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Ephrin-Eph Receptors and Their Therapeutic Implication: A Comprehensive Review

Sakshi, Komal*, Kapil Kumar Verma, Rahul Kumar, Kritika, Dishant Dhiman

*Minerva College of Pharmacy, Indora, Kangra, Himachal Pradesh, India**

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ABSTRACT:

The Eph receptor tyrosine kinases and their membrane-bound ephrin ligands constitute a pivotal cell communication system orchestrating a multitude of physiological processes, including embryonic development, tissue patterning, neural plasticity, and immune response. Their unique ability to facilitate bidirectional signalling allows them to modulate the behaviour of both the receptor-expressing and ligand-expressing cells upon contact. This comprehensive review delineates the molecular architecture and signalling mechanisms of the Eph/ephrin system, highlighting its critical roles in neural development, vascular patterning, bone remodeling, and glucose homeostasis. We further explore the system's dual role in pathology, particularly in cancer progression, angiogenesis, and drug resistance, where its dysregulation can either promote or suppress tumorigenicity in a context-dependent manner. Finally, we discuss emerging therapeutic strategies—including CRISPR/Cas9 gene editing, nanoparticle-based drug delivery, and artificial intelligence-driven drug design—that target the Eph/ephrin axis, underscoring its significant potential for pioneering next-generation precision medicine interventions.

1. Introduction

The Eph proteins are the largest superfamily of receptor tyrosine kinases, and they have a variety of roles in both adult and developmental processes, most notably in the regulation of tissue regeneration [1]. Eph receptors and their ligands, known as ephrins (Eph receptor interacting proteins), are important participants in a variety of clinical diseases and are thus potential targets for therapeutic intervention [2,3,4]. Figure 1 depicts eph receptors and their ligands. Since Eph /=085rsA and Eph B receptors share structural characteristics and domains, the overall structure of all Eph receptors is extremely conserved. The key sequence variations between Eph A and Eph B receptors are found in a low affinity ephrin binding site area of the ligand binding domain, which is probably involved in identifying ephrin subclasses [5].

Almost forty percent of the 58 human RTKs are members of the Ep.23h receptor family, which has grown significantly over evolution [6]. Here, we give a summary of the biological effects and signaling processes of ephrin and eph receptors, with a focus on new research. Other recent reviews provide more in-depth details on particular facets of downstream signaling networks and Eph receptor/ephrin biology [7]. The conserved Eph receptor-binding domain of both ephrin classes is joined to the plasma membrane by a linker segment, the length of which is subject to alternate splicing. A glycosylphosphatidylinositol (GPI) anchor holds the ephrin-As to the cell surface, but they can also be released to activate distant Eph A receptors [8,9].Eph A receptors bind promiscuously to ephrin-A ligands (five members) while Eph B receptors bind promiscuously to ephrin-B ligands (three members) with some potential crosstalk between groups [10].

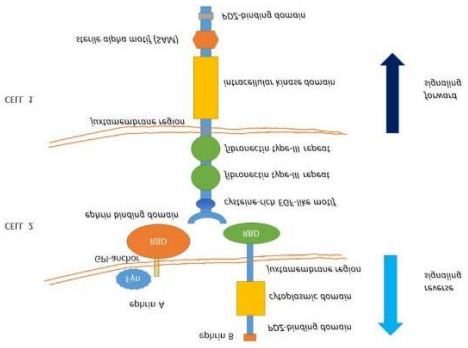

Figure1. Eph receptors and their ligands.

The best kinase activity is achieved when Eph receptors bind to their ligands, causing oligomerization and transphosphorylation (11,12). Both epha and ephrins have two functions: they can operate as ligands and receptors. They can mediate interactions that affect the

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behavior of both Eph-expressing cells (forward signaling) and Ephrin-expressing cells (reverse signaling) thanks to this bidirectional signaling. [13] In cells that express Eph, forward signaling is mediated by Eph's kinase activity, which autophosphorylates juxta membrane tyrosine residues and initiates downstream signaling cascades [14].The Eph family of receptors is now known to include two classes of receptors that consist of 9 Eph A members and 5 Eph B members classified according to sequence homology [15]

Ephrin ligands and receptors

One of the largest groups of proteins associated with plasma membranes, RTKs are crucial for how cells react to signals from the outside of the cell. RTKs are involved in a broad range of cellular processes, including migration, differentiation, and proliferation. From nematodes to vertebrates, eph receptors—the largest family of RTKs—have been largely conserved throughout evolution [16,17]. Their Ephrin ligands can activate tricellular signaling proteins after binding to the extracellular domain [16]. The modulation of cytoskeletal dynamics and cell-cell adhesion, which are crucial for activities that depend on cell motility and morphology, including cell migration, neural pathfinding, and tissue separation, are the most significant downstream effects of ephrin-Eph signaling [18,21].

2. ROLES OF EPHS AND EPHRINS IN IMMUNE CELL ACTIVATION

Immune cell activation is one of the first steps in launching an immune response. Evidence suggests that immune cell activation may be mediated by ephrin ligands and eph receptors. It is still unclear, yet, how signaling from Eph-ephrin ligation affects activation and how the expression of these molecules in cis and trans on various immune cell subsets affects this process due to the paucity of findings in the literature. Additionally, when it comes to innate immune cells,initial recognition leads to activation that can be amplified through feedback loops once the adaptive immune response has been initiated. Below we outline what is currently known about the involvement of Eph receptors in activating both innate and adaptive immune cells.[22]

Innate Immune Cells

There are very few reports on the contribution of Eph receptors and ephrin ligands to the activation of innate immune cells. However, there is evidence suggesting a role for Eph receptors, specifically EphB2, in modulating dendritic cell (DC) responsiveness to toll-like receptor (TLR) ligation by pathogen associated molecular patterns [23].

