Regulation and misregulation of Eph/ephrin expression

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The erythropoietin-producing hepatocellular (Eph) receptors form the largest family of receptor tyrosine kinases. Upon interaction of the Eph receptors with their ligands the ephrins, signaling cascades are initiated downstream of both receptor and ligand, a feature known as bidirectional signaling. The Eph receptors and ephrin ligands mediate important roles in embryonic development, particularly in establishing tissue organization by mediating cell adhesion or cell repulsion. In several adult tissues, at least one Eph/ephrin pair is found to play critical roles in tissue physiology and homeostasis. In recent years numerous members of this family have gained considerable attention since changes in their expression levels are a typical feature in cancer cells. Despite the fact that Eph/ephrin developmental expression profiles are well documented, little is known on transcriptional and post-transcriptional mechanisms that permits their highly specific, graded, complementary or overlapping expression patterns. Therefore understanding the transcriptional and post-transcriptional mechanisms regulating Eph/ephrin expression has far-reaching significance in biology. This review provides an overview of the mechanisms regulating Eph/ephrin expression. We highlight important emerging mechanisms of Eph/ephrin regulation or misregulation such as epigenetics and miRNAs.

Introduction

The Eph receptors and their ligands, the ephrins, belong to the largest family of receptor tyrosine kinases.[1-3] Ephrin ligands are divided into two subclasses, A and B, depending on their mode of attachment to the plasma membrane. The ephrinA subclass ligands (A1–A5) are tethered to the membrane via a glycosylphosphatidylinositol (GPI) anchor, whereas the ephrinB subclass ligands (B1–B3) are transmembrane proteins.[3] Correspondingly, there are two Eph receptor subclasses, A and B, that exhibit preferential affinities for the two ligand subclasses;[4] yet promiscuity between ligand and receptor subclasses has also been identified.[5] Ephrins and Eph receptors require direct cell-cell contact for their activation. A unique feature of this family is that interaction of Eph receptors with their corresponding ephrin

ligands triggers signaling in both the receptor-hosting cell (termed forward signaling) and the ligand-hosting cell (termed reverse signaling).[6] Most studies to date have focused on the biological consequences of Eph/ephrin interactions, primarily in a developmental context, where they have been found indispensable for neural crest cell migration, axon guidance, the formation of tissue boundaries and vascular development.[1,3] Over the last decade studies have highlighted the involvement of Eph receptors and ephrins in organ function and in disease in the adult.[7-12] For instance, Eph/ephrins have been implicated in modulating cell migration, growth and invasiveness in cancer.[13]

Substantial progress has been made in dissecting the molecular mechanisms downstream of Eph/ephrin bidirectional signaling, several of which have shown regulation of the actin cytoskeleton by small GTPase proteins of the Ras superfamily.[14] In addition to the considerable insight gained into the functioning of this family of proteins, these studies have correspondingly exposed the highly complex and diverse gene expression patterns of Eph (*eph*) receptors and ephrin (*efn*) ligands. In many tissues, specific Eph receptors and ephrin ligands have complementary domains of expression, whereas in other tissues family members may overlap in their expression.[7,15,16] In addition to their complementary or overlapping expression domains, the receptor/ligand pairs can also be expressed in gradients[17] indicating sophisticated control mechanisms. One challenge therefore, has been to understand the transcriptional and post-transcriptional control of Eph receptors and ephrin ligands. Not surprisingly, a large extent of our knowledge on the transcriptional and post-transcriptional control of Eph receptors and ephrins has been gained form studying receptor/ligand expression in development or in tumor growth and metastasis. This review will highlight data that support clear associations between transcriptional and post-transcriptional effectors of Eph receptor and ephrin ligand regulation in developmental processes, adult tissues and in carcinogenesis.

