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Pericytes Make Spinal Cord Breathless after Injury

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Abstract

Traumatic spinal cord injury is a devastating condition that leads to significant neurological deficits and reduced quality of life. Therapeutic interventions after spinal cord lesions are designed to address multiple aspects of the secondary damage. However, the lack of detailed knowledge about the cellular and molecular changes that occur after spinal cord injury restricts the design of effective treatments. Li and colleagues using a rat model of spinal cord injury and in vivo microscopy reveal that pericytes play a key role in the regulation of capillary tone and blood flow in the spinal cord below the site of the lesion. Strikingly, inhibition of specific proteins expressed by pericytes after spinal cord injury diminished hypoxia and improved motor function and locomotion of the injured rats. This work highlights a novel central cellular population that might be pharmacologically targeted in patients with spinal cord trauma. The emerging knowledge from this research may provide new approaches for the treatment of spinal cord injury.

Keywords

pericytes; spinal cord injury; blood flow; microenvironment; scar

Eberth, a German scientist, described in the late 1800s a population of contractile cells in small blood vessels (Armulik and others 2011), which were called the Rouget cells in honor of a French scientist, who described them only 2 years later (Rouget 1873). Fifty years later, these cells were renamed as pericytes due to their anatomical location around capillaries (Zimmermann 1923). Pericytes have long projections encircling the blood vessel walls (Hirschi and D'Amore 1996). They communicate with endothelial cells along the length of

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the vasculature by paracrine signaling and physical contacts (Diaz-Flores and others 1991; Paiva and others in press; Azevedo and others 2017). Originally, the precise identification of pericytes distinct from other perivascular cells was not possible. The limited capability of microscopy in the early years resulted in the still widely held notion of the pericyte as a cell type limited exclusively to the physiological function of vascular stability, acting merely as a supporting cell. Nevertheless, in more recent years, the rapidly expanding insights into the physiological roles of this cell type have finally attracted the attention of multiple research groups that discovered several, sometimes unexpected, functions for pericytes. Pericytes collaborate with astrocytes to regulate the maintenance of the functional integrity of the blood-brain barrier (Bell and others 2010; Santos and others in press). They also regulate the blood flow (Biesecker and others 2016; Hall and others 2014; Mishra and others 2016; Peppiatt and others 2006) and participate in vascular development, maturation, and remodeling, as well as contributing to its normal architecture and permeability (Enge and others 2002; Hellstrom and others 2001). Moreover, they play immune functions by regulating lymphocytes activation (Tu and others 2011) and by attracting innate leukocytes that exit through the sprouting vessels (Stark and others 2013). Additionally, pericytes contribute to the clearance of toxic cellular by-products, have direct phagocytic activity, and can affect blood coagulation (Castejon 2011; Coatti and others 2017; Fisher 2009; Kim and others 2006). Pericytes also have some plasticity and may work as stem cells, participating in the formation of several other cell types, including possibly neuronal cell types (Birbrair and Delbono 2015; Birbrair and others 2011; Birbrair and others 2013 a; Birbrair and others 2013b; Birbrair and others 2013d; Birbrair and others 2014b; Birbrair and others 2014c; Birbrair and others 2017a; Birbrair and others 2017b). It has been suggested that the higher the number of pericytes, the greater the blood pressure within the tissue in which they reside, and therefore the greater the degree of control of the vessels in that tissue (Shepro and Morel 1993). This could explain why more pericytes can be identified on vessels with larger diameters (Sims 2000). There is also a considerable heterogeneity in the number of pericytes that cover the blood vessels in different tissues; this may be linked to the function in the tissues where they reside. In the central nervous system, the ratio of pericytes to endothelial cells is approximately 1:1 (Shepro and Morel 1993), implicating the high importance of pericytes in the central nervous system physiology.

Spinal cord injury is a clinically devastating condition that leads to sudden loss of motor, autonomic, and sensory function under the level of the injury. The number of people around the world who suffer this type of trauma is estimated to be around half a million every year (Domingo and others 2012). The acute set of events after a lesion leads to several cellular and molecular responses in the spinal cord, from which some are understood and well characterized, while others remain unknown (Rossignol and others 2007). The lack of detailed knowledge about the mechanisms that occur after spinal cord injury restricts the design of effective treatments. Understanding the pathophysiological cellular and molecular changes triggered by spinal cord trauma is a primary goal in the search for new approaches to treat and prevent chronic disability in spinal cord injury with a mechanism-based approach.

