[3]. EPH and EPHRIN, receptor kinases EPH and their ligands EPHRIN (EFN), were classified according to the structures of the ligands, the EPHRINs. GPI-anchored-type ligands were called EPHRIN-As and transmembrane-type ligands were called EPHRIN-Bs. The corresponding receptors recognizing each ligand were called EPH-As and EPH-Bs. The relationships are mostly exclusive except for EPHA4-EPHRINB2 and EPHB4-EPHRINA2. Thus, we can say that the EPH-EPHRIN (or EPH-EFN) system has been recognized as a major player in human gastrointestinal carcinogenesis for more than 20 years[4]. In this paper, we review the accumulated data on alterations in EPH receptors in human gastrointestinal tract cancers by each category.

The mutations and a summary of the up-regulation and down-regulation of the EPH receptors are shown in Tables 1 and 2. Readers can access a database containing updates on alterations of genes of interest in specific organs[5] at the web site http://www.sanger.ac.uk/genetics/CGP/Studies/.

EPHA FAMILIES IN HUMAN GASTROINTESTINAL CANCERS

EPHA1

The original isolation paper described the over-expression and not the amplification of *EPHA1* in human colorectal cancer[1]. However, the significance of *EPHA1* in human cancers is far from being solved. Although *EPHA1* was first suspected to be an oncogene (growth factor receptor-like epidermal growth factor receptor), many investigators have recently focused on its down-regulation in human tumors and its possible clinical significance[6,7]. On the other hand, from the standpoint of the pro-angiogenic activity of EPHAs, Chen *et al*[8] reported that the silencing of *EPHA1* induces an anti-angiogenic effect in human hepatocellular carcinoma. Recently, down-regulation by epigenetic silencing was shown to be correlated with a poor survival outcome in patients with colorectal cancer[7,9]. Furthermore, Wang *et al*[10] extended their observation on colorectal cancer to gastric cancer; that is, they reported the correlation between *EPHA1* expression and gastric cancer metastasis and survival. Contrary to the situation reported by Dong *et al*[6] in colorectal cancer, *EPHA1* up-regulation was related to a poor survival outcome and the metastasis of gastric cancer.

EPHA1 expression is possibly regulated by environmental factors. Doleman *et al*[11] reported that *EPHA1* expression and *EPHB4* are influenced by n-3 fatty acid eicosapentaenoic acid (EPA). This observation may imply the important involvement of *EPH* pathways in the mechanism responsible for the presumed health benefits of polyunsaturated fatty acids (PUFA).

Table 1 Somatic mis-sense mutations of erythropoietin-producing hepatoma receptors in colon and stomach (http://www.sanger.ac.uk/genetics/CGP/Studies/, August 30, 2010)

	Amino acid substitutions		Organs
EPHA2	777G>S		Stomach
EPHA3	792S>P	806D>N	Colon
EPHA6	649R>S	813K>N	Stomach
EPHA7	768S>I		Colon
EPHA8	179R>C	873D>N	Colon, Stomach
EPHB1	719I>V	743R>Q	Stomach
EPHB4	889R>W	1030I>M	Colon,Stomach

EPH: Erythropoietin-producing hepatoma.

EPHA2

Most research published so far about the relationship between *EPHA2* expression and human gastrointestinal cancers has indicated that *EPHA2* up-regulation in tumor cells results in a more aggressive nature[12-14]. In addition, *EPHA2* has been extensively investigated from the standpoint of cell and vascular biology. The ligand for this receptor is EPHRINA1 (EFNA1), isolated as an acute phase reactant induced by TNF in endothelial cells[15]. This observation has tempted many investigators to study the expressions of *EFNA1* and its receptor *EPHA2* in tumor cells and their relation with tumor angiogenesis. In human cancers, Kataoka[12] demonstrated an increased microvessel density in *EPHA2* over-expressing colorectal cancers. The mechanisms by which the overexpression of EPHA2 contributes to the aggressive behavior of cancer cells have been widely debated. Fang *et al*[16] discussed the importance of receptor phosphorylation and the kinase activity of EPHA2 toward the aggressive and migratory nature of tumor cells. Miao *et al*[17] on the other hand, reported that the activation of *EPHA2* inhibits the Ras/MAPK pathway, that is, the activation of *EPHA2* may reduce the aggressive nature of tumor cells. The degradation of *EPHA2* is dependent on ligand inducible phosphorylation[18]; thus, the clinico-pathological effects of *EPHA2* activation should be assessed, including the complex situation of the genetic profile of the tumor cells themselves and their microenvironment.

