

WJSC 6th Anniversary Special Issues (2): Mesenchymal stem cells**Brain mesenchymal stem cells: The other stem cells of the brain?**

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Abstract

Multipotent mesenchymal stromal cells (MSC), have the potential to differentiate into cells of the mesenchymal lineage and have non-progenitor functions including immunomodulation. The demonstration that MSCs are perivascular cells found in almost all adult tissues raises fascinating perspectives on their role in tissue maintenance and repair. However, some controversies about the physiological role of the perivascular MSCs residing outside the bone marrow and on their therapeutic potential in regenerative medicine exist. In brain, perivascular MSCs like pericytes and adventitial cells, could constitute another stem cell population distinct to the neural stem cell pool. The demonstration of the neuronal potential of MSCs requires stringent criteria including morphological changes, the demonstration of neural biomarkers expression, electrophysiological recordings,

and the absence of cell fusion. The recent finding that brain cancer stem cells can transdifferentiate into pericytes is another facet of the plasticity of these cells. It suggests that the perversion of the stem cell potential of pericytes might play an even unsuspected role in cancer formation and tumor progression.

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Core tip: Mesenchymal stem cells (MSCs), in addition to their potential to differentiate into cells of the mesenchymal lineage, have immunomodulatory properties and can transdifferentiate to generate neural cells at least *in vitro*. These stem cells are found in almost any adult tissue, including brain. The existence of similarities between MSC and pericytes points to brain pericytes as the other stem cell population of the adult brain in addition to neural stem cells. This raises fascinating perspectives on the potential of brain pericytes in nervous system maintenance and repair. The recent finding that brain cancer stem cells transdifferentiate into pericytes is another facet of the plasticity of these cells. It suggests that the perversion of the stem cell potential of pericyte might play an even unsuspected role in cancer formation and tumor progression.

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INTRODUCTION

The history of multipotent mesenchymal stromal cells started when colony-forming unit fibroblastic cells (CFU-F) with osteogenic potential were obtained from bone marrow cultured cells^[1-3]. Accordingly, CFU-F cells were defined as self-renewing non-hematopoietic bone marrow stromal stem cells (BMSCs). They were isolated on the basis of their plastic adherence, and characterized both by their ability to form colony when plated at low-density and to differentiate into osteoblasts^[3]. Thereafter, BMSCs were shown to differentiate *in vitro* and *in vivo* into other cells of mesenchymal lineage including chondrocytes and adipocytes^[4]. Cells similar to BMSCs are also isolated from non-marrow fetal tissue such as placenta, cord blood, fetal liver and lung, as well as from adult tissues including muscle, adipose tissue, dental pulp, lung and brain^[5-8]. These fetal and adult stem cells have the same ability as BMSCs for self-renewal and for differentiation into osteoblasts, chondrocytes and adipocytes *in vitro*. They also exhibit, at least *in vitro*, transdifferentiation capacity (see below). These cells are referred as mesenchymal stem cells or as multipotent mesenchymal stromal cells (MSCs). However, the question remains if these ubiquitous cells behave *in vivo* as genuine stem cells or if their stem cell potential is a cell culture artifact^[9]. The existence of these MSCs in virtually all postnatal organs does not necessarily mean that these cells behave as stem cells during development. For example, their physiological function could be limited to postnatal regenerative processes. Hence, the concept of mesenchymal stem cell, initially well-defined and restricted to a multipotent progenitor for skeletal tissues and residing within the bone marrow has progressively evolved towards an all-encompassing concept including multipotent perivascular cells of almost any tissue^[9]. Importantly, there is not an exclusive and universal marker for immunophenotyping MSCs. Therefore, their immuno-characterization relies on a combination of both positive and negative markers. Positive markers can include CD11b, CD13, CD19A, CD73, CD105, CD146, CD271, nestin, nerve/glia antigen 2 (NG2), platelet-derived growth factor receptor β (PDGFR- β), while negative markers usually are endothelial, and hematopoietic stem cell proteins (Table 1)^[10-12]. An additional remarkable feature is that MSCs lack or have a low expression of MHC class II and of the costimulatory molecules CD40, CD80, CD86, CD134 and CD142^[13]. In relation to this, MSCs have strong anti-inflammatory and immunomodulating potentials^[14]. MSCs exert their inhibitory effects on T-cell proliferation by mechanisms involving both cell to cell contact between MSC and T lymphocytes, and secreted factors such as prostaglandin E2 (PGE2), inoleamine 2,3-dioxygenase and nitric oxide^[14]. As in many biological processes, this immunosuppressive effect is dose dependent and depends on the ratio between MSCs and T cells. Indeed low ratios of MSCs can even enhance T cell proliferation^[14]. In addition, MSCs prevent the differentiation of monocyte into dendritic cells, and modulate natural killer cell activ-