Pericytes in Spinal Cord Injury

In a recent article in *Nature Medicine*, Li and colleagues demonstrated that pericytes can be an important target for rehabilitation after spinal cord injury (Li and others 2017). The authors discovered that pericytes play a key role in the regulation of capillary tone and blood flow in the spinal cord below the site of injury by using a rat model of spinal cord injury and in vivo microscopy (Fig. 1) (Li and others 2017). Their experiments revealed that pericytes overexpress the enzyme aromatic L-amino acid decarboxylase (AADC) after spinal cord injury. Furthermore, AADC generates, from dietary amino acids, trace amines (tryptamine and tyramine), which in turn act through receptors on the pericyte itself. This activation by trace amines causes pericytes to locally constrict blood vessels, reducing blood flow, leading to tissue ischemia (Li and others 2017). Strikingly, inhibiting AADC or trace amine receptors after spinal cord injury diminished hypoxia and improved motor function and locomotion of the injured rats (Li and others 2017). This work provides a new possible central cellular population to be pharmacologically targeted in patients with spinal cord injury. Here, we discuss the findings from this study and evaluate recent advances in our understanding of the roles of pericytes in the spinal cord (Fig. 2).

Pericytes: A Heterogeneous Population

Li and colleagues consider pericytes as a homogeneous cell population in their study. Nonetheless, pericytes have been shown to be heterogeneous regarding their distribution and phenotype (Dias Moura Prazeres and others in press). Pericyte heterogeneity was first described a long time ago. Pericytes were distinguished into three types according to their location in the blood vessels: capillary, pre-capillary, and post-capillary (Zimmermann 1923). Capillary pericytes are highly elongated, extend mainly in the long axis of the blood vessels, are spindle-shaped, and have multiple short secondary processes (Nehls and Drenckhahn 1991). Pre-capillary pericytes have several circular branches that tend to wrap themselves around the vessel (Nehls and Drenckhahn 1991). The post-capillary pericytes cover the abluminal surface of post-capillaries and are shorter stellate-shaped cells. More recent studies have identified several molecular markers to identify pericytes, such as nerve/glia antigen 2 (NG2) proteoglycan (CSPG4) (Ozerdem and others 2001), aminopeptidase N (CD13) (Kunz and others 1994), platelet-derived growth factor receptor β (PDGFR β) (Lindahl and others 1997; Winkler and others 2010), and many others (Morikawa and others 2002). Pericyte heterogeneity was also confirmed based on their marker expression profiles (Sena and others 2017). For example, pericytes localized on venules express desmin and alpha smooth muscle actin proteins, while pericytes on capillaries express desmin but usually are negative for alpha smooth muscle actin (Morikawa and others 2002; Nehls and others 1992). Also, ATP sensitive potassium channel Kir6.1 is highly expressed in pericytes in the brain but undetectable in pericytes in the skin and heart (Bondjers and others 2006). In the bone marrow, arterioles-associated leptin receptor (LEPR)-pericytes are distinct from sinusoid-associated LEPR+ pericytes (Birbrair and Frenette 2016; Khan and others 2016; Kunisaki and others 2013; Sena and others in press). In the skin, NG2+ and NG2- pericytes have been described (Stark and others 2013). In the skeletal muscle, two populations of pericytes were distinguished based on the presence or absence of Nestin-GFP expression (Birbrair and others 2013c). Although most of spinal cord pericytes express the well-

established pericytic markers PDGFR β , NG2, and CD13 (Goritz and others 2011), the expression of some other molecular markers is heterogeneous in this tissue. For instance, the presence of two pericyte subpopulations (type-1 [NG2-DsRed⁺/Nestin-GFP⁻] and type-2 [NG2-DsRed⁺/Nestin-GFP⁺]) was reported around blood vessels in the spinal cord of bigenic NG2-DsRed/Nestin-GFP mice (Birbrair and others 2014a). Also, pericytes that express YFP differ from the ones that express desmin and α SMA in glutamate aspartate transporter (Glast)-CreER/R26R-YFP bigenic mice (type-A [desmin⁻/ α SMA⁻/Glast-YFP⁺] and type-B [desmin⁺/ α SMA⁺/Glast-YFP⁻]) (Goritz and others 2011). The level of overlap between the pericyte subpopulations described in these two genetic mouse models remains unknown. Also, the embryonic origin and the developmental relationship of spinal cord pericyte subtypes are yet to be elucidated (Prazeres and others in press). Li and colleagues used NG2 and CD31 to identify the pericytes in the spinal cord, which does not distinguish pericyte subsets (Li and others in press). Thus, whether only a fraction of pericytes promote blood vessel constriction after spinal cord injury still needs to be elucidated.

Spinal Cord Pericytes and Scarring

A spinal cord pericyte subpopulation has been recently shown to take part in the formation of the scar tissue after a lesion, which is a major obstacle to axonal regeneration in patients with this condition (Birbrair and others 2014a; Goritz and others 2011). The lesion induces an increase in the number of a pericyte subtypes, while the number of the other pericytes remains unchanged (Birbrair and others 2014a; Goritz and others 2011). Interestingly, some spinal cord pericytes dissociate from endothelial cells, losing contact with the blood vessels after the lesion. It will be interesting to understand whether the pericytes that participate in scar formation differ from the ones that regulate capillary blood flow after spinal cord trauma.

