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Editor: Kazuhiro Hongo, M.D., Shinsui University, Matsomoto, Japan

Review Article

Neurovascular patterning cues and implications for central and peripheral neurological disease

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Received: 06 December 16 Accepted: 28 June 17 Published: 06 September 17

Abstract

The highly branched nervous and vascular systems run along parallel trajectories throughout the human body. This stereotyped pattern of branching shared by the nervous and vascular systems stems from a common reliance on specific cues critical to both neurogenesis and angiogenesis. Continually emerging evidence supports the notion of later-evolving vascular networks co-opting neural molecular mechanisms to ensure close proximity and adequate delivery of oxygen and nutrients to nervous tissue. As our understanding of these biologic pathways and their phenotypic manifestations continues to advance, identification of where pathways go awry will provide critical insight into central and peripheral nervous system pathology.

Key Words: Angiogenesis, axon guidance, neurogenesis, neurosurgery, vascular endothelial growth factor

Access this article online
Website: www.surgicalneurologyint.com
DOI: 10.4103/sni.sni_475_16
Quick Response Code:

INTRODUCTION

The ability to perceive and integrate multiple sensory inputs and produce an appropriate and directed response explains much of the evolutionary success of kingdom Animalia. Neurons began as specialized cells capable of generating electrochemical gradients and propagating electric potentials to neighboring cells. As primitive nervous systems evolved, from simple nerve nets to distinct nerve cords with eventual cephalization, the parallel branching of vascular channels made development of the human central and peripheral nervous systems possible.[7,102]

The increasing efficiency and complexity of evolving nervous systems necessitated greater metabolic demands and distributive capacity of the organism. During development, patterning cues generate rostrocaudal and dorsoventral domains that ultimately go on to differentiate into tissues and organs. Given the graded complexity and rapid cycles of proliferation necessary to generate the cell required for specification of tissues and organs, respiring organisms have developed expansive parallel vascular networks (consisting of arteries, veins, and capillaries) capable of delivering oxygen and nutrients and removing waste from nerve tissue [Figure 1]. The gross organizational similarities between nervous and vascular networks supplying various organs

How to cite this article: Gamboa NT, Taussky P, Park MS, Couldwell WT, Mahan MA, Kalani MY. Neurovascular patterning cues and implications for central and peripheral neurological disease. Surg Neurol Int 2017;8:208.
http://surgicalneurologyint.com/Neurovascular-patterning-cues-and-implications-for-central-and-peripheral-neurological-disease/

of the human body were first documented by anatomist Andreas Vesalius in the 15th century. Although neural tissue is derived from the ectoderm and vascular tissue from mesoderm, continually emerging evidence supports similarities in their branching patterns based on shared mechanistic underpinnings.[22,144] Through genetic, biochemical, and molecular approaches, the exact mechanisms regulating their common wiring have been the subject of increasing interest.

Evidence continues to emerge demonstrating how neuronal axon growth, branching and arborization, and angiogenesis rely on similar growth factors and receptors for their parallel and seemingly intertwined development. As more complex neuronal circuitry evolved, it seems that the later-evolving vascular networks may have co-opted their molecular mechanisms to ensure close proximity and adequate delivery of oxygen and nutrients to traveling nerves. In this review, we examine the similarities and differences between neurogenesis and angiogenesis, the current evidence regarding their mechanisms, their reliance on one another for normal physiology, and the aberrancies in these processes that precipitate neurosurgical pathology.

NEUROGENESIS

Axonal growth cones

The nervous and vascular systems appear grossly similar, consisting of highly branched networks that parallel one another throughout the human body; however, at a microscopic level, their initial formation appears quite distinct. Neurons begin by thrusting a long axon outward, headed by the sensory neuronal growth cone. The path of this growth cone is dictated largely by attractant and repulsive guidance proteins secreted by individual target cells along with the specific expression pattern of receptors on the growth cone itself.[107] As the growth cone pokes and prods the environmental milieu of guidance cues, it samples its surroundings through the rapid cycling of actin-stabilized filopodial extensions.[22,34] These terminal nerve processes are capable of sensing attractive and repellant cues, guiding them to their final targets with significant precision. Once the growth cone makes contact with suitable target cells (e.g., striated skeletal myofiber or target nerve cells), the microtubules and organelles rapidly flow toward the contact point in preparation for terminal arborization and ultimate synaptogenesis.

Modern genetic and molecular techniques have revealed highly conserved families of guidance molecules involved in axonal guidance. These guidance molecules can either attract or repel the neuronal growth cone, are capable of operating over both short and long distances, and can influence the bundling of axons together into nerve fascicles.[136,163] The four major axon guidance cue families are the semaphorins, slits, netrins, and ephrins. Each of these secreted guidance proteins interacts with a cognate transmembrane receptor on the growth cone surface to trigger attraction, adhesion, or repulsion by the traveling axon [Figure 2]. In addition to these canonical families of axon guidance proteins, classic morphogens are increasingly appreciated for having a key role in axon guidance and overall nervous system development.[67]

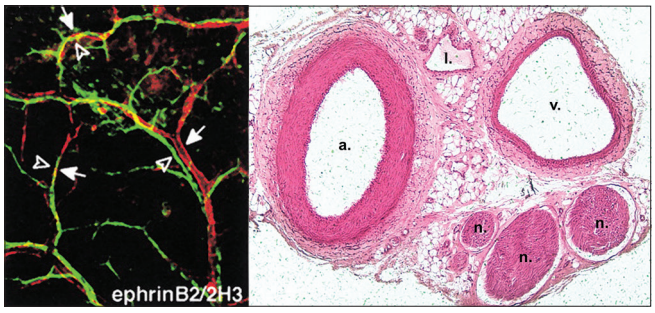

Figure 1: Parallel alignment of developing arteries and nerves. (Left) Whole-mount immunofluorescence confocal microscopy with antibodies to endothelial marker PECAM-1 and neuronal marker Tuj-1. Note the coalignment of main sensory nerves (green) with their arteries (red). Reproduced with permission.[115] (Right) H and E-stained section of neurovascular bundle at 400 × total magnification showing close proximity of nerve fascicles (n.) with parallel arterial (a.), venous (v.), and lymphatic (l.) supply (courtesy of Marie McMahon, Ph.D. in the Department of Natural Sciences at Miramar College, San Diego, CA)