ity by the release of inhibitory factors such as PGE2 and transforming growth factor- β ^[14]. MSCs also have anti-inflammatory action by reducing the production of tumor necrosis factor (TNF)- α and interleukin (IL)-12 and by increasing the synthesis of IL-10 by macrophages^[14]. These anti-inflammatory and immuno-modulatory capacities of MSCs are already exploited *in vivo*. MSC-based treatment is beneficial in several models of graft-*vs*-host disease and in auto-immune diseases such as collagen-induced arthritis, experimental autoimmune encephalomyelitis, type 1 diabetes mellitus disease and inflammatory bowel disease models^[14-17]. Clinical trials are currently underway for these different pathologies^[15,18]. The ability of MSCs to home in damaged tissues, associated with their capacity to secrete bioactive molecules such as growth factors, and their immunosuppressive and anti-inflammatory properties, suggest that these cells protect tissues from damage and facilitate tissue repair independently of their capacity to generate differentiated cells^[18].

For all these reasons, MSCs became the focus of intense researches in tissue engineering and regenerative medicine. These cells could provide an answer both to the ethical concerns raised by the therapeutic use of human embryonic stem cells and to their scarce availability. Furthermore, as MSCs are easily isolated from adult tissues, they offer the advantage to allow autologous transplantation. Importantly, experimental studies performed with MSCs revealed an additional property: MSCs have a greater differentiation plasticity potential than previously envisioned. For example, they can transdifferentiate into urothelial, myocardial, and epithelial cells^[19-21]. Numerous studies also report the *in vitro* transdifferentiation of MSCs into neural and glial cells^[22-30]. At the moment, the potential of MSCs to regenerate human tissues *in vivo* is not clearly defined. Current research is ongoing to resolve this critical issue by improving MSC culture engineering and cell transplantation technology. A better characterization of the therapeutic potential of MSCs according to their tissue of origin is also a critical issue.

WHEN MSCs TRANSDIFFERENTIATE INTO NEURAL CELLS: FACTS AND ARTIFACTS

The observation that MSCs transdifferentiate into neurons was first obtained with bone MSCs, and then extended to MSCs isolated from different adult tissues including adipose tissue, bone marrow, and brain^[5,31-34]. Brain implanted marrow stromal cells also differentiate into glial cells^[25]. Importantly, grafting MSCs in several brain lesion models reduces neuronal deficits^[35-42]. However, current evidence suggests that in the experimental models used, the repair and functional improvements reported are primarily mediated by paracrine or cell-cell interactions rather than by the successful engraftment and the *in situ* transdifferentiation of implanted MSCs into neural cells^[43-47]. Regarding MSC transdifferentia-

Table 1 Major positive and negative markers used for identifying bone marrow mesenchymal stem cells and pericytes

