All MSCs Are Pericytes?

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In this issue of *Cell Stem Cell*, Crisan et al. (2008) document a subpopulation of human perivascular cells that express both pericyte and mesenchymal stem cell (MSC) markers in situ. The isolated population can expand and is clonally multipotent in culture, establishing that MSCs found throughout fetal and adult tissues are members of the pericyte family of cells.

The publication by Crisan et al. (2008) is a landmark paper which presents a large body of work that defines, refines, confirms, establishes, and validates both the in situ and in vitro links between adult human mesenchymal stem cells (MSCs) and perivascular cells, summarily referred to here as pericytes. A 20 member international team from two clinical departments, two institutes, and two centers, the Stem Cell Research Center and the Cell Factory (a harbinger of the next generation of mass-produced cell-based therapies?) was coordinated by the senior author, Bruno Péault, in Pittsburgh. The importance of this contribution is that it brings together a large body of previous research to directly compare the in vivo location and cell marker signatures of two important cell types, the MSC and the pericyte, and documents their identity. The observations clearly show that cells with MSC markers also express pericyte markers; this result allows me to provocatively speculate that all MSCs are pericytes. This relationship is further emphasized by using cell sorting for pericytes (CD146+, CD34−, CD45−, CD56−) and subsequent in vitro expansion to document that the sorted cells or clones are multipotent for osteogenic, chondrogenic, adipogenic, and myogenic lineages in vitro, which are hallmarks of MSC identity (Caplan, 2007). The experiments examine many organs and tissues from multiple fetal and adult donors. The group is expert in myogenesis, so there is considerable focus on whether satellite cells (committed myogenic precursors) are distinct from the pericyte population. Indeed, pericytes exhibit distinct phenotypic and functional traits from satellite cells across the entire range of tissues examined (Crisan et al., 2008). Although not commented upon, I suspect that the cells from fetal tissues and older adult tissues gave different quantitative results in the in vitro expansion and differentiation assays. That said, it must be stated that the function of MSCs/pericytes is anticipated to be quite different in developing tissues compared to their predicted role in the homeostasis of adult tissue. Last, the MSCs/pericytes do not form teratomas, and their differentiation spectrum seems to be limited; thus, this cell population is distinct from embryonic stem cells.

In regard to the in situ function of pericytes, there are several open questions: do MSCs/pericytes respond to vasoactive drugs that regulate blood flow and pressure? Do pericytes directly contribute to tissue repair/regeneration by differentiation into mesenchymal phenotypes such as osteoblasts, adipocytes, myoblasts, etc.? Do pericytes have other functions? Péault and his collaborators clearly state and document that the pericytes do not differentiate into hematopoietic or neural phenotypes in adults, yet the vascular/perivascular location of hematopoietic and neural stem cells in early fetal tissue (Kiel et al., 2005; Hirshi and D'Amore, 1996) implies that other stem cells inhabit the perivascular niche. This observation also clearly documents that not all pericytes are MSCs.

With regard to the response to focal injury, I envision two quite different pericyte functions: as suggested by Brighton et al. (1992) and others in the 1980s and 1990s, the healing of broken bones (i.e., callus formation) clearly involves the osteochondrogenic properties of local MSCs/pericytes. In addition, the endochondral replacement of cartilage by vasculature would bring MSCs/pericytes into both embryonic and adult tissue fields that could directly differentiate into vascular-driven bone in both orthotopic (Caplan and Pechak, 1987) and heterotopic locations (Caplan, 1990). This model is in keeping with the differentiation-focused discussion of Crisan et al. (2008).