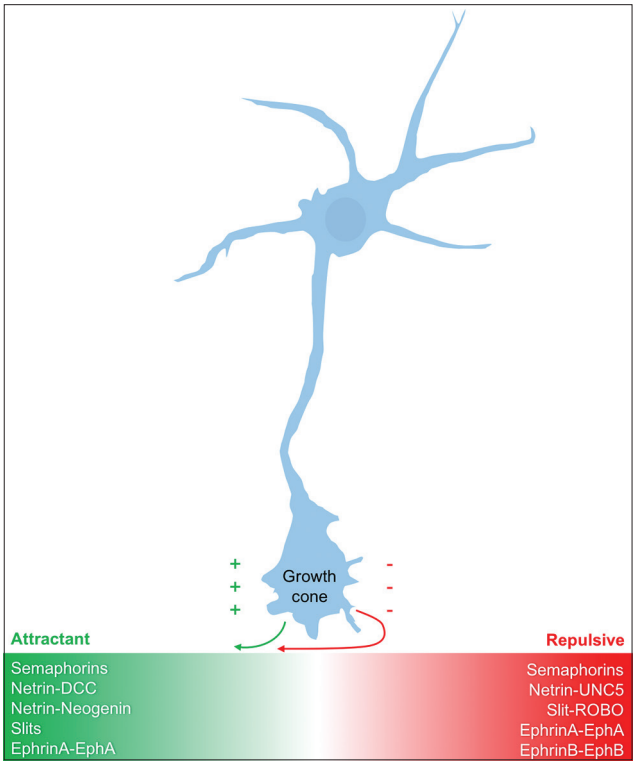

Figure 2: Schematic representation of growth cone response to classic family of axonal guidance cues: semaphorins, netrins, slits, and ephrins. Guidance cues can trigger an attractant response (green) or a repulsive response (red) in the traveling axonal growth cone

Semaphorins

Semaphorins are a large, diverse, and phylogenetically conserved family of both secreted and membrane-associated proteins.[89,174] Although they were initially characterized as repellants, a secreted semaphorin (Sema3A) has been demonstrated to also function as a chemoattractant depending on intracellular concentrations of cyclic nucleotides.[155,156] Semaphorin proteins act through multimeric receptor complexes. Membrane-bound semaphorins bind to plexin receptors, whereas secreted class 3 semaphorins (Sema-3a–3G) instead bind to obligate coreceptor neuropilins (e.g., neuropilin-1, neuropilin-2), which function as non-signaling coreceptors with a specific plexin, forming a holoreceptor complex. Plexin receptor activation initiates an intracellular signaling cascade, which ultimately results in the local disassembly of the axonal growth cone's filopodial cytoskeletal components (i.e., growth-cone collapse).[177] Interestingly, although neuropilins were initially described for their role as class III-semaphorin receptors, new evidence demonstrates neuropilins acting as vascular endothelial growth factor-165 ($VEGF_{165}$) isoform-specific coreceptors, thus performing dual roles in both nerve and blood vessel development.[117] In 1999, Kawasaki *et al*.[83] demonstrated that absence of a functional neuropilin-1 receptor precipitated embryonic lethality via impaired heart and blood vessel development, thus substantiating its essentiality in vasculogenesis and angiogenesis. Furthermore, a recent study demonstrated that, with specific silencing of VEGFR2, vascular permeability was still induced via neuropilin-1-mediated effects.[69,140] In addition to its effects on vasculature, inadequate repulsion via semaphorin cues has been shown to result in defects of axonal projection (i.e., trajectory errors, ectopic termination).[51] Recent studies have implicated semaphorin proteins in the dendritic pruning of hippocampal neurons, thus showing critical importance of these proteins for nervous system development, maintenance, and maturation.[11,100,128]

Netrins

Netrins are a small family of evolutionarily conserved proteins that are either secreted (netrin-1, netrin-3, netrin-4) or membrane-bound via glycosylphosphatidylinositol (GPI)-anchoring (netrin-G1, netrin-G2). Netrins were first identified in studies of *Caenorhabditis elegans* as ventral midline-derived chemoattractants that helped guide axons to the midline through binding to the DCC (deleted in colorectal carcinoma) family of receptors.[36,85] Specialized floor plate cells located at the ventral midline of the embryonic mouse brain have been shown to secrete a gradient of netrin-1.[85] Netrin-1 mutants and DCC-knockout mice demonstrate a lack of development of the corpus callosum and hippocampal commissure and have a markedly reduced or completely absent anterior commissure, thus demonstrating the importance of netrin-1 in the development of laterally directed cortical axons.[43,149] Similar results were demonstrated in *C. elegans* using the netrin-1 homolog, Unc-6.[121] Netrins interact with Unc-5, DCC, and neogenin receptor families and, like semaphorins, are capable of acting as chemotropic attractants or repellents. In addition to these functions, recent studies have shown a critical role of netrins in angiogenesis by stimulating endothelial proliferation, migration, and endothelial tube formation.[165,171] Investigators have demonstrated that netrin-1 and Unc-5b are expressed at high levels in endothelial tip cells. Other experiments have also demonstrated that knockout of UNC5B in the murine model results in aberrant extension of tip cell filopodia with excessive vascular branching, thus reaffirming the importance and overlapping of these neuronal guidance cues in both neurogenesis and angiogenesis.[103] Recent studies have shown that netrin-1 signaling can inhibit vascular sprouting of UNC5b-expressing endothelial cells.[17,90,103] Collectively, these results indicate a need for further research regarding netrins, their receptors, and their effects on blood vessel growth and maintenance.

