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Editorial

Neurovascular interaction

The nervous system is supported by elaborate vascular networks that supply it with massive amounts of oxygen, nutrients, and blood. In fact the brain, which accounts for only a small percentage of the total body mass, requires 15% of the total cardiac output and 20% of the total oxygen used in the body. The eye contains photoreceptors, arguably the most metabolically demanding cell in the body and is, by weight, the most vascularized tissue. This correlation of high demand and robust vascular supply is observed widely across the central and peripheral nervous systems, and the manner in which the activity of neural networks is matched with adequate supply depends on robust oxygen and nutrient detection and response elements. These elements operate within neurovascular units (NVUs) that sense changes in metabolic demand and respond by releasing cytokines and other signaling cues to increase local blood flow. Through this system blood flow can also be continually and rapidly rerouted into neural networks that require it the most.

Blood flow in the nervous system is regulated in part by multicellular neurovascular units (NVUs). NVUs consist of combinations of neurons, vascular endothelial cells, pericytes, astrocytes, microglia and extracellular matrix. Cells within NVUs also collaborate to generate the blood-brain barrier (BBB) to limit attacks from pathogens and to prevent peripheral blood cell-induced inflammation. Some examples of NVUs are oberved in cerebrovascular zones in the brain; between Müller glia, intraretinal blood vessels, and retinal interneurons in the retina; and between peripheral glia and motoneurons in the peripheral nervous system. Dysregulated neurovascular coupling contributes to several disease processes including neuroinflammation, ischemia, pathological angiogenesis, and neurodegeneration and are characteristic of stroke, Alzheimer's disease, Parkinson's disease, ALS, diabetic retinopathy, and age-related macular degeneration.

Neurovascular signaling is also important for the developing nervous system and for vascular maintenance in adulthood. During development, neurons and glia work together to regulate angiogenesis, vascular patterning, and vascular pruning. In adults, neurons and glia can rapidly adapt to reduced blood flow by regulating blood vessel caliber and permeability. As we age, production of pro-angiogenic cytokines is reduced, blood vessels regress, and tissues throughout the nervous system can become ischemic. In extreme cases, hypoxic neurons and glia overcompensate by generating excessive VEGF or other cytokines that induce chronic inflammation and neovascularization. A classic example is diabetic retinopathy: in this disease excessive VEGF is produced by hypoxic neurons and glia located within nascent avascular areas of the retina. Treatments include laser photocoagulation to destroy the ischemic areas and anti-VEGF therapies.

Many independent groups are aggressively working to develop new and disease modifying therapies to repair diseased neurovascular units. In this special issue of Neurochemistry International, we recognize some of the experts in the field who are conducting these studies. As an editorial team, we decided to highlight three topics: the involvement of NVUs in brain development/physiology, cataloging NVU disorders in the brain, and characterizing novel NVUs in the retina and peripheral nervous system. In this special issue the reader will discover new advances in neurovascular biology, and a comprehensive overview of the molecular and cellular basis of neurovascular signaling in CNS development and disease.

We also chose to highlight work from NVU studies performed in the retina. We believe that these studies not only inform vision research, but inform neurovascular studies in other systems more broadly. The retina, an extension of the CNS, is referred to as a “window into the brain” because it shares many anatomical and functional characteristics with the rest of the nervous system. Furthermore, the retina is largely a closed system, readily accessible, can be monitored using in vivo modalities, and development of the vasculature has been well characterized.

1. Section 1: The involvement of NVUs in brain development/physiology

The first section of this special issue focuses on nervous system phsyiology, including neuronal circuit formation and energy homeostasis during developmental and adulthood. Takashima et al. (2019) review the current understanding of neurovascular wiring to regulate neocortical development. They focus on periventricular vessels as niche of neural progenitors and the mechanisms that control neural progenitor expansion and differentiation and cellular dynamism involving in the establishment and maintenance of neocortical cytoarchitecture. Similarly, Fujioka et al. (2019) review the latest research on the role of vascular-guided neuronal migration in the embryonic and adult brain. They also highlight the roles and the mechanisms of vascular-guided neuroblast migration in the case of brain injury such as ischemic stroke, and discuss the implications of these findings for therapeutic approaches involving neuronal regeneration. This article is followed by a primary research article that reported the expression of GINS members, which related to DNA replication, in the embryonic development of nervous system. Jia et al. (2019) found that the expression of PSF1 and SLD5, two of GINS complex members, may contribute to the regulation of neuroepithelial cell proliferation during neural tube formation. Morita-Takemura and Wanaka (2019) close this section by characterizing blood to brain communication in the hypothalamus to maintain energy homeostasis. They summarize findings on the structural

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plasticity and active transport system in median eminence, which lacks a typical blood-brain barrier, and suggest that the median eminence may be a gateway to arcuate nucleus for circulating molecules to control metabolism.