Markers	MSCs	Pericytes	EC	HSPCs	NSPCs
CD10	+ [12]	+ [12]			
CD13	+ [12]	+ [12]			
CD29	+ [12]	+ [12]		+ [91]	+ [92]
CD44	+ [12]	+ [12]		+ [93]	+ [92]
CD73	+ [12]	+ [12]	+ [94]		
CD90	+ [12]	+ [12]		+ [95]	+ [92,96]
CD105	+ [12]	+ [12]	+ [97]		
CD140B	+ [12]	+ [12]			
CD146	+ /low [12,90]	+ [12]	+ [98]		
CD166	+ [12]	+ [12]		+ [99]	
NG2	+ [12]	+ [12]	- [11]	- [100]	
Nestin	+ [101,102]	+ [72]			+ [103]
CD14	- [12]	- [12]			
CD31	- [12]	- [12]	+ [104]		
CD34	- [12]	- [12]	+ [105]	+ [105]	
CD45	- [12]	- [12]			
CD133	- [12]	- [12]	- [106]	+ [107]	+ [108]
CD117	- [12]	- [12]		+ [109]	+ [110]
CD144	- [12]	- [12]	+ [111]		
vWF	- [112]	- [113]	+ [114]		

In the absence of any universal and specific marker to define mesenchymal stem cells, their immunophenotyping relies on the use of combinations of both positive and negative markers. Note that MSCs profile may vary depending on the cell culture conditions^[88], or with their *in situ* localization^[89]. Expression of the cell surface antigens CD73, CD90, CD105 and non-expression of CD14, CD34, CD45 are useful criteria to define bone MSCs and pericytes. MSCs: Mesenchymal stem cells; EC: Endothelial cells; HSPCs: Hematopoietic stem and progenitor cells; NSPCs: Neural stem and progenitor cells.

tion into neural cells, a notable controversy arose when it was reported that, (1) the rapid *in vitro* morphological differentiation of MSC into neuron-like cells following administration of DMSO or cAMP elevating agents such as forskolin or IBMX can be linked to actin depolymerization resulting in cytoplasm retraction and not through neurite extension^[48-50]; and (2) the transformation of MSCs into neurons *in vivo* can result from the fusion of MSCs with brain cells rather than to MSC transdifferentiation^[51]. Therefore, additional criteria are now applied when studying MSC transdifferentiation. For example, reporting neuronal differentiation of MSCs now requires observation of morphological changes, the demonstration of neural biomarkers expression, neurotransmitter responsiveness or electrophysiological recording, and absence of cell fusion^[28,33,49,52,53]. Note however, that all MSCs are not equal and that their differentiation potential can be related to their tissue of origin^[6]. This suggests that brain-derived MSCs could have a greater potential for neural differentiation than bone MSCs. Hence, the difficulty to obtain functional mature neurons by differentiating bone MSC can be explained both by their origin and by cell culture conditions which are far to provide the cues found in the brain microenvironment. Accordingly, recent experiments using brain derived MSCs instead of bone marrow MSCs, provide additional evidence on the potential of brain MSCs to transdifferentiate into neuro-

nal cells at the clonal level and on the basis of stringent criteria^[54]. A notable point is that these observations are made *in vitro*. Therefore, it remains to establish whether the transdifferentiation of MSCs is a cell culture artifact with potential applications in cell replacement therapies for implanting pre-differentiated neurons, or is it also a physiological process contributing to brain development or repair. Part of the answer might be given by determining where MSCs reside in the organism and which cell behaves as MSC *in vivo*. Recent findings show that MSCs are perivascular cells such as pericytes^[11,55,56].