EPHA2 and its major ligand EFNA1 are perturbed by various metabolites including deoxycholic acid (DCA) and its derivative. Li *et al*[19] showed the up-regulation of EPHA2 by DCA in colorectal cancer cells. This may be another example of the involvement of EPH pathways and endogenous metabolites in addition to *EPHA1* and PUFA.

EPHA3

There have been few reports on the alteration of *EPHA3* in human tumors until a recent high throughput sequencing project identified a high prevalence of a somatic mutation in *EPHA3* in human cancers[20,21]. The somatic mutation in *EPHA3* resides in D806 where the residue is evolutionally conserved (Table 1). The prevalence does not seem to be high in any population; actually, no mutations of *EPHA3* were observed in follow-up studies of

Table 2 Up and down regulations of erythropoietin-producing hepatoma receptors in human cancers[4]

	Up-regulation		Down-regulation		
	Overexpression	Amplification	Promoter methylation	Loss of heterozygosity	Others or unknown
EPHA1	Stomach		Colon	Colon	Colon
EPHA2	Stomach, colon, esophagus			Colon	(Melanoma)
EPHA3			(Lung)		
EPHA4	Colon				
EPHA5					
EPHA6					
EPHA7	Stomach, colon		Stomach, colon		
EPHA8				Stomach, colon	
EPHB1					
EPHB2	Stomach, colon	Stomach	Colon	Colon	(Prostate)
EPHB3		Colon			
EPHB4		Colon	Colon	Colon	
EPHB5					
EPHB6	(Neuroblastoma)				

No published data in the blanks. Parenthesis indicate non-GI tract cancers. EPH: Erythropoietin-producing hepatoma.

Table 3 Receptors and ligands corresponding

	EFNA1	EFNA2	EFNA3	EFNA4	EFNA5	EFNB1	EFNB2	EFNB3
EPHA1	x							
EPHA2	x	x	x	x	x			
EPHA3	x	x	x	x	x			
EPHA4	x	x	x	x	x		x	x
EPHA5	x	x	x	x	x			
EPHA6		x						
EPHA7		x			x			
EPHA8	x	x	x	x	x			
EPHB1						x	x	x
EPHB2						x	x	x
EPHB3						x	x	x
EPHB4						x	x	x
EPHB5								
EPHB6						x	x	x

x indicates a known interaction. Each binding constant is shown in the reference Bowden *et al*[27]. EPH: Erythropoietin-producing hepatoma.

46 Japanese patients with colorectal cancer reported by Shao *et al*[22]. Cell signaling studies using a culture system disclosed a role of *EPHA3* in the formation of a cell's shape[23]. Thus, changes in *EPHA3* are likely to produce particular morphological and biological characteristics in the tumor cells carrying these changes, although no correlation between the *EPHA3* status and the clinico-pathological features of gastrointestinal cancers has yet been described. Although the clinical relevance is unknown, there is a report investigating the LINE-1 methylation pattern in the introns of *EPHA3* in tumor cells[24].

EPHA4

The over-expression of *EPHA4* has been reported in gastric and colorectal cancers[25,26]. In both cancers, the over-expression of *EPHA4* is an ominous sign with a shorter survival period and frequent liver metastasis respectively. *EPHA4* is the only type A receptor that binds a B family ligand, EPHRIN(EFN)B2, in addition to a type A ligand, EPHRIN(EFN)A2 (Table 3). A structural study has been conducted to reveal the stereoscopic interactions between several members of EPH receptors and EPHRIN(EFN)s[27]. The potential significance of *EPHA4* over-expression in clinical oncology and the possibility of its use as a therapeutic target remain unknown.

EPHA5

There is no information regarding alterations in *EPHA5* in human gastrointestinal cancers. *EPHA5* is not expressed in the intestine at any age, as reported by Islam *et al*[28].

EPHA6

Research on *EPHA6* in the gastrointestinal tract is sparse. *EPHA6* is commonly expressed in the testis and brain[29].

EPHA7

Since the first description of the down-regulation of *EPHA7* in colorectal cancer[30], several papers have assessed the expression of *EPHA7* in human gastrointesti-

nal cancers[31], human lung cancer[32] and prostate cancer[33]. The biological basis for these clinicopathological observations and their significance in oncology remain to be investigated. The promoter methylation of *EPHA7* was the first example of down-regulation by methylation in *EPH* receptors but a subsequent survey of other *EPH* receptors, including *EPHB* receptors in colon cancer, produced negative results[34]. Another topic concerning *EPHA7* is its secretory form. The secretory form of *EPHA7* contains only the extracellular part of the molecule and does not anchor at the cell membrane. Its biological and clinical significance remain unknown. A secretory form of *EPHA7* is known to exist in malignant lymphoma[35] and lung cancer[32] but no study has been conducted on the presence of the secretory form of *EPHA7* in clinical gastrointestinal cancer.