2. Section 2: Cataloging NVU disorders in the brain

Section 2 contains articles highlighting the importance of neurovascular interactions in a range of brain disorders and disease pathways. The first three articles focus on the contribution of specific NVU cell types including astrocytes, vascular cells, and bone marrow-derived macrophages (BMDM). McConnell et al. (2019) provide a detailed and mechanistic overview of astrocyte contributions to neurovascular dysfunction in neurological disease. They review the relationship between neurovascular impairments and astrocyte dysfunction, especially accompanying BBB impairments and blood flow dysregulation in wide-ranging disorders. They also discuss the advantages of targeting astrocytes to prevent energy supply and demand mismatches. Winkler et al. (2019) highlight recent work that showcases emerging understanding of the critical roles of mural cells and endothelial cells in neurovascular coupling. They review the latest research on key molecular pathways of normal cerebrovascular coupling including angiogenesis, BBB formation, and cerebral blood flow regulation. They focus on the role of mural cells, including pericytes and vascular smooth cells, in NVU biology. They also describe how aberrant cell signaling contributes to formation of brain arteriovenous malformations and discuss how the pathways may be targeted for future therapeutic drug development. Finally, Srivastava et al. (2019) provide evidence of significant microenvironment-depedent diversity of BMDMs, and summarize emerging aspects of their opposing roles in either exacerbating the injuries or promoting neuronal recovery after stroke.

In this section the reader will also find a series of articles that touch on molecular mechanisms of neurovascular disease and therapeutic strategies. Naveed et al. (2019) summarize findings on the role of inflammation and neurovascular dysfunction in cerebral injury and neurodegeneration. The article highlights molecular and cellular inflammatory cascades during neurovascular injury, and includes a comprehensive list of pathways and targets for neurological disorders. MacLearn et al. (2019) continue on the theme of neuroinflammation by summarizing the contributions of receptor for advanced glycation end products (RAGE) in neurovascular dysfunction. RAGE is a multi-ligand receptor of various ligands including S100, HMGB1, and amyloid-β peptide. The review article highlights how RAGE-dependent cell-intrinsic and cell-cell communication contributes to disease pathogenesis of CNS vascular dysfunction and neurodegeneration, and summarizing work done to develop potential therapeutic modalities that target the RAGE pathway. Lee-Hotta et al. (2019) review the latest research on the role of K + -Cl$^-$cotransporter 2 (KCC2), a regulator of neuronal intracellular Cl$^-$, in nervous system injury and rehabilitation. The authors discuss the implication of KCC2 downregulation in disorders such as spasticity and neuropathic pain, and propose potential of targeting BDNF-TrkB signal and exercise for functional recovery after neuronal injury through upregulation of KCC2. Ozaki et al. (2019) close this section by describing therapeutic strategy against ischemic stroke from the viewpoint of neurovascular unit. The review highlights the functional relationship of NVU components with major focus on endothelial cells. They also discuss therapeutic strategies for ischemic stroke from four points of view: angiogenesis; neurotrophism; neuroprotection of NVU components; and regenerative therapy.

3. Section 3: Characterizing novel NVUs in the retina and peripheral nervous system

In the final section, we leave the brain to highlight neurovascular research in skin and retina. Interestingly, wound healing is delayed in denervated skin. Kiya and Kubo (2019) describe this phenomenon in more detail and review the contribution of neuropeptides and/or neuron-derived growth factors to angiogenesis and skin wound healing. Three primary research articles follow that focus on the importance of NVUs in retina development and disease. Alevy et al. (2019) show the significance of Kctd7, progressive myoclonic epilepsy-associated gene, in retinal neurovascular patterning and function. They show that Kctd7 is expressed in a subject of retinal interneurons (bipolar cells), and that its deletion in mice results in enhanced vascular coverage and an increased number of retinal bipolar cells. Kctd7 deficient mice also have significant functional defects. This work is exciting since an interplay with bipolar cells and their vasculature has not been shown previously. In the next manuscript, Miwa et al. (2019) also examine intraretinal NVUs. They utilize a model of oxygen-induced retinopathy which is used to model features of diabetic retinopathy and retinopathy of prematurity. Based on previous work from their lab, they target hypoxia-inductively factors (HIFs), which respond to ischemia and operate upstream of VEGF. Their report suggests that HIF inhibition may be effective for treating pathological angiogenesis and neurodegeneration. Finally, Bucher et al. (2019) explore the role of Dp427, the long dystrophin gene product, in retinal function and vascular patterning. They report an interesting finding, severe proliferative retinopathy, in a Duchenne muscular dystrophy (DMD) patient. They then characterized the effects of Dp427 perturbation in transgenic mice, and showed that ischemia-induced neovascularization may be further exacerbated with aging. The authors conclude by suggesting that DMD patients be more closely monitored and treated to avoid catasatrophic neovascularization and vision loss.

We hope that this special issue will lead to new research programs and findings that advance our knowledge in neurovascular biology, and perhaps lead to novel therapeutic algorithms for neurovascular diseases. We hope you enjoy the special issue.

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