Slits

During development of the embryonic nervous system, commissural axons are initially attracted by cues derived from netrin-DCC interaction. Once axons are at the midline where netrin levels are highest, this attractive signal must be silenced to prevent stalling or recrossing. This silencing is mediated largely by Slit proteins, which, like netrins, are also made by ventral midline cells in the developing embryo.[35,41] Silencing is achieved when Slit proteins bind to receptors of the Robo (Roundabout) family, which subsequently form a multimeric complex with DCC, thereby stifling netrin's attractant effects and preventing aberrant midline recrossing.[158]

Slits are a family of large secreted glycoproteins initially discovered for their repellant effects in *Drosophila melanogaster* (fruit fly) axons crossing the ventral midline, but they have also shown dual functionality as attractant cues to navigating axons.[27,35] These repulsive cues from Slit proteins are mediated via receptors of the Robo family, which propagate an intracellular response via cytoplasmic kinases (namely, Abl tyrosine kinase) and GTPases with subsequent cytoskeletal modifications.[86,123] In addition to Slit-mediated effects on axon and dendritic branching, recent studies have demonstrated important roles of Slit-Robo signaling during angiogenesis.[40] In 2003, Park *et al*.[127] discovered a vascular-specific Robo homolog, Robo4, which was exclusively expressed by murine vascular endothelium during embryonic development. Their studies also concluded that Robo4 inhibited endothelial cell migration. Additional studies have shown that, while Robo4 inhibits angiogenesis, Slit2/Robo1 interaction induces migration of human umbilical vein endothelial cells (HUVECs) *in vitro*.[15,79] Moreover, the repulsive axon guidance protein Slit3 has demonstrated bifunctionality

as a potent pro-angiogenic growth factor essential for vascular development in murine embryogenesis.[175] Nonetheless, additional studies are needed to further elucidate the roles of Slits and Robos in the embryonic development of the vascular system.

Ephrins

Eph receptor tyrosine kinases (RTKs) and their membrane-bound ligands, the ephrins, act principally as short-range axon guidance molecules and play important roles in the developing nervous system through their effects on axon guidance and synaptogenesis.[82,104] Interactions between Eph and ephrins are known to mediate cell-contact–dependent signaling and have been implicated as critical mediators of patterned cellular organization.[61,66,120] Ephrins and Eph receptors are split into two classes: Ephrin-As, which are tethered to the cell membrane via GPI-linkage and bind EphA receptors; and Ephrin-Bs, which have a transmembrane domain and bind EphB receptors.[170] Eph proteins activate signaling pathways that affect the cellular cytoskeleton, leading to cellular repulsion, or in certain instances, cell adhesion. Similar to semaphorin-plexin–induced filopodia cytoskeletal disassembly, Eph/ephrin signaling also leads to axonal growth cone immobilization and collapse.[81] The effects of Eph/ephrin on axonal growth have been shown to be essential for axonal projection from retina to tectum, retina to lateral geniculate nucleus (LGN), hippocampus to lateral septum, and thalamus to cortex.[45,56,57] Recent advances have shown Ephrins and Eph receptors also play important roles in dendritic spine formation and synaptic plasticity.[124] Interestingly, these same molecular cues have been shown to control vascular development and were some of the first demonstrated factors to be selectively expressed in arterial or venous vasculature.[169] Loss-of-function studies in murine models showed that ephrin-B2 and its receptor Eph-B4 are expressed selectively in developing arteries and veins, respectively, and are critical to maintenance of these vessels.[3] Numerous studies have demonstrated an important role of Eph/ephrin signaling in the demarcation of arterial–venous boundaries, indicating they are critical to the process of angiogenesis. Similar to our understanding of the other classic axonal guidance cue families, our knowledge and understanding of the dual functionality of Eph/ephrin on developing nervous and vascular systems is continuing to unfold, although continually emerging data are garnering appreciation for the shared but diverse effects these proteins exert. The extent of phenotypic homology of temporo-spatial relationship of these signaling pathways between vertebrates and invertebrates is an ongoing area of investigation.

MORPHOGENS

Morphogens are signaling factors that direct cell fate and tissue development in a restricted region of tissue by providing gradient-mediated positional information. Morphogens exert their effects by being produced in a particular region of tissue and then diffusing from this source, thereby establishing gradients. The asymmetry of gradients produced by morphogens allows for production of different cell types across the gradient. This is further complicated by overlapping regions of signaling gradients produced by multiple morphogens. Two factors determine whether a secreted protein can be classified as a morphogen: first, it must act in a concentration-dependent manner on its target cells/tissues; and second, it must exert a direct effect from a distance. A large number of morphogens have been identified to date, although the canonical morphogen families include the hedgehog (Hh), Decapentaplegic (DPP)/transforming growth factor-β (TGF-β)/bone morphogenetic proteins (BMPs), and Wnt signaling pathways [Figure 3]. Morphogens may have context-dependent effects during various windows of development. The Notch signaling pathway, for example, has an inhibitory role during neurogenesis but promotes specification of neuronal subtypes at later developmental windows.[73] Morphogen gradients are essential in embryonic development of all organ systems throughout the body because they act as graded positional cues essential for specification of cell fate and ultimate tissue patterning. In addition to their embryonic roles in body patterning, their important roles in both axonal guidance and angiogenesis are being supported by increasing evidence.[24,32]

Hedgehog family

In the early 1980s, the fundamental problem in developmental biology of how a single-celled zygote could give rise to complex, highly organized, segmented organs and tissues was solved through the discovery of mutations in genes controlling anterior–posterior body axis polarization in *Drosophila* embryogenesis.[122] The *Drosophila* hedgehog (Hh) was identified as one of the genes essential for wild-type anterior–posterior body patterning and segmentation in fruit flies. The function of Hh signaling in vertebrate embryos acts similarly but through three different ligands – Sonic hedgehog (Shh), Desert hedgehog (Dhh), and Indian hedgehog (Ihh). Shh is secreted by the notochord and floor plate cells at the ventral midline of the developing embryonic neural tube.[74,78] Shh has been shown to induce a range of ventral spinal cord cell fates in a concentration-dependent manner and can exert direct effects at a distance through specification of neural tube cell fate.[18,139] Genetic and molecular studies have elucidated the mechanism underlying Hh signaling: Hh binds to the inhibitory receptor Patched (Ptch1), which leads to relief of inhibition of the transmembrane signaling receptor Smoothened (Smo). This activates downstream signaling and activation of the transcription factor Gli2, mediating