Transcriptional Regulation

Historically, studies have focused on the transcriptional regulation of several of the Eph receptors, mainly in the context of developmental segmentation and patterning. Homeobox (HOX)-containing transcription factors emerged as one of the key regulators of Eph receptor expression.[18-33] These transcription factors contain a well conserved DNA binding motif, the

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homeodomain, which binds to the promoter of target genes to regulate their expression. Their spatially restricted expression patterns[34] may have a central role in establishing the graded and segmental gene expression patterns of Eph receptors during embryogenesis. There exists evidence for direct regulation of Eph receptors by HOX proteins. For instance the homeobox proteins HOXA1 and HOXB1 have been shown to activate rhombomere-specific *ephA2* expression in the developing mouse brain,[31] and HOXA2 was found to regulate *ephA4* in rhombomeres 3 and 5.[32] While these studies have been performed essentially in the mouse hindbrain, recent studies on endothelial cells and angiogenesis have shown the necessity for HOXA9 in the regulation of *ephB4*.[27] In studying gene regulatory patterns in developing mouse limbs, it was shown that *ephA7* is a direct downstream target of HOXD13 and HOXA13.[35,36]

The *efnA2* promoter is targeted by otx2, a homeobox transcription factor.[37] In fact, this study demonstrated that *efnA2* regulation by otx2 was important for the patterning and morphogenesis of the brain. EphA4 and ephrinA4 genes, *ephA4* and *efnA4,* have been shown to be inversely regulated. Specifically, *ephA4* is positively regulated by Twist1 while *efnA4* is negatively regulated by Twist1 and the homeobox homolog, MSX2, in coronal suture development.[38,39] Additional evidence for the inverse control of *ephA4* and *efnA* expression has been shown in the establishment of topographic motor projections in the limb by Lim homeobox proteins.[21] While the exact genetic mechanisms underlying this regulation remain to be identified the authors show that Lim1 promotes *ephA4* gene expression in motor neurons, while Lmx1b, the LIM homeobox transcription factor 1-β, inhibits ephrinA expression in the mesenchyme.

In addition to HOX-transcription factors, a handful of other transcription factors have been shown to regulate the expression of Eph/ephrins. The chick brain factor 1 (CBF1) is shown to directly regulate *efnA5* expression during development of the retinotectal map in the chick.[40] The *efnA4* promoter can be bound by the transcriptional activator nuclear factor-Y (NF-Y) in activated lymphocytes.[41] Likewise, NF-Y, in addition to Meis1 and MAZ have been shown to physically interact with the *efnB2* promoter following extensive analysis of this promoter in prenatal angiogenesis.[42] Identified transcriptional regulators of *ephB2* include TCF4 and β-catenin in the intestinal epithelium.[21,43] The transcription factor *valentino* (*val*), the zebrafish ortholog of mouse mafB/Kreisler, a bzip transcription factor, was shown to establish the mutually exclusive expression domains of *ephB4* and *efnB2* in the zebrafish caudal hindbrain.[36] The zinc-finger transcription factor Zic2 was shown to regulate the expression of *ephB1* in retinal ganglion cells; a process essential for the development of the ipsilateral projection at the mammalian optic chiasm midline.[44] Exciting new evidence shows that Eph/ephrin gene expression may be modulated by mechanical forces in different tissue types, including bone and dental pulp.[45,46] The molecular mechanisms underlying mechanical force regulation of Eph/ephrin expression in these contexts, however, are largely unknown. Recent data obtained from endothelial progenitor cells exposed to shear stress showed inverse transcriptional regulation of *efnB2* and *ephB4*.[47,48] The increase in *efnB2* expression was found

to be due to Sp1 activation and binding specifically to the *efnB2* promoter. These findings put forward the notion that shear stress induces ephrinB2 gene expression resulting in the differentiation of endothelial progenitor cells into arterial endothelial cells.

Our understanding of the transcriptional regulation of Eph receptors and ephrin ligands in developmental processes is in its early stages. Importantly, over the last decade, our knowledge surrounding transcriptional regulation of Eph/ephrin expression in pathological processes has expanded. These discoveries stem largely from studies on cancer, where misregulation of Eph receptors and ephrin ligands is a typical consequence.