B Cells

Eph receptors and ephrin's have been identified on both human [24, 25,26] and mouse [27] B cells. Eph receptors and ephrin ligands are also expressed differentially on naïve and activated B cells [25]. This suggests that they may contribute to processes facilitating B cell activation as exemplified by naïve human B cells which upregulate EphB2 leading to increased proliferation and antibody production. In B cells, EphB2 has been demonstrated to be regulated by the microRNA miR-185 and its effects on B cell activation appear to occur at least in part through interactions between EphB2 and the Src-p65 and Notch1 signalling pathways [28].

T-cells

Human peripheral T cells have been found to express Eph and Ephrins; according to one study, between 10% and 12% of CD4+ and CD8+ T cells express EphB6 [29]. All three ephrin B ligands have been shown in numerous studies to affect T cell cooperation, T cell co-stimulation, and improving signaling via the T cell receptor (TCR). TCRs and eph B receptors colocalize on the surface of activated T cells in signaling rafts. Furthermore, Ephrin B1-mediated T cell stimulation via Eph B receptors raises LAT phosphorylation and activates the signaling molecules p38 and p44/42 MAPK (30, 31), offering a molecular explanation for potential interactions between Eph receptors and TCR complex elements. In particular,EphB6 has been shown to have a critical role in T cell activation with EphB6 deficient mice displaying reduced activation, phosphorylation, and/or recruitment of the T cell signalling molecules ZAP-70, LAT, SLP-76, PLCγ1, and P44/42 MAPK (32). Administration of anti-EphB6 antibodies, which can cause EphB6 clustering and subsequent signalling on T cells, increases the response of mature T cells to weak TCR ligation as measured by canonical activation marker expression (CD25, CD69) and cytokine production (interferon

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(IFN)-γ, interleukin (IL)-6) as well as T cell proliferation (33).

2.Physiological Roles of Eph Receptors and Ephrin Ligand

Eph receptors and ephrin ligands must be present on the surface of two interacting cells of the same or distinct types in order for their spatial arrangements to function. Therefore, in order to initiate forward and/or reverse signaling in certain cell types, physical contact is required. As explained below, these receptor-ligand pairs' contact-mediated physiological roles in axon guidance, neuronal development, vascular patterning, and wound healing have been well-documented**.**

Neural Development.

Eph-ephrin interactions are also necessary for neuronal plasticity, neuron survival, neuroblast migration, and neural progenitor cell proliferation. Neuroblasts migrate in the subventricular zone of the lateral ventricles in the adult mammalian brain when ephrin ligands activate EphB1, EphB2, EphB3, and EphA4 (34) In the hippocampus of adult mice, ephrin-A5 is necessary for the survival of newborn neurons, the growth of cells in the hippocampus dentate gyrus, and the control of the hippocampus's vasculature (35). The role of EphA7 and ephrin-A2 on progenitor cell proliferation in mice indicates that Eph and ephrins also function as negative modulators in the nervous system (36)influence of ephrin-B3 (37), and EphB3 (38) in the adult subventricular zone, and regulation of hippocampus neural progenitor growth by ephrin-A2/A3 mediated activation of EphA7 (39). Thus, activation of Eph receptors by ephrin's is critical for the maintenance, proliferation, and inhibition of neural progenitors during neurogenesis.

Vascular Development.

The functions of ephB4 and ephrin-B2 in the dorsal aorta and cardinal veins are well-known. Ephrin-B2 identifies artery endothelial cells, whereas EphB4 identifies venous endothelial cells (40). Their functions in establishing the borders between veins and arteries are demonstrated by the interaction of the Eph receptor in veins and ephrin-B2 in arteries (41). The mouse retinal system (43,44) and the zebra fish model of vascular development (42) both support these findings. EphB4 and ephrin-B2 are necessary for the development of vascular valves, which control unidirectional flow within the lymphatics (46). The lymphatic vasculature is a branching network of blind-ended capillaries and collecting lymph arteries (45). Involvement of ephrin-B2 has been confirmed by its ability to induce VEGFR3 internalization (47) as well as lymphatic system remodelling (48). Ephrin-B2 is also necessary for blood vessel network stabilization (49).

4. MOLECULAR STRUCTURE AND SIGNALLING

Signaling and Structure. The biggest family of receptor tyrosine kinases, eph receptors were discovered in the late 1980s (50). They are made up of two fibronectin type III repeats, a cysteine-rich region, and a glycosylated extracellular domain with the immunoglobulin-like ligand binding site (Figure 1). A juxta membrane domain, a tyrosine kinase domain, a sterile alpha motif, and a PDZ-(Postsynaptic density 95-Discs Large-Zonula occludentes-1) binding motif are all present in the intracellular region, which is connected by a single transmembrane spanning domain (50,51). Eph receptors bind membrane-bound ligands, the ephrins, and both receptors and ligands are classified into two subclasses A or B according to their binding characteristics and structural similarities.

Class B ephrins have a transmembrane domain and a brief cytoplasmic segment with conserved tyrosine residues and a PDZ-binding motif, while class A ephrins are membrane bound via a glycosylphosphatidylinositol anchor. All A-type ephrins are preferentially bound by class A Eph receptors, while all B-type ligands are bound by class B Eph receptors. EphA1 mainly binds ephrinA1, EphA4 binds both A- and B-type ligands, and ephrinA5 binds Eph A receptors in addition to EphB2 (Figure 2), but there are few exceptions.