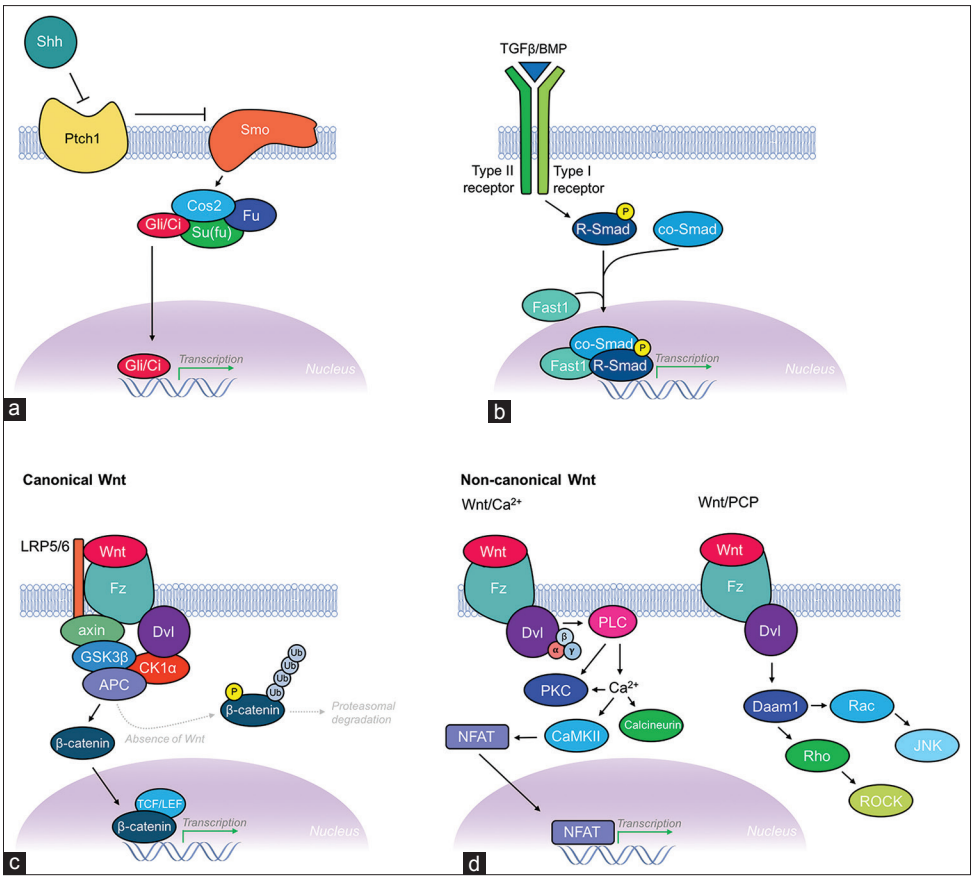

Figure 3: Schematic illustration of the Shh, TGF-β/BMP, and Wnt morphogenic signaling pathways. (a) Shh signaling pathway. Hhs like Shh are known to activate signaling through binding their receptor Patched (Ptch1; a 12-pass transmembrane protein). This leads to relief of inhibition of Smoothened (Smo; a 7-pass transmembrane protein), which then leads to a downstream intracellular signaling cascade. Smo then associates with the Gli/Ci-containing complex, which includes Costal 2 (Cos2), and the protein kinase Fused (Fu) and Su (fu) (suppressor of fused). Together, this complex acts constitutively to suppress the pathway by activating proteolysis of Gli/Ci, thus acting as a transcriptional repressor. Activation of Hh signaling reverses this regulatory inhibition of Gli/Ci, allowing transcription of Hh target genes. (b) TGF-β/BMP signaling pathway. Members of the DPP/BMP/TGF-β family of morphogens regulate cell fate and proliferation through binding to the extracellular domain of type I and type II TGF-β receptors, causing dimerization and autophosphorylation of the type I receptor's intracellular kinase domain. Targets of the type I receptor are the receptor-regulated Smads (R-Smads), which are subsequently phosphorylated inducing their association with co-Smads before translocating to the nucleus where they combine with other DNA-binding proteins (Fast1) to initiate transcription of TGF-β/BMP target genes. (c) Canonical Wnt signaling pathway. The canonical Wnt signaling pathway (β-catenin dependent) pathway controls gene expression through stabilization of intracellular β-catenin. Binding of Wnt to its receptor Frizzled (Fz; a 7-pass transmembrane protein), with coreceptor LRP-5/6, leads to Dishevelled (Dsh) activation and suppression of GSK3β activity, thus preventing phosphorylation, ubiquitination, and proteasomal degradation of β-catenin. This requires formation of a complex scaffolded by axin and adenomatous polyposis coli (APC) proteins. Increased concentrations of β-catenin transform lymphoid enhancer factor (LEF)/T-cell factor (TCF) from transcriptional repressor to activator thereby leading to transcription of Wnt target genes. (d) Non-canonical signaling pathways. The two non-canonical Wnt signaling pathways include the Wnt/Ca^{2+} pathway and the Wnt/planar cell polarity (PCP) pathway. The Wnt/Ca^{2+} pathway also involves binding of Wnt to Fz and subsequent Dsh activation, but instead signals via heterotrimeric G-proteins (α, β, γ subunits) leading to activation of phospholipase C (PLC) and increased intracellular Ca^{2+} concentrations, while simultaneously activating protein kinase C (PKC). Increased Ca^{2+} leads to activation of calcineurin and CaMKII. CaMKII induces activation of the transcription factor NFAT, which leads to transcription of Wnt/Ca^{2+} target genes involved in cell adhesion and migration. The Wnt/PCP pathway also involves Wnt binding Fz leading to recruitment and activation of Dsh, which then forms a complex with Dishevelled-associated activator of morphogenesis 1 (Daam1). Daam1 subsequently activates the G-protein Rho, which leads to activation of Rho-associated kinase (ROCK), a major regulator of the cellular cytoskeleton. Dsh also forms a complex with Rac, which activates JNK and leads to actin polymerization

transcription of target genes and ultimately cell fate specification [Figure 3a].[6,33,75] Shh has been shown to be important in axonal guidance for commissural neurons,[16,26,173] retinal ganglion cells,[42,60,145] and midbrain dopaminergic neurons,[62] and recent evidence suggests that it may guide axons via a transcription-independent pathway. Following a similar theme, hedgehog signaling has also been shown to be capable of inducing angiogenesis through noncanonical pathways.[28,63]