Although the clinical significance is still unclear, Kim *et al*[36] reported a single nucleotide polymorphism (SNP) at the *EPHA7* locus, rs2278107; this SNP was related to the chemoresponsiveness to fluoropyrimidine-based adjuvant chemotherapy for colorectal cancer[36].

EPHA8

EPHA8 was screened for mutation in Japanese colorectal cancer but no mutations were found[22], similar to other *EPHA* receptors such as *EPHA3* and *EPHA7*. The *EPHA8* receptor induces the sustained up-regulation of MAP kinase; thus, it is supposed to play a role in tumor cell growth and proliferation[37]. *EPHA8* is expressed during the fetal period of intestinal morphogenesis[28] and missense mutations in stomach cancer and colon cancer are known (Table 1).

EPHB1

EPHB1 has been investigated in terms of signal transduction involved in the biological behavior of tumor cells[38,39], but little information is available on its status in human clinical cancer. An *EPHB1* mutation was recently identified in ovarian cancer and missense mutations have also been found in gastric cancer[40] (Table 1).

EPHB2

EPHB2 is the most extensively studied member of *EPH* receptors in the field of oncology. Kiyokawa *et al*[2] reported the overexpression of *EPHB2* in human gastric cancer and assigned it to the chromosomal locus at 1p36 which many investigators have assumed to be a tumor suppressor locus of human colon cancer because of the frequent loss of heterozygosity that has been documented[41]. Subsequently, Oba *et al*[42] demonstrated the loss of heterozygosity of the *EPHB2* locus in human colorectal cancer. Furthermore, Batlle *et al*[43] argued that *EPHB* receptor activity could suppress the progression of colorectal cancer and *EPHB2* is now viewed, at least in some contexts, as a tumor suppressor or a suppressor against tumor progression[26,44-48], although different aspects have also been discussed[49]. A group led by Hans Clevers put forward the comprehensive idea of *EPHB2-EPHRINB1* interplay at the bottom of human colon crypts[50,51]. They showed the clear territory of *EPHB2* and *EPHRINB1* in a human colorectal crypt, its important role in cell positioning and the ordered developmental migration of intestinal cells using *EphB2/EphB3* knockout mice[51]. This view is now prevalent[52] and they have further refined the concept of a stem cell unit in human gastrointestinal crypts[53,54]. Based on the mutually exclusive localization of *EPHB2* and *EPHRINB1*, Cortina suggested that tumor compartmentalization arising from the repulsive action of cells expressing *EPHB2* and *EPHRINB1* is a possible mechanistic basis for tumor suppression by the *EPHB2-EPHRINB1* system[55].

Then, what happened to the previous interpretation for the over-expression of *EPHB2* in human cancer[2,56,57]? Mao[58] reported *EPHB2* as a therapeutic antibody drug target for *EPHB2* over-expressing tumors. Mutation analyses in kinase genes have been very popular and somatic mutations of *EPHB2* have also been reported in many cancers[59,60], including GI tract cancers[61,62].

However, these mutations occur mostly in the microsatellite repeats of tumors with microsatellite instability or nonsense mutations causing RNA decay. No naturally occurring missense mutation that may positively or negatively influence the kinase activity of *EPHB2* has ever been reported. At this moment, we can only say that individual tumors may have an individual *EPHB2* status in an individual environment. The prevalence of methylation in the *EPHB2* promoter, on the other hand, is low compared with RASSF2 and O-6-methylguanine-DNA methyl transferase (MGMT) in early colorectal tumors[63].

There are reports investigating the possible contribution of germline *EPHB2* variants to rare polyposis syndrome[64,65]. The detailed mechanistic basis controlling the *EPHB2-EPHRIN* (*EFN*) *B1* system has also been investigated. Tanaka *et al*[66] reported that C-terminal *EFNB1* regulates matrix metalloproteinase secretion and that the phosphorylation of *EFNB1* regulates the dissemination of gastric cancer cells in an animal model[66]. He also showed the successful suppression of peritoneal dissemination in an animal model using an *EFNB1*-derived peptide[67]. The translational approaches using this method (use of EFNB1 peptide to suppress human cancer dissemination) have not yet been shown.

EPHB3

The localization and function of *EPHB3* partially overlaps with *EPHB2* in a Paneth cell compartment. *EPHB3* also has *EFNB1* as a ligand. Both are controlled by the beta-catenin/Tcf4 pathway[51].

Chiu reported that the over-expression of *EPHB3* enhanced cell-cell contact and suppressed tumor growth in HT-29 human colon cancer cells[68]. The defect in the positioning of Paneth cells is thought to arise from the disruption of the *EPHB2-EPHB3* system[69]. Clinicopathological information on *EPHB3* alone (not accompanied with *EPHB2*) in human gastrointestinal tract cancers remains limited. A clinical interpretation of the over-expression and/or amplification of *EPHB3* (Figure 1) in gastrointestinal cancer[70,71] awaits further investigations.