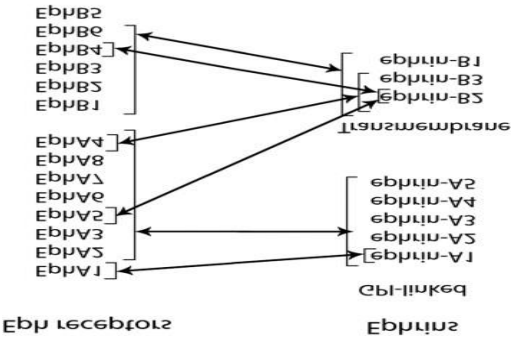

Figure 2: Major interactions of Eph receptors and ephrin ligand

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Overall organisation and regulation of the Eph receptor intracellular domains

A tyrosine kinase domain is attached to the Eph N-terminal ectodomain by a single transmembrane α-helix that extends intracellularly to a juxta membrane (JM) region. A linker connects the tyrosine kinase domain to a PDZ domain-binding motif and a sterile-alpha motif (SAM) domain (Figure 3) (56) We describe the structural and functional properties of each of these intracellular domains below. These extra protein–protein interaction domains suggest that Eph receptors regulate intricate intracellular signaling networks.suggesting that phosphorylation of the JM region is required to unleash an active conformation. The second role is to provide binding sites to SH2 domain-containing proteins.

The juxta membrane region and the kinase domain

A JM area is a structurally defined peptide linker that is situated N-terminal to the tyrosine kinase domain and ranges in length from 35 to 40 amino acids (Figure 4 and 5). The JM region has two functions. By keeping the protein in an inactive shape and preventing access to the substrate and nucleotides, it plays a part in controlling the intrinsic kinase activity of its neighboring kinase domain (56). It has been demonstrated that mutations of the two conserved tyrosine residues in the JM region (referred to as JX1 and JX2) to phenylalanine totally eliminate EphA4's kinase activity (57).

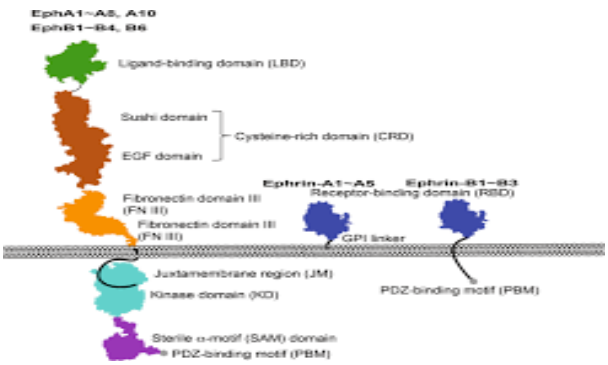

Figure 4: Sequence alignment of Eph receptors' kinase domain and juxta membrane region. a sequence alignment of each Eph receptor's kinase domain (KD) and juxta membrane (JM) region. The conserved residues essential for kinase catalytic activity are indicated by grey shading, which also draws attention to residues that, when phosphorylated, act as docking sites for proteins containing SH2 domains. The catalytically important residues that have changed in EphB6 and EphA10 are indicated in bold. The following annotations apply to the anticipated secondary structures, which are based on the crystal structure of the EphB2 kinase domain (PDB: 1JPA): Helix structures are represented by bars, whereas β-strands are represented by arrows. b An overview of the essential catalytic motifs required for kinase activity in comparison to those present in EphA10 and EphB6.

The SAM domain linker and the SAM domain

The SAM domain is a protein–protein interaction region located at the C-terminus of the Eph receptor kinase domain (Figure 4). Five helices that control homo-/het-dimerization or oligomerization make up the highly conserved modular SAM domain (60,61). The α1, α3, and the C-terminal region of the α5 helices are the main structural components involved at the dimerization interface, according to the crystal structure of homo-dimeric EphA4 SAM (PDB: 1B0X). Mutagenesis experiments showed that SAM domain dimerization was impaired when important residues at this interface, such as L940, M972, and M976, which are comparatively conserved in other Eph receptors, were substituted (60). However, two more interaction surfaces in the crystal structure of the EphB2 SAM domain (PDB: 1B4F) have shown a potential oligomerization process.

Eph receptor forward signalling

Eph receptors and ephrin ligands play a major part in cell communication because they are attached to the presenting cells. Both ephrin and Eph receptors have the ability to start signal transduction in each of the cells that present ligands and receptors when they come into contact with another cell. "Forward signaling" is the signaling that is started by the Ephrin-ligated Eph receptors, whereas "reverse signaling" is the signaling that is started by the Eph-bound ephrins (Fig. 6a). Because it is fueled by "canonical receptors," which are responsible for transducing signals from ligand activation, Eph forward signaling has garnered increased attention..

Eph receptors' function in controlling key pathways, including through Ras/MAPK, which regulates pro-liberation, and Rho/Rac GTPases, which govern actin organization, has been well examined elsewhere (62). As

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an illustration of Eph forward signaling, we will thus concentrate on the PI3K-Akt/PKB signaling axis downstream of Eph receptors. We will also demonstrate how the Sac homology 2 (SH2)-containing proteins, which are essential for both Eph forward and reverse signaling, can transmit the signals when the Eph receptors are phosphorylated. A study stating that certain Eph receptors, such EphA2, are receptor, cell type, and context dependent suggests that the Eph-mediated signaling pathways are primarily receptor-, cell type-, and context-dependent (63) can promote both tumour progression and suppression. The tyrosine kinase domain of Eph receptors plays a central role in forward signalling, such that upon ligand stimulation, the ephrin-bound Eph receptors undergo dimerization, which results in transphosphorylation and activation of the receptor kinase domains (Fig. 6a)). The interaction with various guanine nucleotide exchange factors (GEFs) is a good example of how Eph receptors can function as scaffold proteins. Ephexin1 is an EphA4 substrate, since Sahin et al. showed that it required EphA4 kinase activity to activate an upstream GEF of Rho small GTPases in fibroblasts. RhoA activity was increased by phosphorylated ephexin1, which resulted in the development of stress fibers.