Transforming growth factor-β family

DPP, BMP, and TGF-β are all members of the TGF-β superfamily of morphogens. About the time dorsal neurons are formed at the dorsal midline of the developing embryo, roof plate cells express many of

these members of the TGF-β family as they are required for the dorsal specification of developing neurons.[94] This family of morphogenic proteins regulates cell fate through dimerization of type I (activin receptor-like kinase 1; ALK1) with type II (TGFBR2) TGF-β receptors, resulting in intracellular phosphorylation and activation of the type I receptor's kinase domain [Figure 3b]. Target proteins include receptor-regulated Smads (R-Smads), which are then phosphorylated and associate with co-Smads before translocating to the nucleus for transcriptional activation.[9]

BMPs are known to guide commissural axons through type I and type II TGF-β receptors. In addition, the individual receptor subunits are thought to play a role in downstream signaling events in axon guidance, thus differing specification of cell fate. BMP7:GDF7 heterodimers that are secreted by the roof plate cells have been shown to repel commissural axons ventrally and are also capable of inducing collapse of commissural axon growth cones.[10,21] Finally, TGF-β has been shown to be essential for vascular morphogenesis and blood vessel maturation through mural cell induction, differentiation, and promotion of extracellular matrix production.[125,132]

Wnt family

Wnts are a large family of 19 highly conserved glycoproteins that have three known signal transduction pathways and can initiate different intracellular signaling cascades determining cell fate, proliferation, migration, and polarity. Wnt signaling pathways can be classified into canonical (β-catenin dependent) and noncanonical (β-catenin independent).[29] The canonical pathway is thought to be primarily involved in cellular proliferation and differentiation. It is triggered through interaction of Wnt with Frizzled (Fz) and LRP5/6 [Figure 3c]. This leads to stabilization of intracellular β-catenin, which results in its nuclear translocation and association with transcription factors TCF (T cell factor) and LEF (lymphoid enhancer-binding factor). The noncanonical pathways include the Wnt/PCP (planar cell polarity) and Wnt/Ca^{2+} pathways. In the Wnt/PCP pathway, Wnt interacts with Fz, which leads to activation of a signaling cascade involving Jun-N-terminal kinase (JNK) and the small GTPases Rac1 and RhoA. The Wnt/PCP pathway contributes primarily to cell polarity and tissue morphogenesis. In the Wnt/Ca^{2+} pathway, Wnt interacts with Fz, which triggers Fz-mediated heterotrimeric G-protein activation, leading to subsequent activation of phospholipase C, which leads to an increase in intracellular Ca^{2+} concentration [Figure 3d].[118]

Wnts have been shown to act as axonal guidance cues for post-midline crossing commissural and corpus collosal axons,[72,84,105] axons of the corticospinal tract,[101] and axons of the monoaminergic [serotonergic (5-HT) and dopaminergic (mdDA) neurons] of the brainstem.[46] Moreover, Wnt3 has been shown to be expressed in a decreasing gradient in the neural tube from medial to lateral and to play an important role in mediolateral organization of the optic tectum.[147] Similarly, Wnt signaling has been discovered to play an established role in early endothelial cell differentiation,[168] embryonic vessel remodeling,[24,30] and establishment of vascular networks in organ systems.[32,98,159]

VASCULAR PATTERNING

Vascular development consists of two disparate yet closely interconnected developmental programs – vasculogenesis and angiogenesis. Vasculogenesis is the development of vascular beds from progenitor cells early in the development, whereas angiogenesis is the sprouting of new vessels from pre-existing vasculature. Each of these processes and the signaling cues regulating them will be discussed further below.

Vasculogenesis

Whereas individual axons can traverse vast distances, as evinced by the sciatic nerve, endothelial cells take a more modest approach. Although they cannot individually travel as far, the assembly and proliferation of endothelial cells allows them to mirror the movements of neuronal axons. Vasculogenesis begins with the differentiation of vascular progenitor cells, termed angioblasts, into endothelial cells that migrate and coalesce to form primitive vascular cords.[1,138] These mesenchymal-derived cords then form a lumen (tubulogenesis) and further differentiate following an arterial or venous fate, ultimately forming the central axial vessels (i.e., the dorsal aortae and cardinal veins).[126]

Similar to the glial cells supporting the neuronal circuitry of the cerebrum, the endothelial cells rely heavily on vascular smooth muscle cells and pericytes for their growth, maturation, and vessel stabilization. Soon after differentiating, the endothelial cells begin to secrete platelet-derived growth factor (PDGF) to recruit vascular smooth muscle cells from the surrounding mesenchymal and neural crest-derived embryonic tissue.[55] In response to these signals, vascular smooth muscle cells envelop the endothelial cell-lined vessels, reciprocating with the secretion of growth factors of their own (e.g., angiopoietin).[108] Through autocrine and paracrine hormonal signaling, endothelial and vascular smooth muscle cells converse with one another, ensuring proper interaction. This close approximation of endothelium with vascular smooth muscle allows the fine-tuning of vessel caliber, while also allowing the secretion of extracellular matrix (ECM) proteins, which give vessels structural integrity and elasticity.