Targeting Pericytes

Would it be possible to develop targeted therapies to block at the same time scar tissue formation as well as hypoxia in the spinal cord after a lesion? From a drug development perspective, pericytes provide a central cellular target with a stereotyped molecular repertoire and responses to signals. Nevertheless, as pericytes have important physiologic functions, what will turn out to be quite challenging will be to narrow deleterious pericyte functions while preserving the healthy ones.

Pericytes are anatomically defined by their perivascular location in the blood vessel wall in close contact with endothelial cells (Birbrair and others 2015). However, anatomical targeting may not be adequate, because not all perivascular cells are pericytes. In addition to pericytes, other cell types have been described as perivascular, such as adventitial cells (Crisan and others 2012), vascular smooth muscle cells (Wanjare and others 2013), fibroblasts (Soderblom and others 2013), macrophages (Bechmann and others 2001), and microglia (Guillemin and Brew 2004). None of pericyte markers are specific, since they are also expressed by other cell types; and their expression in pericytes is highly dependent on the developmental stages (Armulik and others 2011). Thus, pericytic markers used in the study of Li and colleagues could refer to other cell populations (Li and others 2017). For

instance, both the NG2 proteoglycan and metalloprotease aminopeptidase N (CD13) can be expressed by macrophages (Licona-Limon and others 2015; Yotsumoto and others 2015). Also, NG2 is a marker of oligodendrocyte progenitors (Birbrair and others 2013b). Thus, after spinal cord injury, it is possible that other perivascular populations were confounded with pericytes. Additionally, pericytes that do not express NG2 were also recently described in the placenta (Stark and others 2013). This raises questions on whether NG2-pericytes are present in the spinal cord, and whether they behave similarly to those described by Li and others (2017). Classical electron microscopy studies of pericytes reveal their location under the vascular basal lamina (Allsopp and Gamble 1979), in contrast to other perivascular cells. Thus, whether the function of the perivascular cells described in this study belongs to pericytes still needs to be clarified. The combination of pericyte molecular markers with immunolabeling of the basal lamina in transgenic mouse models will confirm the nature of those cells.

Li and colleagues suggest that trace amines are produced by pericytes, since AADC is expressed densely in pericytes (Li and others 2017). Nevertheless, other cells also express AADC, such as macrophages (Gaskill and others 2012) and glial cells (Li and others 1992) and may contribute to the raised levels of these amines after spinal cord injury. The detailed mechanism that leads to AADC-immunoreactivity in pericytes is yet unclear and will need to be revealed in future studies. Moreover, Li and colleagues show that the tryptamine produced by pericytes acts on 5-HT1B receptors on pericytes themselves to induce vasoconstriction (Li and others 2017). However, they do not show whether pericytes are the only cells expressing 5-HT1B receptors. In fact, besides pericytes and neurons (Massot and others 1999), other cell types, including endothelial cells (Ahn and Balaban 2010), smooth muscle cells (Razzaque and others 2002), and dendritic cells (Idzko and others 2004), may express 5-HT1B receptors. Thus, it is possible that this pericyte-derived tryptamine also acts on several other cells after spinal cord injury. Future studies will reveal the influence of other cell types expressing 5-HT1B on the outcome of chronic spinal cord injury (Fig. 2).

Genetically modified mice have been widely applied to study cell types within diverse tissues microenvironments (Borges and others 2017; Lousado and others in press). The ability to delete single genes in specific cell types in adult mice has allowed us to answer specific questions regarding the roles of different cell populations in the regulation of several physiologic and pathologic processes (Andreotti and others 2017). In the spinal cord microenvironment after injury, the exact identities of all cells that play important roles in the pathogenesis of this condition remain uncertain. Li and others (2017) have proposed that pericytes promote ischemia in the spinal cord indirectly through the expression of AADC. However, AADC has not been conditionally deleted from spinal cord pericytes, so there is no direct evidence that pericytes are the only/main functionally important source of trace amines. These issues may be addressed by analyzing the effect of genetic ablation of the AADC-expressing pericytes on the blood flow in the spinal cord after a lesion. Additionally, the generation of AADC floxed mice to be crossed with pericyte-specific inducible CreER driver, such as NG2-CreERT2 (Asada and others 2017), will allow us to delete AADC in pericytes. In addition to studies employing genetic mouse models, transcriptomic and single cell analysis represent fundamental tools that will help us understand the roles of pericytes within the spinal cord.