Misregulation

Transcriptional regulation of *ephB2* has been studied extensively since alterations in its expression levels occur in several cancers.[49-52] Loss of *ephB2* expression is observed in many tumors, and is particularly studied in colonic adenomas and carcinomas.[53,54] The downregulation of *ephB2* in early and advanced colorectal cancers was found to be due to c-Rel binding to a negative regulatory element in the *ephB2* promoter.[52] On the other hand, upregulation of the EphB2 gene is associated with pancreatic ductal adenocarcinoma where it has been shown to be transcriptionally regulated by the Basic transcription factor 3 (BTF3).[55]

Another Eph receptor commonly linked to cancer and believed important in tumor metastasis and angiogenesis is *ephA2*.[56,57] The EphA2 promoter was reported to be a direct transcriptional target of the Ras-Raf-MAPK pathway in breast cancer cell lines.[58,59] In addition these studies have shown a negative feedback loop between *efnA1* expression and *ephA2* levels, indicating that this regulation may contribute to receptor-ligand reciprocal expression patterns. Similarly, evidence exists for MAPK dependent regulation of *ephA2* in UV radiated induced apoptosis.[60] Altogether these studies show several mechanisms underlying the misexpression of Eph receptors and ephrins. In addition to the transcriptional mechanisms controlling *Eph/ephrin* expression, epigenetic mechanisms have also been studied.

Epigenetic regulation. A major step in epigenetic regulation of gene expression is gene inactivation by hypermethylation of CpG islands located in the promoter regions (for extensive reviews see refs. 61 and 62). Specific enzymes and methylated DNA binding proteins play a major role in epigenetic regulation of gene expression. Alterations in CpG island methylation can affect gene expression in normal and cancer cells.[63-66] The possible regulation of Eph receptors and ephrin ligands by epigenetics has been under considerable study. For example, the *ephA5* receptor is a major player in regulating patterning of the topographic connections of retinal ganglion cells during visual system development.[67] New findings have shown that CpG islands in the *ephA5* promoter display site-specific differences in methylation that could preferentially activate or repress promoter activity and may contribute to graded *ephA5* gene expression in the tectum.[68] More studies, however, have focused on aberrant methylation patterns of Eph receptor and ephrin genes in cancer. Methylation of CpG promoter sequences of *ephA1, ephA2, ephA7, ephB2, ephB4* and

ephB6 has been reported in several human tumors, including colorectal, prostate and breast cancer.[69-73] The EphA3 gene promoter region isolated from human embryonic kidney cells is also found to be rich in CpG islands that may regulate *ephA3* transcription in hematopoietic tumors.[74] A recent study using acute lymphoblastic leukemia bone marrow samples and cell lines provided a thorough analysis of CpG island methylation of almost all of the Eph receptors and ephrin ligands.[75] Specifically the authors demonstrated hypermethylation of the promoter regions of the *ephA2*, *ephA4*, *ephA5*, *ephA6*, *ephA7*, *ephA10*, *ephB1*, *ephB2*, *ephB3* and *ephB4* receptors, in addition to the *efnA1*, *efnA3*, *efnA5*, *efnB1* and *efnB2* ligands. More detailed analyses were performed on the EphB4 promoter region showing that hypermethylation renders *ephB4* a tumor suppressor gene in acute lymphoblastic leukemia.