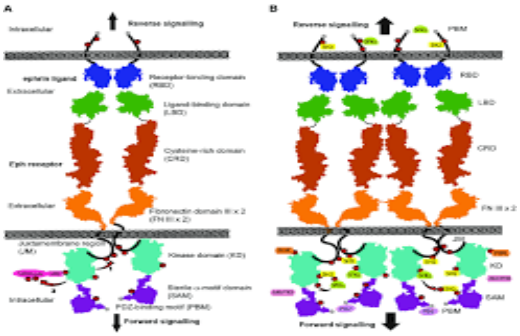

Figure 5: Forward (and backward) signaling is activated by the dimerization and oligomerization of Eph receptors. The tyrosine kinase domain of the Eph receptor is autophosphorylated when Ephrin causes the dimerization of Eph receptors. Proteins with SH2 domains can be recruited by autophosphorylation of the kinase domain, the SAM domain, and the juxta membrane area. These proteins may then be substrates for phosphorylation by the Eph receptor tyrosine kinase domain. The phosphorylation of the C-terminal tail of class B ephrins by Sac family kinases (SFKs) results in the induction of reverse signaling pathways in cells that produce ephrins ligated to the Eph receptors. b Ephrin-induced dimerized Eph receptors have the ability to cluster into signaling centers by further oligomerise.

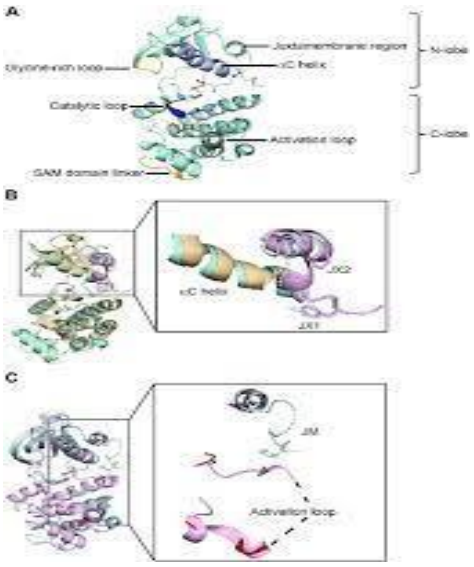

Figure 6 Structural features of the Eph receptor kinase domain. Key structural features of the Eph receptor kinase domain are highlighted in the EphA3 kinase domain crystal structure (PDB: 2QO2). Note that this kinase domain adopted an inactive conformation. b Superposition of the C-lobes of EphA3 (PDB: 2QO2, in cyan) and EphB2 (PDB: 1JPA, in brown) kinase domain structures show a very similar alignment of the juxta membrane regions. The distortion of the αC helix, coordinated by the unphosphorylated juxta membrane region, leads to an inactive form of the kinase domain. c Superposition of the C-lobes from the inactive (PDB: 2QO2, in cyan) and the active (PDB: 2QO9, in pink) EphA3 kinase domain structures reveal the impact of unphosphorylated juxta membrane region on the activation loop. The unphosphorylated juxta membrane region (in cyan) of 2QO2 causes misalignment of the activation loop (in red), giving rise to an inactive conformation of the kinase domain. The phosphorylated juxta membrane region of 2QO9 dislodges from the kinase domain and cannot be seen in the crystal structure. This results in a more ordered activation loop (in pink), which stabilises the kinase domain in its active conformation.

The notion that GPI-anchored ephrin's that do not span the plasma membrane can signal upon interaction with

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their cognate Eph receptor is supported by previous observations where other GPI-anchored proteins, mainly present on hematopoietic cells, activate cellular signalling responses upon cross-linking or binding to their natural ligands (Brown 1993).

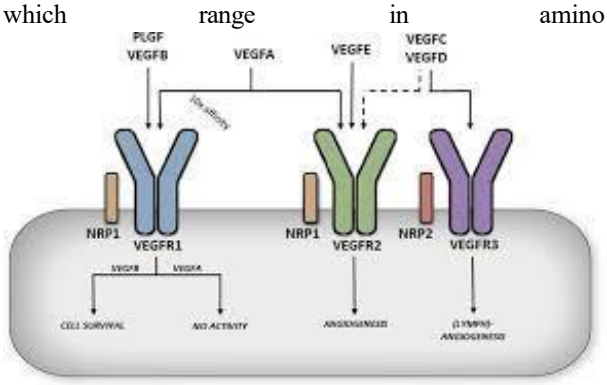
Crosstalk of VEGF and Notch signalling pathways

VEGF pathway (Figure 7). Five receptors (VEGFR1, VEGFR2, VEGFR3, NRP1, and NRP2) and five ligands (VEGF/VEGF-A, PLGF, VEGF-B, VEGF-C, and VEGF-D) are present. While VEGFR3 is mostly found in lymphatic ECs, VEGFR1 and VEGFR2 are expressed on the cell surface of the majority of blood ECs. VEGFR1, VEGFR2, NRP1, and NRP2 are bound by VEGF-A; VEGFR1 and NRP1 are bound by VEGF-B; VEGFR2, VEGFR3, and NRP2 are bound by VEGF-C; VEGFR2 and VEGFR3 are bound by VEGF-D; and VEGFR1, RPN1, and NRP2 are interacting with PLGF. Blocking the VEGF pathway has been accomplished in a number of ways, including using monoclonal antibodies like bevacizumab (A) and

VEGF-trap (B) to target VEGF-A, specific antibodies (C) to inhibit VEGFR2, and a range of small-molecule VEGF RTK inhibitors that prevent ligand-dependent autophosphorylation of VEGFR2 (D).

VEGF ligands and receptors

The VEGF pathway has five receptors (VEGFR1, VEGFR2, VEGFR3, NRP1, and NRP2) and five ligands (VEGF/VEGF-A, PLGF, VEGF-B, VEGF-C, and VEGF-D) (Figure 1), with VEGF and VEGFR2 seemingly being the main participants in endothelial cells (ECs). Following signal sequence breakage, alternative exon splicing of the VEGF gene produces five isoforms, which range in amino



acid content from 121 to 206 (VEGF121, VEGF145, VEGF165, VEGF189, and VEGF206).