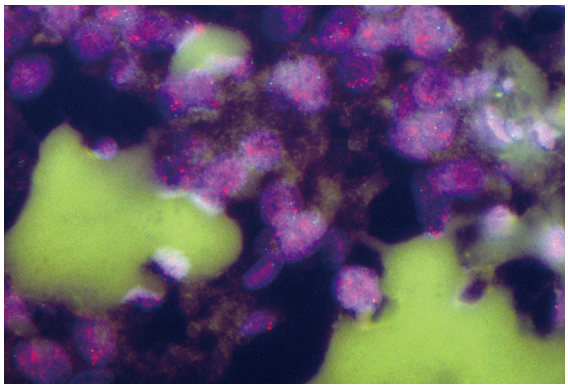

Figure 1 Fluorescence in situ hybridization of *EPHB3* (bacterial artificial chromosome RP11-328G15, red) in gastric cancer cells. Numerous red signals (more than 5) in a cell with two centromeres (green), indicating *EPHB3* amplification, are shown. The methodological details have been previously reported[69,70].

EPHB4

Kumar reported that *EPHB4* over-expression is more prevalent than *EPHB2* over-expression and the cyclic AMP-responsive element binding protein-binding protein (CBP) complex reciprocally regulates *EPHB2* and *EPHB4* (CBP complex suppresses *EPHB2* and induces *EPHB4* expression)[48]. *EPHB4* is thought to act in an *EPHB4-EPHB6* system[72] to regulate cancer cell invasiveness. The structure and dynamism on *EPHB4-EFNB2* was investigated[73,74] and the translational application of this basic knowledge awaits further investigation.

EPHB6

EPHB6 is the oldest *EPH* family member to attract enthusiastic interest from cancer researchers, especially neuroblastoma researchers. *EPHB6* is unique in that there is no kinase activity. It is one of the major genes involved in the clinico-biological behaviors of neuroblastomas[75-77]. Unlike other *EPHBs*, a suppressor role of *EPHB6* has been pointed out from an early stage of research[78-80], although its over-expression has been identified in leukemic cells[81]. A functional enigma of *EPHB6*, a kinase defective receptor affecting tumor invasiveness, has been gradually clarified in the fields of lung cancer research[82] but the role of *EPHB6* in carcinogenesis in the human digestive tract is not clear, although its alteration such as promoter methylation in lung adenocarcinoma, has been recently reported[83]. Recently, some missense variants have been reported in familial colorectal cancer[84]. Somatic changes in colorectal cancers according to ethnic stratification have revealed *EPHB6* to be one of the most frequently deleted genes in African Americans[85].

EPH RECEPTORS AS THERAPEUTIC TARGETS

Choi *et al*[86] reported the discovery of *EPHB2* receptor kinase inhibitors. They also performed crystallographic analyses of *EPHA3* and *EPHA7* in complex with their inhibitors and discussed the possibility of generating new inhibitors using a structure-based design[86]. This discovery and other structural studies[27,73,87] should pave the way for the development of drugs that specifically inhibit tumor cells over-expressing these receptors.

EPHA2 has been considered as a target for anti-angiogenesis therapy for a long time[8,88-92]. The EPHA2-Fc receptor was used to inhibit an *EFNA1-EPHA2* forward signal and to reduce neovascularization in rodent retina[91].

CONCLUSION

Although the *EPH* family is well known to be involved in the development of neural and vascular systems, their pivotal contributions to cancer biology, especially in clinical settings, remain to be elucidated. Enthusiasm regarding the use of *EPHs* as cancer therapy targets remains less than that of expectations for other groups of kinase receptors such as *EGFR, HER2, MET* and *RAF*[40,93]. The unique biological nature of *EPHs* such as bidirectional signaling and the presence of a secreted form, however, may provide a possible clue to manipulating the regulation of *EPH-EPHRIN* systems for human gastrointestinal cancer therapy. Gastrointestinal cancers have a special niche in Asian diseases in terms of their heterogeneity and uniqueness in etiology, both genetic and environmental[94]. An extensive search of EPH-EPHRIN systems in Asian gastrointestinal cancer patients will provide an important tool for the clinical management of Asian gastrointestinal cancer patients.

The real scale of the involvement of those genes in carcinogenesis in the human gastrointestinal tract still remains unclear and several research groups including Asians continue the search for molecular alterations of the EPH-EPHRIN system that may be relevant to detection and treatment of gastrointestinal cancers. The information stated here will be updated every year in future.

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