A second function of the MSC/pericyte in settings of focal injury has recently been outlined by my colleagues and me (da Silva Meirelles et al., 2008) and focuses on the fact that MSCs secrete huge amounts of bioactive molecules that contribute to immunomodulatory functions and, separately, offer so-called "trophic activities" by structuring a regenerative microenvironment (Dennis and Caplan, 1997). An important aspect of this complex secretory capacity of MSCs is that Crisan et al. (2008) have documented that MSCs/pericytes migrate in response to digested ECM and other chemotactic stimuli, which could recruit MSCs from both local and surrounding sites to the focal injury. The fabrication of certain bioactive molecules by the MSCs inhibits T cells by affecting antigen presentation and T cell progenitor expansion. This immunomodulatory activity will protect the injury site from immune surveillance and, thus, forestall autoimmunity sensitization to the damaged tissue. Also, by dampening chronic inflammatory activity, the activated MSCs will inhibit apoptosis due, in part, to ischemia; inhibit the entrance or formation of myofibroblasts and, thus, inhibit scar formation; stimulate the mitosis of tissue-intrinsic progenitors whose progeny reform the damaged tissue; and, by reassuming their pericyte function and locations, may stimulate and stabilize angiogenesis and vessel reformation.

Are all MSCs pericytes? Certainly, all pericytes are not MSCs, since both large and small vessels are surrounded by perivascular cells with highly differentiated functions quite separate from the activities associated with the osteo-, chondro-, or adipogenic progeny of MSCs. In

addition, other stem cells, for example, neural or hematopoietic stem cells, appear to reside in perivascular locations in situ (Hirshi and D'Amore, 1996). Since MSCs isolated from different tissues exhibit distinct sensitivities to inductive bioactive molecules in culture, it follows that this reactivity reflects the tissue of origin. Most well studied are the adult marrow-derived MSCs, which are often used as the standard. The inductive conditions for marrow MSCs are quite different from those required by fat-derived MSCs (Estes et al., 2006), as may be expected due to the diverse microenvironments present on the tissue side of the vasculature in which the pericytes reside. The MSCs from marrow and fat are both multipotent, but the inductive stimulus, TGF-β, for chondrogenesis for marrow MSCs must be supplemented with BMP-6 for fat MSCs. Clearly, such variation in inductive requirements must be taken into account when designing expansion and differentiation protocols for use in future therapeutic applications.

Although my colleagues and I have been working with marrow MSCs for over 20 years and have published on markers of MSCs, their perivascular localization in human skin, their multipotency, and their secretion of bioactive factors (Caplan, 2007), we and others have never performed a comprehensive and detailed comparison of the in situ and in vitro traits of MSCs and pericytes. The team led by Bruno Péault provides a solid set of observations that clearly links the MSC and pericyte. There will be a number of exceptions, but my suggestion is that all MSCs are pericytes, and this manuscript gives a formal context to better understand, in both embryos and adults, how the MSC/pericyte contributes to the formation, maturation, and homeostasis of all vascularized tissues.

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The Center of the Spinal Cord May Be Central to Its Repair

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A recent *PLoS Biology* report from Meletis et al. (2008) strongly suggests that ependymal cells are a key source of endogenous stem cells in the spinal cord. Advances in understanding endogenous neural stem cells may facilitate repair of the injured central nervous system.

Repair of the injured spinal cord is one of the "holy grails" of medicine. The development of strategies to protect and repair the injured spinal cord has been facilitated by the identification of key mechanisms of secondary injury, by the characterization of extrinsic barriers to axonal regeneration, and by the discovery of neural stem cells within the adult central nervous system (CNS) (Rossignol et al., 2007).

Complex and interrelated secondary injury processes are now increasingly understood, and they provide many potential targets for therapeutic intervention. Also critical has been the discovery that central axons are capable of regenerating but are prevented from doing so by inhibitory molecules expressed on central myelin and in the postinjury extracellular matrix (Rossignol et al., 2007). These discoveries have led to treatments now in early-stage human clinical trials (Figure 1) (Baptiste and Fehlings, 2008).

Neural precursor cells are emerging as another potential means to repair the injured CNS (Karimi-Abdolrezaee et al., 2006). The precise source(s) of endogenous neural precursor cells has been controversial; however, in the brain, evidence supports a role for cells in both