Angiogenesis induction

Given the rapidly changing metabolic needs of various tissues throughout the human body, the vascular system

has evolved mechanisms to meet the oxygen and nutrient requirements of nearby respiring tissues. Angiogenesis, which is the sprouting of new vessels from pre-existing vasculature, allows nearby blood vessels to sense tissue hypoxia and respond appropriately.[49] In an area of low oxygen tension, the transcription factor hypoxia-inducible factor-1α (HIF-1α) escapes a hydroxylation "tag" by prolyl hydroxylase (PHD) enzymes, ultimately evading the von Hippel-Lindau protein (pVHL) complex and preventing ubiquitin-proteasome–mediated degradation [Figure 4].[112,154] Consequently, tissue hypoxia leads to a rise in HIF-1α, which translocates to the nucleus to act as a fundamental transcription factor for numerous pro-angiogenic genes.[23,92] HIF-1α upregulates the expression of VEGF-A, matrix metalloproteinase-2 (MMP-2), fibroblast growth factor (FGF), and TGF-β, which allow endothelial cell proliferation and basement membrane and ECM remodeling necessary for growth of new blood vessels towards the target hypoxic tissue.[93,148] HIF isoforms are also critical for initiation of blood islands and their contribution to early vasculogenesis.

VEGF-A stimulates endothelial cell proliferation and migration and is critical for both vasculogenesis and

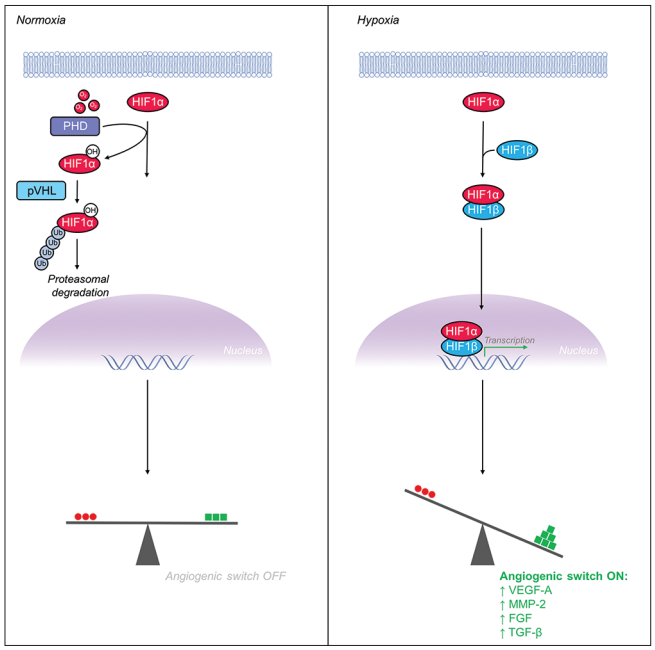

Figure 4: Hypoxia inducible factor-1α (HIF-1α) is a major transcriptional regulator whose levels increase in hypoxia, leading to flipping the "angiogenic switch" on. (Left) Under normoxic conditions, HIF-1α is hydroxylated by prolyl hydroxylase (PHD) enzymes and the VHL-mediated ubiquitin proteasome pathway rapidly degrades HIF-1α, maintaining low levels of intracellular HIF-1α. (Right) Under hypoxic conditions, the PHD enzymes, which require oxygen as a substrate, are unable to hydroxylate HIF-1α's proline residue thus leading to escape from the degradation pathway and increased levels intracellular HIF-1α. Accumulation of HIF-1α leads to formation of a heterodimer with HIF-1β before translocating to the nucleus to serve as a potent activator of pro-angiogenic gene expression

angiogenesis. VEGF-A induces angiogenesis through binding to its primary tyrosine kinase receptor VEGFR2 and initiating the RAS/RAF/MEK/ERK signaling cascade.[68] Moreover, multiple isoforms of VEGF-A have been shown to exist, each with varying functionality.[172] VEGF-A accomplishes this through alternative splicing of an 8-exon mRNA transcript of the *VEGFA* gene. These different isoforms of VEGF-A are distinguished by the presence or absence of heparin-binding domains, and thus heparin/ECM affinity. $VEGF_{189}$ contains two heparin-binding domains and is thus highly ECM-bound, whereas $VEGF_{121}$ lacks heparin affinity making it the highly diffusible VEGF variant. $VEGF_{165}$ is the most highly expressed isoform and possesses intermediate characteristics attributed to its moderate heparin affinity.[44,47] Transgenic mice exclusively expressing the highly diffusible $VEGF_{120}$ isoform were found to develop enlarged vessels with few branches, whereas mice solely expressing the highly bound $VEGF_{189}$ formed narrow vessels with supernumerary branch points.[58] These different VEGF-A isoforms thus allow for the establishment of VEGF gradients in the extracellular milieu, playing a critical role in the physiologic balance of vessel size and branching.[143] Whereas the VEGF signaling pathway is critical in the early stages of vasculogenesis, the more mature vascular states are influenced by TGF and PDGF signaling cascades regulating pericyte and smooth muscle fates.

Sprouting and tip cell selection

Capillary endothelial cells, much like the neuronal growth cones, are capable of sensing and responding to environmental cues by sprouting and growing towards chemotactic signals. Initially, quiescent endothelial cells specify into tip and stalk cells in a process controlled largely via the Notch pathway.[2,129] Endothelial tip cells are the vascular counterpart of axonal growth cones and act to spearhead the vascular sprout with their numerous rapidly cycling actin-stabilized filopodial extensions. Tip cells are induced in response to VEGF-A binding to its main receptor, VEGFR2, which leads to increased surface expression of the Notch ligand, Delta-like ligand 4 (Dll4).[95,119,153] Upregulation of Dll4 denotes the tip cell phenotype while simultaneously suppressing the tip cell gene expression in neighboring endothelium via Notch signaling [Figure 5].[65,137] High Notch signaling in nearby cells leads to decreased surface expression of VEGFR2, which results in a stalk cell phenotype.[80] Notch signaling activation in stalk cells also leads to increased VEGFR1 levels, as well as expression of multiple Notch target genes, namely Notch-regulated ankyrin repeat protein (Nrarp) and subsequent Wnt signaling.[30] It should be noted, however, that tip and stalk cells are merely transient phenotypes, not differentiated cell fates. It is thought that fine-tuning of Notch signaling duration and amplitude thus likely determines tip and stalk