The protein VEGF121 is easily diffusible. The extracellular matrix almost entirely encloses VEGF189 and VEGF206. The most common and physiologically significant isoform is VEGF165, which has intermediate characteristics when secreted but a sizable portion that is still attached to the matrix and cell surface (21). VEGFR1 (Flt-1) and VEGFR2 (Flk-1, KDR) are two related receptor tyrosine kinases (RTKs) that VEGF binds to; VEGFR2 is the primary mediator of VEGF effects. Instead of binding VEGF, the third receptor, VEGFR3 (Flt-4), binds VEGF-C and VEGF-D. During neural guidance, neuropilins (NRP1 and NRP2) convey repulsive signals and bind class 3 semaphore (64).

While NRP2 interacts with VEGF, PLGF, and VEGF-C, NRP1 binds to VEGF, PLGF, and VEGF-B as well. As co-receptors, NRP1 and NRP2 promote VEGF-stimulated signaling and improve VEGF-VEGFR2 interactions (65,66). While VEGFR3 is found on all ECs in developing blood vessels but becomes mostly limited to lymphatic ECs and specific fenestrated blood ECs in adulthood, VEGFR1 and VEGFR2 are mostly expressed on the surface of vascular ECs (67). The activation of VEGFR2 promotes the mitogenic, angiogenic, anti-apoptotic, and permeability-enhancing actions of VEGF by causing autophosphorylation and downstream signaling via pathways like PI3K/Akt. ECs may be deceived by VEGFR1 activation, which inhibits VEGF availability to VEGFR (70).

There is growing evidence that VEGFR1 may also have important roles in haematopoiesis and in the recruitment of Angio competent bone marrow progenitors that may home in on the tumour vasculature and promote angiogenesis (68,69)

Notch ligands and receptors

Numerous biological processes, such as cell-fate determination, cellular differentiation, proliferation, survival, and apoptosis, are impacted by the Notch system, an intercellular signaling pathway that has been conserved throughout evolution (71,72). In mammals, four Notch receptors (Notch1-Notch4) and five Notch ligands (Jagged1, Jagged2, delta-like 1 (DLL1), DLL3, and DLL4) have been identified. Both the receptor and the ligand are transmembrane proteins with extensive extracellular domains made up of repetitions that resemble epidermal growth factor (EGF). Two proteolytic cleavages of the Notch receptor occur when

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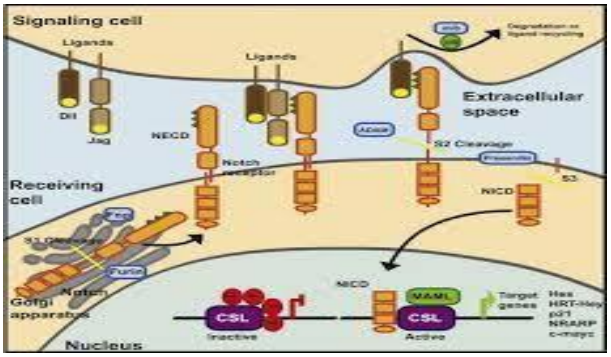
the ligand binds to the receptor between adjacent cells, starting the activation of Notch signaling (Figure 2).

ADAM-family metalloproteases (ADAM10 or TACE (TNF-alpha-converting enzyme; also known as ADAM17)) mediate the first cleavage, whereas gamma secretase, a protein complex consisting of presenilin, Nicastri, PEN2, and APH1, catalyzes the second (73). The Notch intracellular domain (NICD) is liberated from the cell membrane by the last cleavage and then moves into the nucleus. The transcription of Notch target genes is then activated when NICD binds with the DNA-binding protein CBF1/RBP-Jk appa and works with Mastermind to displace corepressor proteins from RBP-Jk appa.

Hey1-knockout mice have no apparent phenotypical defect whereas Hey2-deficient mice exhibit a quite strong, albeit variable, phenotype of cardiac impairment with high postnatal lethality.



The Notch pathway is shown in Figure 8. Prior to being delivered to the cell surface, where it exists as a heterodimer, Notch is synthesized as a precursor protein and processed by a furin-like convertase (S1 cleavage) in the Golgi. A series of proteolytic cleavages are triggered when two adjacent cells' Notch receptors interact with Notch ligands, such as Delta-like or Jagged. ADAM-family metalloproteases like ADAM10 or TNF-alpha converting enzyme (TACE, also called ADAM17) catalyze the initial cleavage (S2 cleavage), which creates a substrate for the gamma-secretase complex to cleave S3. The Notch intracellular domain (NICD) is liberated from the cell membrane by this cleavage.

5. Physiological roles

Neural Development, Plasticity, and Regeneration

Numerous studies have been conducted on the nervous system's ephrin and eph receptor functions. Electrical impulses move from axonal to dendritic processes via specialized junctions known as synapses in the complex networks that neurons form. Here, postsynaptic ion channel receptors are activated by neurotransmitters produced from the presynaptic terminal in response to electrical signals, which causes the postsynaptic neuron to send out additional chemical and electrical signals. Numerous characteristics of the neurons, including their capacity to create synapses, are regulated by the network of neuronal processes imbedded among the surrounding glial cells. Both the communication between neurons and glial cells as well as between neurons themselves depend on eph-ephrin bidirectional signaling (74, 75).

Formation of Neuronal Associations In the developing nervous system, where they play well-known functions in establishing neuronal connectivity by directing axons to the proper destinations and controlling the creation of synaptic connections, eph receptors and ephrins are highly expressed. Eph receptors and ephrins dispersed in gradients or forming borders are essential for the paths of several axonal projections (76,75,77). Over time, various guanine nucleotide exchange factors for Rho GTPases and other Ras/Rho regulatory proteins have been linked to axon guidance by Eph receptors. A GTPase-activating protein for Rac1, α2-chimaerin, has only recently been linked to four concurrent investigations as a crucial EphA4 effector (78,79).