MSCS ARE PERIVASCULAR CELLS

Pericytes are perivascular cells, or more strictly speaking peri-endothelial vascular mural cells (Figure 1). Pericytes form an incomplete layer on the abluminal surface of capillary endothelial cells. They wrap capillary endothelial cells and both cell types are surrounded by the basal lamina^[57] (Figure 2). For many years, pericytes have been viewed as supportive vasculature cells involved in the regulation of capillaries blood flow and contributing to the blood-brain barrier^[58]. Nowadays, known functions of pericytes also include a role in angiogenesis, in matrix proteins and bioactive molecules synthesis (vascular endothelial growth factor, placental growth factor, leukemia inhibitor factor, CXCL12, basic fibroblast growth factor, nerve growth factor, platelet-derived growth factor B...), in vessel stabilization and in the regulation of vascular tone^[59]. Importantly, these cells are now considered as a potential reservoir of stem or progenitor cells for adult tissue repair. Regarding this stem cell potential, it has been known as early as 1995 that pericytes can differentiate into an osteogenic phenotype^[60]. Ten years after, perivascular cells were also demonstrated to differentiate into adipocytes^[61]. The definitive proof that MSCs are perivascular cells such as pericytes was done in 2008 in two landmark studies showing that a subset of perivascular cells from adult tissues, identified on CD146, NG2 and PDGF-R β expression, exhibit in culture the same osteogenic, chondrogenic, adipogenic and myogenic potentials than MSCs^[11,55]. In addition, these perivascular cells express MSC markers including CD10, CD13, CD44, CD73, CD90 and CD105^[11,12]. A consequence of the demonstration of a perivascular origin for MSCs was a burst of interest in pericyte research with the number of annual entries in PubMed for the keyword “pericyte” increasing from 83 in 1993 to 445 in 2013. With hindsight, the finding that some MSCs are pericytes is not incongruous^[11,56]. Stem cells must reside in a specialized environment (the stem cell niche), and the presence of MSCs in almost all adult tissues suggests a ubiquitous distribution for MSC niches. This is consistent with the omnipresence of capillary blood vessel mural cells. In addition, this perivascular location allows the rapid recruitment of MSCs to the site of focal lesions where they could act as microenvironmental regulators for tissue regeneration^[62]. Since tissue regeneration requires functional blood ves-

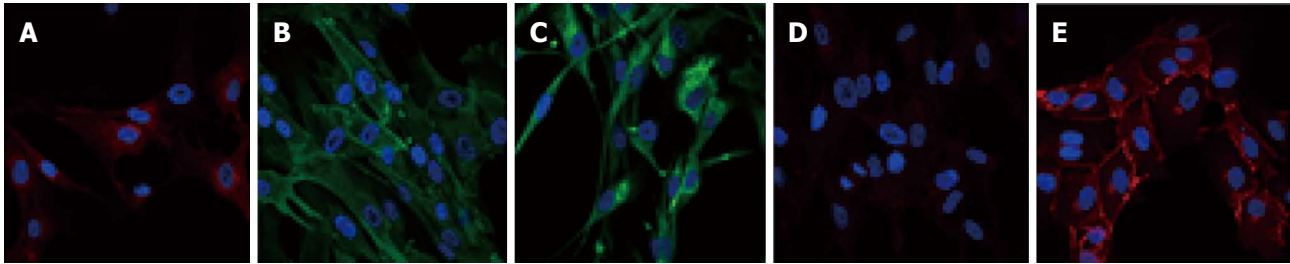


Figure 1 Pericyte immunophenotyping. Pericytes express antigens allowing their identification. However, there is currently no specific marker to identify them. Therefore, to distinguish pericytes from other cell types, both positive and negative markers are used. For example, pericytes are known to be positive for platelet-derived growth factor receptor β (PDGFR- β)/CD140b (A), Alanine aminopeptidase N/CD13 (B), and for the stem cell protein nestin (C). Pericytes are also negative for VE-Cad/CD144 (D) that is detected in human brain endothelial cells (E). Specific antigenic labeling is in green or red and nuclei are 4',6-diamidino-2-phenylindole stained (blue).