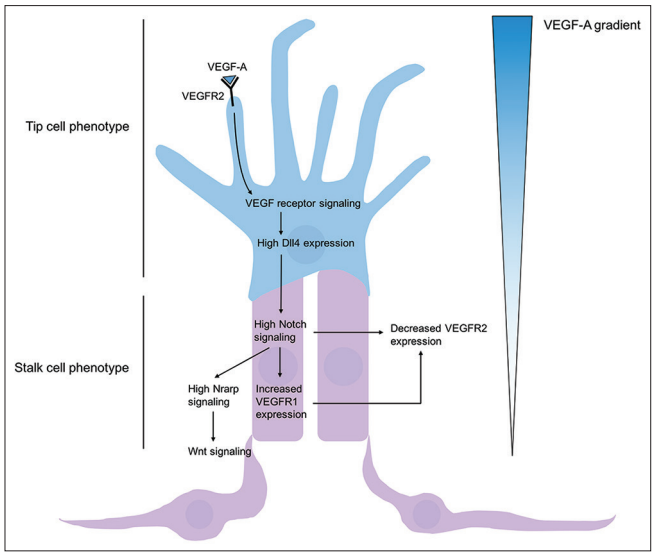

Figure 5: Regulation of tip and stalk cell formation. VEGF-A gradient determines tip cell selection, and subsequent Dll4-Notch signaling induces stalk cell phenotype of nearby endothelium. High concentrations of VEGF-A bind and activate VEGFR2, leading to increased expression of membrane-restricted Dll4 in the tip cell. Dll4 acts in a juxtacrine manner with Notch1 receptors, thus promoting Notch signaling of adjacent epithelium and leading to gene expression promoting a stalk cell phenotype. High Notch signaling leads to high Notch-regulated ankyrin repeat protein (Nrarp) and Wnt signaling

transition duration, thereby affecting vessel branching frequency.[132]

ABERRANT SIGNALING IN NEUROVASCULAR PATHOLOGY

The intimate association and codependency of nervous and vascular tissue in the central and peripheral nervous systems is essential for normal development and physiology. Aberrancies in these processes drive much of neurosurgical pathology. Through a better understanding of the mechanisms underlying normal physiology of nervous and vascular tissues, understanding of dysregulation from a genetic and molecular approach can lead to new therapeutics or treatment approaches for neurosurgical patients.

Arteriovenous malformations

Arteriovenous malformations (AVMs) are vascular lesions that are characterized by a tangle of abnormal vessels that directly shunt blood from arterial to venous circulation without an interposed capillary bed. Cerebral AVMs most commonly occur sporadically but can also be associated with genetic disorders such as hereditary hemorrhagic telangiectasia (HHT) (Osler–Weber–Rendu disease), Wyburn–Mason syndrome, or Sturge–Weber syndrome.[13,14,164] Although they were initially thought to be static pathological entities, AVMs are now thought to be highly dynamic tangles of vasculature, characterized by phases of rapid growth, remodeling, regression, and even *de novo* formation after successful complete resection.[5,53,54,70,88] Moreover, these collections of abnormally formed, thin-walled, tortuous vascular connections between the arterial and venous circulation predispose patients to hemorrhagic stroke, seizure, focal neurologic deficits, and numerous other clinical manifestations.[76,131]

The behavioral heterogeneity of AVMs is thought to stem largely from their altered gene expression.[135] The aberrant expression of >900 genes has been associated with AVMs, with upregulation of >300 and downregulation of >500 genes.[99,151] These genes encode numerous growth factors, ECM matrix proteins, cell adhesion molecules, Shh, and inflammatory factors.[113,114] VEGF, a potent mitogen involved in both vasculogenesis and angiogenesis, is normally suppressed in adult cerebral vasculature. VEGF has been demonstrated to be highly expressed in children with recurrent cerebral AVMs.[141] Specifically, the VEGF expression is found to be the highest in the intimal and medial layers of vessels in AVMs.[141] In addition, studies have shown increased expression of the FLT1 (VEGFR1), FLT4 (VEGFR3), and Flk-1 (VEGFR2) receptor subtypes in AVMs. Normally, VEGFR2 is expressed by vasculature of the developing fetal brain. The overexpression of embryologic growth factors and their receptors is thought to play a primary role in the pathogenesis of AVMs, as overexpression of VEGF and other pro-angiogenic factors leads to irregularly branching tortuous vessels that are characteristic of numerous neurovascular pathologies. Furthermore, TGF-β has been found to be mutated in HHT, with cerebral AVMs occurring in 10–25% of patients with this particular genetic disorder.[133] In addition, mutation of the ENG gene, which encodes the protein endoglin, is associated with cerebral AVM formation. Specifically, loss of functional parts of the TGF-β type I receptor, including the ALK1 (activin receptor-like kinase 1) or ALK5 (activin receptor-like kinase 5) proteins, has been demonstrated to contribute to a deficiency in capillary plexus maturation bridging arterial–venous circulations.[161]

In addition to genetic mutations contributing to arteriovenous pathology, the AVM microenvironment itself is thought to contribute to further stimulation of pathologic angiogenesis. Because AVMs act as a pathologic shunt, both ischemia and hypoxia precipitate HIF-1α accumulation, activating the angiogenic switch. Experiments have demonstrated that this hypoxic microenvironment surrounding the AVM can lead to a substantial increase in VEGF (up to 30-fold).[12,59] Lastly, overexpression of matrix metalloproteinases, namely MMP-9, plays an essential role in the pathogenesis of AVMs. The proclivity of AVMs to hemorrhage is thought to be due to a combination of the formation of rapidly proliferating vessels that lack stability and further

destabilization of vascular integrity via metalloproteinases such as MMP-9. MMP-9 has been shown to be increased in brain AVMs and has been the recent target of studies analyzing the effects of dose-dependent inhibitory effects of tetracyclines.[64,91,134,160] Studies evaluating the efficacy of the VEGF-A monoclonal antibody bevacizumab have shown promise in small, limited trials, with other clinical trials currently underway.[39,167] Our understanding of the biology of AVMs in the central nervous system continues to develop, and further investigations into the genetic and molecular makeup are warranted to reveal possible therapeutic targets.