Plasticity of Neuronal Circuits

In the adult brain, eph receptors and ephrins are still present, especially in areas where neuronal circuits are still being remodeled in response to environmental changes (80, 75). In fact, research using mutant mice has demonstrated that the Eph system controls the plasticity of neural connections in regions like the hippocampus, where variations in the size and quantity of synapses are critical for memory and learning. Eph receptor and ephrin synaptic localization has not yet been thoroughly described, but it is increasingly clear that it may vary by brain area and even among synapses from the same neuron (81).For example, as discussed above, in cortical neurons EphB2 is in spine synapses and ephrin-B3 seems

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to be in shaft synapses. B-type ephrin's are presynaptic in area CA3 of the mouse hippocampus and the Xenopus optic tectum but postsynaptic in area CA1 of the hippocampus.

Repair after Injury

Multiple Eph receptors and ephrins have been found to be upregulated in nervous system damage locations. Patterns of developmental expression are sometimes reproduced. In others, cytokines, hypoxia, and other elements found at damage sites control the development of novel patterns. Through their repulsive signaling, certain of the Eph receptors/ephrins produced in brain cells may prevent correct axon regrowth while simultaneously offering guidance signals that allow the re-establishment of suitable connections (82). Eph receptors and ephrins found in meningeal fibroblasts and inflammatory cells that invade the site of damage can also communicate in both directions with Eph proteins that are increased in neural cells, which can have an impact on regeneration.For example, EphB3 expressed in the macrophages recruited to the injured mouse optic nerve promotes sprouting of damaged retinal axons, which express ephrin-B3. Furthermore, the inter play between EphB2 expressed in invading meningeal fibro blasts and ephrin-B2 expressed in reactive astrocytes after rat spinal cord transection appears to promote the segregation of the two cell types and the formation of the glial scar and surrounding basal lamina. It is becoming clear that the EphA4 receptor inhibits neuron regeneration. This receptor is seen in both reactive astrocytes and injured corticospinal axons following spinal cord injuries (83). Examination of EphA4-deficient animals and EphA4 infusion

Glucose Homeostasis and Diabetes

To keep the body's glucose homeostasis, the pancreatic β cells modify the amount of insulin they secrete in response to blood glucose levels. Insulin secretion has long been recognized to be modulated by communication between β cells grouped in pancreatic islets, but the underlying molecular mechanisms were not understood. Eph A receptors and ephrin-A ligands are the means by which β cells communicate, according to a recent study that used mouse models and cultured cells (84). It is noteworthy that pancreatic cells can exhibit differential regulation of ephrin-A forward signaling, which inhibits insulin production, and ephrin-A reverse signaling, which promotes insulin secretion (Figure 9).

Eph A forward signaling takes over when glucose levels are low, which lowers basal insulin secretion. Without affecting ephrin-A reverse signaling, glucose dephosphorylates the Eph A receptor, which results in a downregulation of Eph A forward signaling. As a result, reverse signaling increases insulin secretion when glucose levels are high. Another twist is that whereas ephrin-A ligands are primarily found on the plasma membrane, intracellular insulin secretory granules also contain Eph A receptors.

This suggests that Eph A levels on the plasma membrane, and therefore Eph A-ephrin-A complexes, increase upon insulin release. This causes a negative feedback loop that limits insulin secretion through increased Eph A signalling when glucose levels are low and a positive feedback loop that potentiates secretion through increased ephrin-A signalling when glucose levels are high (Figure 9)

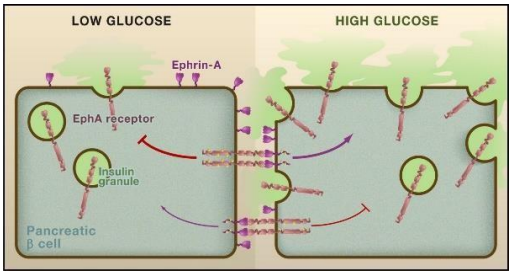

Figure 9 Eph A-Ephrin-A Bidirectional Signalling and Insulin Secretion

Forward signaling predominates at low glucose levels, limiting insulin secretion; reverse signaling predominates at high glucose levels, boosting insulin secretion. While Eph receptor molecules are also found in secretory granules, Ephrin-A molecules are mostly found on the cell surface. Stronger signals are indicated by thicker lines; tyrosine phosphorylation is indicated by yellow circles.

Bone Maintenance and Bone Remodelling

Conditions Skeletal abnormalities may result from developmental deficits in Eph B/ephrin-B signaling. In mice with EphB2/EphB3 and ephrin-B1 mutations, as well as in people with ephrin-B1 mutations that result in the X-linked developmental condition crania frontonasal syndrome, these include cleft palate, craniosynostosis,

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and other bone abnormalities (85,). It's interesting to note that ephrin-B1 heterozygous females' random X chromosome inactivation results in mosaic ephrin-B1 expression in calvaria osteoblast precursors, which leads to aberrant cell sorting and abnormalities in bone growth.

According to a model supported by genetic and other data, ephrin-B1 positive and negative osteoblast precursors form ectopic boundaries, and EphB-ephrin-B1 bidirectional signaling at these boundaries results in impaired gap junction communication. This inhibits osteoblast differentiation and delays the ossification of developing calvariae bones.

The Eph forward signalling pathway responsible for osteoblast differentiation may involve RhoA inactivation. Hence, cell contact-dependent communication between Eph receptors and ephrin's limits osteoclast differentiation and enhances osteoblast differentiation, inducing a shift from bone resorption to bone formation. Indeed, transgenic overexpression of EphB4 in osteoblasts has been shown to increase bone mass in mice.

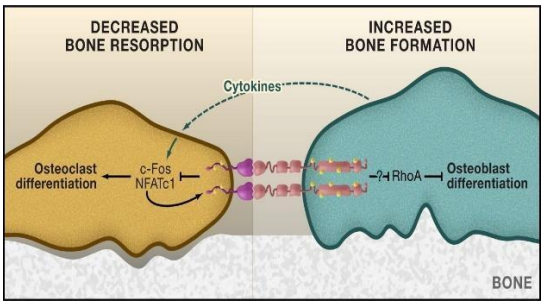

Figure 10: Ephrin-B-Eph B Signaling in Both Directions During Bone Formation Ephrin-B2 is upregulated in osteoclast precursors by cytokines secreted by osteoblasts. Osteoclasts' Ephrin-B ligands interact with osteoblasts' Eph B receptors to produce two-way signals that suppress osteoclast differentiation and encourage osteoblast differentiation.

