Are Mural Cells Guardians of Stemness?  
From Pluri- to Multipotency via Vascular Pericytes

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In the current issue of Circulation, Dar and colleagues report the healing of ischemic limbs in athymic mice by multipotent progenitors derived from human embryonic stem (ES) cells or reprogrammed adult cells. So far, nothing really original; the excitement comes from the demonstration that these ES cell and induced pluripotent stem cell (iPS)–derived regenerative units exhibit the features of vascular pericytes.1 These observations are timely and remarkable inasmuch as the blood vessel, far from being a mere conduit, has lately gained nobility in the eyes of stem cell biologists for its recognized contribution to diverse cell lineages. On the one hand, it is now well accepted that, from fish to humans, specialized blood-forming endothelial cells in the dorsal aorta and, most certainly, other organs supply the embryo with hematopoietic cells.2–4 Another developmental affiliation has been more recently documented between pericytes, also known as mural cells, which ensheathe capillaries, arterioles, and venules and are classically confined to an organizational/structural role in angiogenesis,5 and the elusive mesenchymal stem cell (MSC). Mesenchymal stem cells are adherent stromal cells able to differentiate into cartilage, bone, fat, and skeletal muscle cells in a manner similar to that of conventional mesenchymal progenitors derived from human embryonic stem (ES) cells or reprogrammed adult cells. So far, nothing really original; the excitement comes from the demonstration that these ES cell and induced pluripotent stem cell (iPS)–derived regenerative units exhibit the features of vascular pericytes.11 These observations are timely and remarkable inasmuch as the blood vessel, far from being a mere conduit, has lately gained nobility in the eyes of stem cell biologists for its recognized contribution to diverse cell lineages. On the one hand, it is now well accepted that, from fish to humans, specialized blood-forming endothelial cells in the dorsal aorta and, most certainly, other organs supply the embryo with hematopoietic cells.2–4 Another developmental affiliation has been more recently documented between pericytes, also known as mural cells, which ensheathe capillaries, arterioles, and venules and are classically confined to an organizational/structural role in angiogenesis,5 and the elusive mesenchymal stem cell (MSC). Mesenchymal stem cells are adherent stromal cells able to differentiate into cartilage, bone, fat, and skeletal muscle cells in a manner similar to that of conventional mesenchymal progenitors derived from human embryonic stem (ES) cells or reprogrammed adult cells.6–1011

The hypothesis of a ubiquitous perivascular distribution of native MSC, which would explain the extraction of these cells in cultures from virtually all organs tested, has now been supported by a body of experimental results, and this principle is becoming well accepted.12 From a bioengineering/cell therapy perspective, purified human pericytes have been already used in vivo, in xenochimeras, and for diverse applications including skeletal muscle regeneration, infarcted heart repair, directed osteogenesis, and the construction of vascular prostheses.13 More fundamentally, a central question is whether pericytes are naturally involved in tissue development, renewal, or regeneration, a fact that could never be definitively ascertained in the case of conventional MSC, in the ignorance of the identity of these cells in vivo. Analysis of bone ontogeny in quail/chicken chimeras had revealed that the progenitors of bone marrow stroma are perivascular cells surrounding ingressing blood vessels during endochondral ossification.14 Pioneering albeit largely descriptive observations suggested that the testosterone-producing Leydig cells in the adult testis are regenerated by pericytes in a model of chemical ablation.15 Importantly, cell fate tracking in transgenic mice has now shown that mural cells replenish the stock of white adipocytes16 and, most recently, that skeletal muscle pericytes give rise to satellite cells and directly participate in myofiber regeneration after injury.17 Evidence is therefore growing that pericytes, or at least a subset thereof, can act as stem cells even though the control of this potential in health and disease or injury remains completely unknown.

The cells derived by Dar et al from human ES or iPS cells appear as bona fide pericytes. These cells emerged within spontaneously differentiating embryoid bodies in the absence of a particular conditioning or stimulation, suggesting the generality and fundamentality of this developmental series. These cells express the commonly accepted antigenic markers of pericytes, exhibit robust vasculogenic potential in Matrigel, in culture and in vivo, and can develop in culture into cartilage, bone, fat, and skeletal muscle cells in a manner similar to that of conventional mesenchymal stem cells and pre- and postnatal purified pericytes.18 Principally, such embryoid body–derived pericytes injected into mice with artery ligature–induced leg ischemia restored a functional vascular system and even regenerated skeletal muscle, confirming the myogenic potential demonstrated in vivo for fetal and adult pericytes.12,18

As discussed by Dar et al, native perivascular MSC-like cells have been recently also identified, in addition to the pericycle compartment, among adventitial cells surrounding adult larger arteries and veins. These novel MSC ancestors, which have been typified as CD34+/CD146− cells, can differentiate in culture into CD34+/CD146− pericytes,19,20 suggesting a higher position in the vascular cell hierarchy. It will be interesting to determine whether a similar forerunner is at the origin of pericytes in the human ES/iPS cell model. Overall, the earliest normal ontogeny of pericytes in mammalian extra- and intraembryonic territories has not yet been fully documented. Mural cells represent a heterogenous cell
population in terms of germ line origin because pericytes in the cephalic region are of neurectodermal derivation, unlike these cells in the rest of the organism, which are of mesodermal ancestry.21 As also stressed by the authors, it will be therefore important to further analyze ES and iPS cell–derived pericytes with respect to expression of germ line–specific markers. In this respect, it must also be confirmed that the developmental potential of the pluripotent cell–derived pericytes described by Dar et al is limited to mesodermal cell lineages.

In conclusion, whereas much effort has been already dedicated to the derivation of endothelial cells and, to a lesser extent, vascular smooth muscle cells from ES and iPS cells, this is the first time that pericyte-like cells are thoroughly characterized in this model of early development. Pluripotent cell–derived pericytes exhibit the mesenchymal stem cell potential recently revealed within their adult counterparts. Although this potential may remain repressed in endothelium-adherent pericytes until needed in later life, a previously undescribed role of these cells in embryonic development may be also suspected. As a final note, MSC/pericytes do not only act as sensu stricto progenitor cells but also secrete soluble factors stimulating tissue regeneration.22,23 The model described in the present issue of Circulation may make it possible to determine whether this paracrine activity is intrinsic to emerging mural cells or represents a later adaptation to pathological and traumatic challenges encountered in postnatal life.

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None.

References

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