Importantly, Li and colleagues propose drug targets for clinical interventions after spinal cord injury (Li and others 2017). Antagonism of monoamine receptors and the inhibition of AADC enzyme function after spinal cord lesion produces lasting improvements in spinal cord oxygenation, which ultimately improves motor function. Thus, human patients with spinal cord lesion may benefit from the development of drugs that will block specifically these targets. The design of such drugs will need to take into account their possible side effects, as both targets are not restricted to the spinal cord tissue as well as to a specific cell type.

Neurovascular Coupling

Besides paralysis, spinal cord injury causes serious blood flow complications in humans with spinal cord injury, which is believed to be due to impaired neurovascular coupling (Myers and others 2007; Phillips and others 2013; Phillips and others 2014). This physiological process refers to the coupling of the central nervous system metabolism and blood flow required to sustain the high demand of the neural tissue oxygenation. It involves the interaction between a variety of cell types including neurons, glia, pericytes, and endothelial cells. The unsynchronized metabolism of these cells, caused by spinal cord lesions, leads to changes in the vasomotor tone and hypoxia, as seen in both humans with spinal cord injury (Phillips and others 2014) and rodent experimental models. One of the most remarkable results of this study is that administration of oxygen relieved the hypoxia below the lesion that lasted 20 minutes beyond the inhaled period. This long-lasting effect may reflect that provision of more oxygen recovered localized neuronal activity, which turns out to be capable of eliciting vascular responses including the increase of arteriolar diameters through the release of vasoactive molecules (Phillips and others 2016; Uhlirova and others 2016). Whether the released vasodilators can counterbalance the vasoconstrictor effects of pericytes by acting directly on these cells in the spinal cord tissue is yet unknown. A similar mechanism has been demonstrated in capillary pericytes from the cerebral cortex, which dilates in response to the glutamate-evoked release of the vasodilators prostaglandin E2 and nitric oxide (Hall and others 2014).

Translation into Humans

Experimental animal models of spinal cord injury aim to recreate features of human spinal cord lesion as closely as possible (Metz and others 2000). Given the complexity of the human spinal cord injury, which can include elements of both cord transection and contusion as well as hemorrhage, and is characterized not only by injury to neurons, glia, and other cells but also to myelin (Waxman 1992), no one model can encompass all aspects of the injury. Thus, unfortunately, our knowledge of the pathological aspects of human spinal cord injury remains fragmented. The rat is a tiny animal compared to humans, with a spinal cord that is shorter by more than an order of magnitude. Hence, a steady clinical improvement such as locomotion recovery that needs long-range axon regeneration, as needed in humans, cannot be directly studied in rats. Truly, rodent studies that result in amelioration of locomotion and axonal growth possibly misinform us, since the amount of gray matter that needs reinnervation is much smaller in rats than in humans. Additionally, the clinical recovery after spinal cord injury is also slower in humans than in rats. It will be very

interesting to evaluate whether AADC expression increases in human pericytes after spinal cord trauma, and whether these cells also play an important regulatory role in human blood vessels after medullar lesions in humans. The degree of pericytes-dependent vascular constriction in patients with spinal cord injury may also vary depending on the severity and level of the injury. Pericytes might even play a different role in tetraplegics compared to paraplegics.

Conclusion

Li and colleagues provide a possible cellular mechanism involved in spinal cord neurobiology: pericytes play a key role in the regulation of capillary tone and blood flow in the spinal cord below the site of the lesion (Li and others 2017). This new concept places pericytes as a central cellular population that might be pharmacologically targeted to diminished hypoxia and improve motor function after spinal cord injury. Future studies may reveal the complexity of the injured spinal cord microenvironment and the importance of each of its constituents in much greater detail. Present in all tissues, pericytes may play important roles in the regulation of blood flow in several other ischemic diseases.

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Figure 1.

Pericytes' role in the control of spinal cord blood flow below the site of injury. Pericytes are present around the spinal cord blood vessels. The study of Li and colleagues now suggests a novel very important function for pericytes after spinal cord injury (Li and others 2017). After the loss of neuron-derived monoamines due to spinal cord injury, there is increased expression of the enzyme aromatic L-amino acid decarboxylase (AADC) and, consequently, trace amines (TAs) synthesis in medullary pericytes. Trace amines can bind to monoamine receptors on pericytes, thus causing capillary constriction and reducing blood flow to ischemic levels.

Figure 2.

Hypotheses about the control of blood flow in the injured spinal cord after the loss of neuron-derived monoamines. Li and colleagues suggest that the increase in trace amine synthesis, due to the presence of AADC and monoamine receptors in pericytes, leads to capillary constriction (Li and others 2017). However, AADC could be expressed in the perivascular region by other cell types, such as macrophages and glial cells. In addition, it is possible that monoamine receptors are expressed by several other cell populations. Pericyte heterogeneity also needs to be taken into account, as other roles have been already suggested for pericytes. It should also be taken into consideration the possible presence of NG2-non-expressing pericytes in the spinal cord.