Glioblastoma

Despite advances in technology, surgical technique, and medical therapies, glioblastoma (GBM; WHO Grade IV astrocytoma) remains a lethal disease with rapid progression and inevitable recurrence after conventional therapy with maximal safe surgical resection and subsequent radiation therapy with concurrent temozolomide. Yet, despite its uniformly aggressive phenotype, a hallmark of this particular disease is its genetic heterogeneity. VEGF, HIF-1α, PDGF, TGF-β, FGF, and epidermal growth factor (EGF) all play critical roles in pathologic angiogenesis, a characteristic feature of GBMs.[52,77,157,162] In fact, the presence of hyperplastic, dysfunctional vasculature, sometimes referred to as glomeruloid bodies or vascular tufts (layers of endothelial and smooth muscle cells with a thick basement membrane), is critical to histopathologic differentiation of a grade IV astrocytomas from lower-grade gliomas. In 1971, Folkman first drew the connection between tumor growth and angiogenesis.[48] This led him and other researchers to search for therapies capable of inhibiting pathologic angiogenesis to rapidly dividing nests of cancer cells, depriving a tumor of oxygen and nutrients, thereby slowing disease progression while simultaneously making surgical resection more amenable. Since this discovery, our appreciation of this pathway's complexity and overlap with other physiologic processes and neurogenesis has expanded greatly. Despite VEGF's centrality in tumor angiogenesis, accumulating evidence suggests numerous other growth factors are critical to tumor progression.

Another important growth factor in GBM progression involves TGF-β, which has been demonstrated to be involved in cellular proliferation, differentiation, and apoptotic resistance of tumor cells.[109] In addition, TGF-β and its downstream signaling are known to contribute to ECM remodeling and angiogenesis. Not surprisingly, studies of proteomic expression in GBMs have revealed high levels of TGF-β expression.[20,37] TGF-β induces tumorigenesis and angiogenesis in GBM through Smad2/4 and Smad3/4 signaling pathways.[152] In addition to TGF-β, axonal guidance cues such as netrins and neuropilins are gaining increasing attention for their roles in tumor progression. Recent studies have shown that knockdown of netrin-1 in GBM stem-like cells confers a less aggressive phenotype in GBM[146] and that neuropilin-1 expression plays a vital role in glioma progression.[176] Collectively, new research on the shared signaling mechanisms between neurogenesis and angiogenesis is revealing growth factors not fully appreciated for their role in the pathogenesis of this deadly disease. As our understanding of the overlap between these two pathways and their implications on pathology continues to unfold, new therapeutic targets will quite likely be revealed.

Vestibular schwannomas

Vestibular schwannomas (or acoustic neuromas) are benign intracranial tumors of the myelin-forming Schwann cells ensheathing the eighth cranial nerves. Schwannomas have low malignant potential and often occur in the head and neck (25–40%) but can occur elsewhere in the body.[38] Similar to AVMs, vestibular schwannomas can arise either sporadically (95%) or in the context of certain genetic disorders.[116] Specifically, autosomal dominant mutations of the *NF2* gene (22q12 locus) are known to cause neurofibromatosis type II (MISME syndrome: multiple inherited schwannomas, meningiomas, and ependymomas), a genetic condition associated with a high incidence of bilateral vestibular schwannomas (95%), meningiomas involving other cranial nerves (50–75%), neurofibromas, ependymomas, and gliomas.[8] It is thought that the *NF2* gene acts as a tumor suppressor via its protein product Merlin (schwannomin).[50] Merlin has been demonstrated to play a critical role in the maintenance of cell membrane stability through facilitation of membrane protein–cytoskeletal interactions.[106] In addition, evidence suggests that both sporadic and NF2-related vestibular schwannomas are associated with complete loss of functional Merlin expression in Schwann cells.[4,142] Merlin protein is known to signal through the Rho family of GTPases, such as Rac1, through its association with p21-associated kinase (PAK).[31,71,87,110,150] Merlin normally acts to suppress Rac1 recruitment, preventing loss of contact inhibition, while also remaining capable of translocation to the nucleus to bind DCAF1 and suppress cellular proliferation via inhibition of E3 ubiquitin ligase $CRL4^{DCAF1}$. In brief, wild-type expression of merlin leads to inactivation of $CRL4^{DCAF1}$, thereby inhibiting integrin, PDGF, and Wnt signaling.[19] Collectively, loss of functional merlin expression precipitates schwannoma and other forms of neoplasia via dysregulation of cellular proliferation.[96,97] Studies have also demonstrated that vestibular schwannomas express high levels of VEGFR1.[25,166] Moreover, patients with greater schwannoma tumor burden or recurrent tumors tend to have higher relative levels of VEGFR1 mRNA. While bevacizumab (VEGF-A monoclonal antibody) has been approved by the U.S. Food and Drug Administration in

the treatment of glioblastoma, colorectal cancer, renal cell carcinoma, and other cancer types, some small studies have shown promise in reducing vestibular schwannoma tumor size as well as associated symptomatic improvement.[111,130] Nevertheless, our understanding of the exact biology of this benign tumor is incomplete and thus warrants further research to elucidate the underlying aberrant molecular signaling. Through a better understanding of the altered signaling pathways in pathology, new therapeutic targets can be identified to improve the outcome of patients with neurosurgical pathologies.

CONCLUSIONS AND PERSPECTIVES

Nerves and vasculature follow parallel paths with overlapping anatomy, supplying electrical impulses and much-needed oxygen and nutrients throughout the human body, respectively. The gross organizational similarity between the nervous and vascular systems is evinced by a highly stereotyped pattern of branching that mirrors one another as they travel to supply their target tissues throughout the body. In addition, the parallels between these two systems extend to a genetic and molecular level where evidence of their relatedness and interplay between these two systems continues to accumulate. Through a better understanding of the development of neurovascular pathways and the aberrancies precipitating their pathology, new therapeutic targets will likely be identified.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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