6. ROLES IN PATHOLOGY

CANCER

Through bidirectional signaling and interaction with other signaling systems, eph receptors and ephrins, which are aberrantly expressed in tumors, can significantly impact malignancy (87). Depending on the biological context, these various signaling modalities can have a variety of impacts on cancer cells, some of which may be opposing. Eph/ephrin expression can fluctuate during the course of cancer due to chromosomal amplification or loss, transcriptional control by oncogenic signaling pathways, promoter methylation, and microRNAs, all of which are consistent with their capacity to either enhance or inhibit tumorigenicity (88).

The Eph receptors that are most frequently overexpressed in tumors are EphA2 and EphB4, and their involvement in cancer malignancy is supported by the fact that downregulating their expression usually reduces tumorigenicity. Remarkably, reduced tyrosine phosphorylation frequently corresponds with high Eph receptor expression in cancer cells. This suggests that Eph forward signaling reduces malignancy (89) and that Eph oncogenic actions are caused by unconventional signaling mechanisms (Figure 11). In fact, a large number of Eph cancer mutations that have been identified thus far affect ephrin binding or kinase activity (90,91). However, there are instances in which ephrin-induced Eph receptor activation increases malignancy; in these cases, this is because cancer cells have developed a "oncogene addiction" that allows them to avoid the detrimental consequences of Eph forward signaling (92).

The roles of eph and ephrin in fostering drug resistance are also starting to come to light. For instance, research using tumor xenografts demonstrate that EphA2 can increase resistance to human epidermal growth factor receptor 2 (HER2)-targeted therapy and the antioestrogen tamoxifen in breast cancer, while Ephrin-B2 can increase resistance to anti-VEGF therapy in glioblastoma. Additionally, ephrin-B3 has been linked in cell culture studies to lungs. Examples of non-canonical signaling mechanisms involving Eph receptors and ephrins that happen independently of Eph receptor-ephrin contact and through interaction with other signaling systems.

Brain cancer

The most common kind of primary brain tumor is glioblastoma (94). Because of its "stem cells," which are extremely resistant to radiation and chemotherapy and have the ability to grow tumors again after treatment, it is extremely aggressive. It was recently discovered that the EphA2 and EphA3 receptors limit ERK MAP kinase activity in an ephrin-independent manner, hence promoting the self-renewal of glioblastoma stem cells and inhibiting their differentiation (95). Furthermore, the

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most aggressive tumors had higher levels of EphA2 serine 897 phosphorylation, especially in the stem cell population. This suggests that EphA2 phosphorylation by AKT (Figure 11) plays a significant role in the malignancy of glioblastoma (96).

In fact, glioblastoma xenograft tumorigenicity was significantly decreased by downregulating EphA2 or EphA3 expression through RNA interference or by administering high concentrations of ephrin-A1 Fc (95). However, in line with the documented link between ephrin-A1 downregulation and glioblastoma aggressiveness, EphA2 forward signaling activation can also reduce EphA2 serine 897 phosphorylation and block the AKT-mTORC1 oncogenic pathway.

By enhancing fibroblast growth factor (FGF) receptor oncogenic signaling in an ephrin-dependent way, EphA4, another Eph A receptor, can stimulate glioblastoma cell migration and proliferation (94). Additionally, it has been demonstrated that EphB2, which is increased in glioblastoma due to low microRNA-204 levels, promotes invasiveness while suppressing proliferation in mouse orthotopic xenografts and neutrospheres produced from glioblastoma (94,97,98). Since EphB2 forward signaling is necessary for these effects, blocking EphB2 expression or signaling may aid in preventing glioblastoma cells from infiltrating the brain; however, this should be done in conjunction with measures to prevent proliferation. EphB2 overexpression in mouse neural stem cells devoid of the Ink4a/Arf tumor suppressor resulted in the development of tumors that resembled human ependymomas, and the EphB2 gene is likewise amplified in a subgroup of human ependymomas (99).

Eph system dysregulation in cancer

Expression in tumours

Tumour Angiogenesis

In contrast to their expression in normal tissues, cancer cells may exhibit up- or down-regulation of eph receptors and ephrins (100). This is in line with their dual roles in either accelerating or slowing spread of cancer (101). Eph receptor downregulation in later stages of tumorigenesis can occasionally occur after Eph receptor overexpression at early stages, indicating different roles in tumor growth vs progression (102,103). For instance, in colorectal and breast cancer, there may be opposite regulation of ephrin expression and eph receptor. probably to lessen Eph forward signaling's tumor-suppressive effects. In fact, a positive predictive factor for melanoma and breast cancer may be a high expression of the Eph receptor and ephrin.

Research has shown that EphA2 forward signalling and ephrin-B2 reverse signalling are the main contributors to tumours angiogenesis. This has been demonstrated through both cell-based studies and experiments in mouse tumours models, including studies using EphA2 knockout mice. Interestingly, EphA2 is absent from normal blood vessels during embryonic development and in resting adult vasculature, but it becomes active in tumours blood vessels. Its activation is triggered through interaction with ephrin-A1, which is present on both tumours' endothelial cells and tumours cells.