Altogether, studies on aberrant promoter methylation of Eph receptors and ephrins are providing promising information on the epigenetic regulation of this family of genes. One example is that hypomethylation of the *efnB1* promoter may be an early prognostic event for rheumatoid arthritis.[76]

Post-Transcriptional Regulation

Over the last few years we and others have shown that ephrins and Eph receptors can be regulated post-transcriptionally. One interesting feature of this large family of proteins is that the 3'-untranslated regions (3'-UTRs) of several of the Eph receptors or the ephrin ligands contain regulatory binding sites that are highly conserved in vertebrates.[77,78] An overview of these studies showing Eph receptor or ephrin ligand regulation at the level of mRNA stability or by microRNAs (miRNAs) in physiological and pathological processes is provided below.

mRNA stability. Putative binding sites for RNA-stabilizing and RNA-destabilizing factors have been identified in the 3' untranslated regions (3'-UTR) sequences of several Eph/ephrin transcripts.[77,78] Bioinformatic approaches were used to identify clusters of motifs consisting of cytoplasmic polyadenylation elements (CPEs), AU-rich elements (AREs) and HuR binding sites.[78] Despite the presence of these clusters in numerous members of the Eph/ephrin family, only some were validated. Using HeLa cervical cancer cells and U373MG glioma cells, this study showed that the HuR binding sites in the 3'-UTR region of *ephA2*, *ephA4* and *efnA2* served to destabilize the transcripts, despite the conventional role of HuR as an mRNA-stabilizing protein. Moreover, the authors report that knockdown of HuR greatly regulates Eph/ephrin expression at both the mRNA and protein levels. Altogether, this study suggests that overexpression of HuR, as found in many progressive tumors, could cause variation in Eph receptor and ephrin ligand expression and therefore result in increased tissue invasiveness.

Along the same lines, post-transcriptional regulation of *ephB2* may also be important in cancer metastasis. The EphB2 gene has been implicated as a tumor suppressor gene altered in both prostate cancer and colorectal cancer.[79] Huusko and colleagues[80] reported that the DU 145 prostate cancer cell line carries a truncating mutation of *ephB2* and a deletion of the remaining

allele. This truncated version was subject to Nonsense-Mediated Decay (NMD). Furthermore, the authors identified other missense and nonsense mutations from clinical prostate cancer samples. Overall, the authors proposed that EphB2 may have an essential role in cell migration and maintenance of normal tissue architecture, and that mutational inactivation of *ephB2* may be important in the progression and metastasis of prostate cancer. Nonsense and frameshift mutations in the *efnb1* gene were reported to undergo NMD.[81] In fact these mutations are considered to be contributors to the pathogenic mechanisms reported in the human X-linked malformation syndrome, cranio-frontonasal syndrome (CFNS). Therefore, accumulating evidence implicates mRNA stability as a possible regulatory or deregulatory process in Eph/ephrin expression in cancer and other pathologies. In addition to these processes miRNAs have also emerged as post-transcriptional regulators of Eph/ephrin expression in both developmental and pathophysiological conditions.

miRNAs. Post-transcriptional regulation by miRNAs is important for many aspects of development, homeostasis and disease. MicroRNAs constitute a family of short noncoding RNA molecules of 20 to 25 nucleotides in length that regulate gene expression at the post-transcriptional level.[82,83] In animals, miRNAs typically target sequences in the transcript 3'-UTRs that are only partially complementary to the miRNA, thereby causing a repression in translation of the mRNA.[84] Eph receptors and ephrin ligands have emerged as potential targets for miRNA regulation. A number of studies have correlated changes in the expression levels of Eph receptors or ephrin ligands to modulations in specific miRNA levels. For example, the upregulation of miR-223 following hepatic ischemia injury in mice resulted in a downregulation of the ephrin-A1 transcript, *efnA1*.[85] Similarly, miRNA expression profiling coupled with proteomic analysis following different dietetic regimens has inferred *efnA1* and *ephA2* as potential targets for miR-122, miR-451 and miR-27.[86]

To date there is little evidence for the direct regulation of Eph receptors and ephrin ligands by miRNAs, yet, several members of the family have predicted miRNA binding sites (**Table 1**). This indeed may be a reflection of the complexity of the gradient, complementary and overlapping expression domains of Eph receptors and ephrin ligands. A pioneering study in 2008 showed that ephrin-A3 gene, *efnA3,* was a direct target of miR-210.[87] The authors concluded that *efnA3* modulation by miR-210 had significant functional consequences for endothelial cell response to hypoxia, affecting cell survival, migration and differentiation. A recent report has further shown that miR-210 modulation of *efnA3* underlies one of the molecular mechanisms in preeclampsia.[88] We have identified miR-124 as a post-transcriptional repressor of *efnB1* expression in neural stem cells.[77] In addition we presented evidence for the regulation of miR-124 levels by ephrin-B1 reverse signaling, thus revealing the existence of a mutually repressive interaction between ephrin-B1 and miR-124. More recently it has been shown that *ephA2* is a direct target of miR-26b.[89] *EphA2* is expressed in a number of cancers and has potential roles in the regulation of cancer cell growth, survival, migration, invasion and angiogenesis.[90,91] The authors demonstrated that miR-26b may act as a tumor suppressor in glioma by

Table 1. Representation of predicted and validated miRNAs targeting Eph receptors and ephrin ligands

Ephrin/ Eph receptor	Position: 5'-3' of 3'-UTR	Predicted miRNA binding
EphrinA1	235–241	miR-9 *miR-223*[85] *miR-122, miR-451 and miR-27*[86]
EphrinA2	NA	NA *miR-122, miR-451 and miR-27*[86]
EphrinA3	467–173, 474–480, 791–797	miR-30, miR-130, miR-153 **miR-210**[87]
EphrinA4	NA*	NA*
EphrinA5	NA	NA
EphrinA6	NA*	NA*
EphrinA7	NA*	NA*
EphrinB1	195–201	**miR-124**[77]
EphrinB2	1880–1886, 2871–2877, 2952–2958, 3078–3084,	miR-153, miR-182, miR-200, miR-1 and miR-206,
EphrinB3	901–907	miR-124
EphA1	106–112	miR-29
EphA2	24–30 729–735	**miR-26**[89] miR-141 and miR-200
EphA3	NA*	NA*
EphA4	36–42, 48–54	let-7, miR-17
EphA5	NA*	NA*
EphA6	NA*	NA*
EphA7	776–782, 1815–1821, 1817–1823	miR-137, miR-133, miR-9
EphA8	550–556, 1162–1168, 1322–1328, 1323–1329	miR-138, miR-218, miR-25/32/92, miR-137
EphA9	NA	NA
EphB1	NA*	NA*
EphB2	1403–1409	miR-128
EphB3	775–781	miR-137
EphB4	107–113, 317–323, 318–324	miR-17/93/106, miR-133, miR-9
EphB5	NA	NA
EphB6	NA*	NA*

Predictions of the 5'-3' mRNA sequence position and corresponding miRNA are assessed by TargetScan 5.1. Sites shown have a high probability of preferential conservation between human, rhesus, chimpanzee and mouse. Potential miRNAs derived from experimental evidence are italicized. Validated miRNAs are in bold. NA, Eph receptor or ephrin ligand gene not in TargetScan database; NA*, no highly conserved sites.

directly regulating *ephA2* expression. Therefore, miRNAs, which are involved in the control of a wide range of biological functions and processes, have now been implicated in post-transcriptionally regulating members of the Eph/ephrin family.

The challenge to identify additional post-transcriptional regulating mechanisms for Eph/ephrins continues. Undoubtedly, this will be fraught by the complexity in Eph/ephrin expression patterns, and the means to identify cell-specific, context-dependent regulation. Therefore, future analyses will be valuable for understanding the changes in Eph/ephrin expression levels in normal and disease states.

Concluding Remarks

We are only beginning to understand the regulatory mechanisms governing the expression of Eph receptors and ephrins in development, in adult tissues, and their misregulation in disease. While HOX transcription factors have emerged as one of the key transcriptional regulators of Eph receptor genes in development, data shows that tissue-specific expression of each member of the Eph/ephrin family is also dependent on distinct molecular effectors. This indeed is surprising, given the high conservation between Eph/ephrin subclass members and the noted redundancy in their function. As we are only beginning to unravel the transcriptional control of Ephs and ephrins, it is possible that future studies may uncover common regulatory mechanisms.