An alternative way to facilitate tumours perfusion independent of tumours angiogenesis is the concept of vasculogenic mimicry (104,105) Thereby it is assumed that tumours cells re-express endothelial and mesenchymal markers, normally appearing on embryonic cells. This is accompanied by induction of vascular structures mimicking blood vessels and thus promoting tumours growth. For instance, metastatic melanoma cells are able to constitute channels filled with blood cells. These tubules exhibit a basal lamina but no ECs and the formation seems not to be dependent of b FGF, TGFβ, VEGF, PDGF, TNF-α, hypoxia, or integrins (106). In consequence, the formation of tubular networks on one hand results in better supply with nutrients and oxygen, on the other hand it can facilitate the invasion of tumours cells into the blood flow, thus, promoting metastasis Although the underlying mechanisms are not fully understood, the involvement of receptor tyrosine kinases, especially Eph receptors, is strongly suggested. In an in vitro study Hess and colleagues showed that transient knockout of EphA2 expression in aggressive uveal melanoma tumours cells resulted in inhibition of tubular network formation. Further the authors found that phosphorylation of EphA2 by ephrinA1 leads to activation of downstream signalling kinases such as FAK and PI3 kinase and, furthermore, to the formation of vessel-like networks.

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b. EPHRIN/EPH IN CARDIOVASCULAR DEVELOPMENT

Eph and Ephrin's are dispensable for cardiovascular development, orchestrating processes such as embryonic vasculogenic and angiogenesis. Notably, EphrinB2 and EphB4 are well-known markers of arteries and veins, respectively (107) and function as key modulators throughout cardiovascular development. During vessel formation, EphrinB2 and EphB4 mediate the repulsion and segregation signals necessary for the organization of ECs. (108) For instance, knockdown of EFNB2 in human umbilical arterial ECs (HUAECs) or EphB4 in HUVECs resulted in the intermingling of HUAECs and HUVECs, confirming the crucial role of EphrinB2/EphB4 signalling in arteriovenous segregation (109).

EphrinB2 functions as a proangiogenic effector (110,111) Research employing EphrinB2 mutants has revealed its pivotal role in angiogenesis, with mutations resulting in defective capillary network formation. In transgenic mice model ectopically expressing EphrinB2, defective recruitment of vascular smooth muscle cells (SMCs) has been observed, leading to sudden neonatal death Further research has confirmed that EphrinB2 is required for the normal assembly of the blood vessel wall, particularly in the recruitment and organization of SMCs.31 Moreover, EphrinB2 regulates EC behaviours such as migration and angiogenesis. Specific deletion of EphrinB2 in endothelial and endocardial cells phenocopied the embryonic angiogenesis defects observed in conventional EphrinB2 mutants (112).

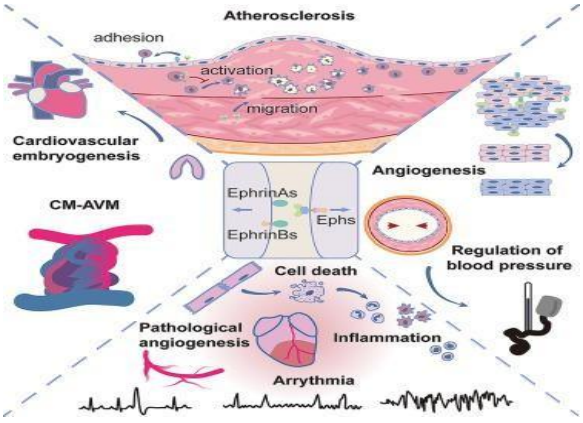

Figure 11. Functions of the Ephrin/Eph family in cardiovascular physiological role

7. Future Perspectives

CRISPR/Cas9 for Gene Modulation of Eph Receptors

Advances in genome editing technologies, particularly CRISPR/Cas9, provide promising opportunities to precisely modulate Eph receptor and ephrin expression. By selectively knocking out or repairing dysfunctional genes, this approach may help in understanding receptor–ligand functions and in developing therapeutic strategies for cancer, neurological disorders, and vascular diseases.

Nanoparticle-Based Delivery Systems

Nanoparticle-mediated drug delivery offers a targeted and efficient method to deliver small molecules, antibodies, or siRNAs against the Eph–ephrin axis. Such systems enhance bioavailability, reduce systemic toxicity, and allow precise delivery to tumor vasculature or disease-specific tissues, improving therapeutic outcomes.

Artificial Intelligence in Drug Design Targeting the Eph–Ephrin Axis

Artificial intelligence (AI) and machine learning algorithms are transforming the drug discovery process. By integrating structural biology, high-throughput screening, and predictive modeling, AI can accelerate the identification of small molecules or biologics targeting Eph receptors. This can shorten development timelines and improve the specificity of candidate therapeutics.

Personalized Medicine and Patient-Specific Eph Expression Profiles

Patient-specific profiling of Eph receptor and ephrin expression patterns opens the path toward precision medicine. Stratifying patients based on molecular signatures can help tailor therapies to maximize efficacy and minimize resistance. Such approaches may integrate genomic, transcriptomic, and proteomic data to create individualized treatment regimens.

8. Conclusion

The Eph–ephrin signaling system represents one of the most versatile cell–cell communication networks in human biology. Its roles extend far beyond developmental processes such as tissue patterning, axon guidance, and vascular remodeling, into critical

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functions in adult physiology and disease. Dysregulation of Eph receptors and ephrins has been implicated in cancer progression, angiogenesis, neurodegenerative conditions, immune modulation, and metabolic disorders, underscoring their broad impact on health and pathology.Despite this wealth of biological insight, the therapeutic potential of the Eph–ephrin axis remains largely untapped. Challenges such as bidirectional signaling, context-dependent effects, and receptor redundancy have slowed progress in translating laboratory findings into clinical therapies. However, advances in gene editing (CRISPR/Cas9), nanotechnology-based delivery systems, and AI-driven drug discovery provide powerful tools to overcome these barriers.Looking forward, there is an urgent need for translational research that bridges fundamental discoveries with clinical application. Strategies that integrate patient-specific Eph expression profiling with targeted drug delivery platforms may offer a new era of precision medicine for conditions ranging from cancer to neurological disorders. By leveraging cutting-edge technologies and interdisciplinary approaches, the Eph–ephrin signaling pathway holds great promise as a next-generation therapeutic target.

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