There is an increasing body of evidence for inverse regulation between Eph receptors and ephrin ligands. Several of the examples demonstrating an inverse regulation between Eph receptors and ephrin ligands in developmental processes and in cancer are discussed in this review.[38,39,47,48] Fewer findings exist for co-regulation of the receptor/ligand pair. One such example revealed that Eph/ephrins act synergistically in the mouse skin to induce angiogenesis in response to local hypoxia.[92] Curiously, one emerging notion is that activation of bidirectional signaling may be one of the cell-specific mechanisms employed to establish positive (or negative) feedback loops regulating Eph/ephrin expression. Our findings for the auto-regulation of *efnB1* following ephrin-B1 activation in trans by EphB2 in neural progenitors[77] strongly suggest that one of the several outcomes of the Eph receptor/ephrin bidirectional activation (or inhibition) may lead to establishing their own highly precise and combinatorial expression patterns. If indeed additional future studies corroborate that Eph/ephrin activity-dependent regulation is involved in establishing Eph/ephrin complementary expression domains, these discoveries will help identify the molecular basis of topographic positioning within the developing embryo and adult. Moreover, such findings may help explain the prominent misregulation of the receptors and ligands in cancer.

Further studies on Eph/ephrin RNA processing mechanisms, including the control of intracellular localization of Eph/ephrin mRNAs and association with translating ribosomes, and the post-transcriptional processing of the different members are necessary to fully understand the mechanisms controlling their expression. Indeed, it is likely an amalgamation of all these factors, genetic and epigenetic, that leads to the highly precise and combinatorial expression patterns of *ephs* and *ephrins*. Unraveling the mechanisms that control Eph receptor and ephrin ligand expression during development will undoubtedly yield important insight into tumorigenesis, as it is probable that tumors exploit similar regulatory mechanisms. It is important to take note that mechanisms beyond transcriptional and post-transcriptional regulatory processes have been presented in the literature. For instance, the attenuation of EphA3 function by ephrinA5 in cis can result in a loss of sensitivity of retinal axons to ephrinAs.[94] A

similar cis-mediated attenuation of Eph receptors function has been reported during spinal motor neuron selection of a limb trajectory.[95] Interestingly, cis attenuation of Eph signaling by co-expressed ephrins has not been widely reported in cancer settings, perhaps owing to the fact that expression of receptors and ligands is usually inversely regulated. Data also exists for bidirectional activity dependent regulation in Eph/ephrin localization and expression. One example of this complexity is found in the work published by Bush and Soriano[93] showing that the mosaic expression of *efnB1* in ephrin-B1 heterozygote animals leads to upregulation of the EphB3 receptor in adjacent, non-ephrin-B1 expressing cells through relief of EphB3 endocytosis and degradation. This finding supports the notion that the Eph/ephrin signaling cascade is involved in setting up complementary domains via post-transductional mechanisms. These data highlight how Eph/ephrin interactions can regulate their functional expression patterns and more importantly offer an additional level in the complexity of understanding the establishment and maintenance in Eph/ephrin expression domains.

The changes in expression profiles of Eph receptors and ephrin ligands in several cancers have made this family of proteins prime targets for cancer prognosis and therapies.[96-99] However, what is important to note is that Eph/ephrins are expressed in numerous organs through adulthood; therefore, any therapy aimed at reducing their expression systemically to treat pathologies will need to account for their requirement in normal tissues. Therefore, details on tissue-specific molecular mechanisms of Eph/ephrin gene regulation will be important to develop more sophisticated and precise therapeutics. Future work should address these important questions to resolve how Eph/ephrin gene expression is controlled in highly diverse biological settings and in cancer.

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