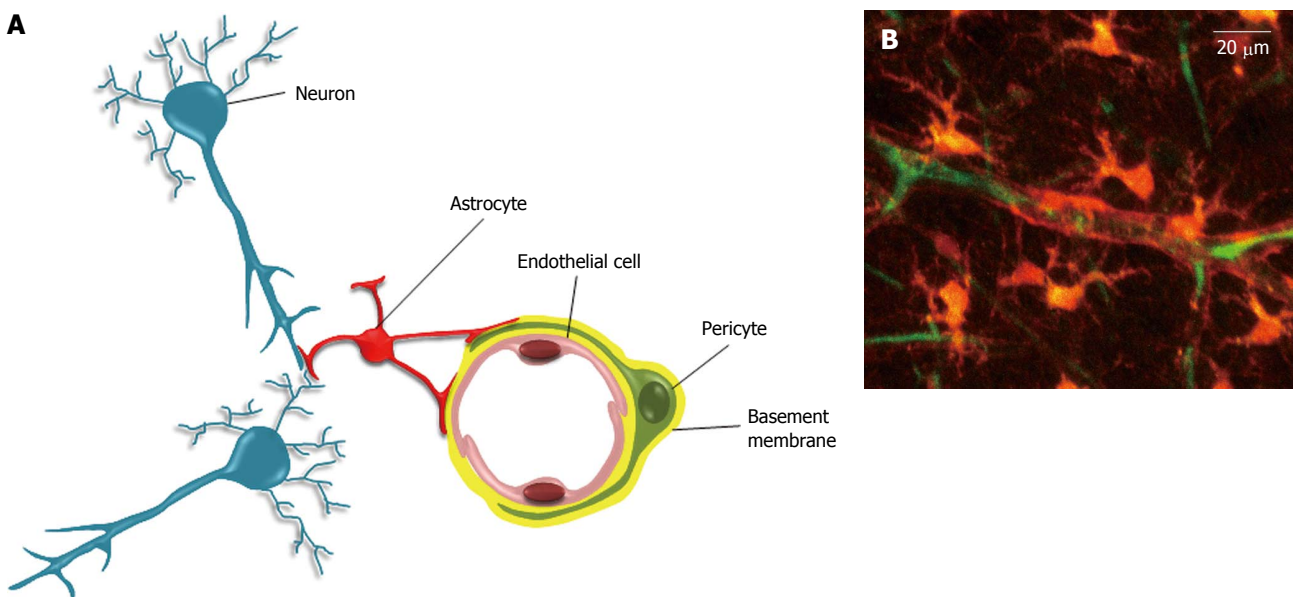


Figure 2 The neurovascular unit. A: The neurovascular unit. In the neurovascular unit, pericytes are located on the abluminal side of endothelial cells (EC). Both cells are ensheathed by the basement membrane (BM). The covering of EC by pericytes is incomplete, and interruptions in BM can allow direct contacts between pericyte and EC. These contacts occur through peg and socket structures, and adherent and gap junctions (not shown)^[59]. The abluminal side of the basement membrane is also contacted by astrocytes endfeet. In addition to these cells, the neurovascular unit also includes neurons, and microglial cells (not shown); B: Two-photon microscopy of a neurovascular unit. Following injection in the rat tail vein, the sulforhodamine-B dye crosses the blood brain barrier and stains astrocytes and pericytes in orange (reproduced from^[115]). The blood plasma is shown in green after *iv* injection of FITC-dextran (Mw 70 kDa). Neurons, endothelial and microglial cells are not shown here.

sels, associating MSCs with endothelial cells in a same “regenerative/healing unit” makes sense. Note that in addition to capillaries, MSCs are also detected in the adventitia of large vessels^[63-65].

CNS PERICYTE AND THE NEUROVASCULAR UNIT

With a human brain capillary network estimated to 400 miles length^[66], and a ratio of about one pericyte for three brain endothelial cells, the human brain pericyte population is far from negligible. Pericytes cover more than 30% of the cerebral capillary surface^[67]. These cells are well-known to be involved in the regulation of angiogenesis, vascular tone and blood brain barrier function. They constitute with endothelial cells, astrocytes and neurons a

critical brain structure named neurovascular unit (NVU). The NVU, in addition to selectively supplying nutrients and oxygen through the blood brain barrier structure, provides a permissive environment for neural stem cell homing and for their proliferation^[68-70]. Note that if most pericytes are of mesoderm origin, forebrain pericytes originate from the neural crest^[71]. The demonstration that MSCs originate at least in part from pericytes raises the question of the stem cell potential of brain pericytes. At a clonal level these cells have the potential to differentiate *in vitro* into adipocytes, chondroblasts and osteoblasts^[54]. Moreover these cells are also able to differentiate *in vitro* toward a neuronal phenotype depending on cell culture conditions^[33,54,72,73]. These observations revive the idea that CNS perivascular cells such as pericytes might contribute to brain repair either directly by generating new

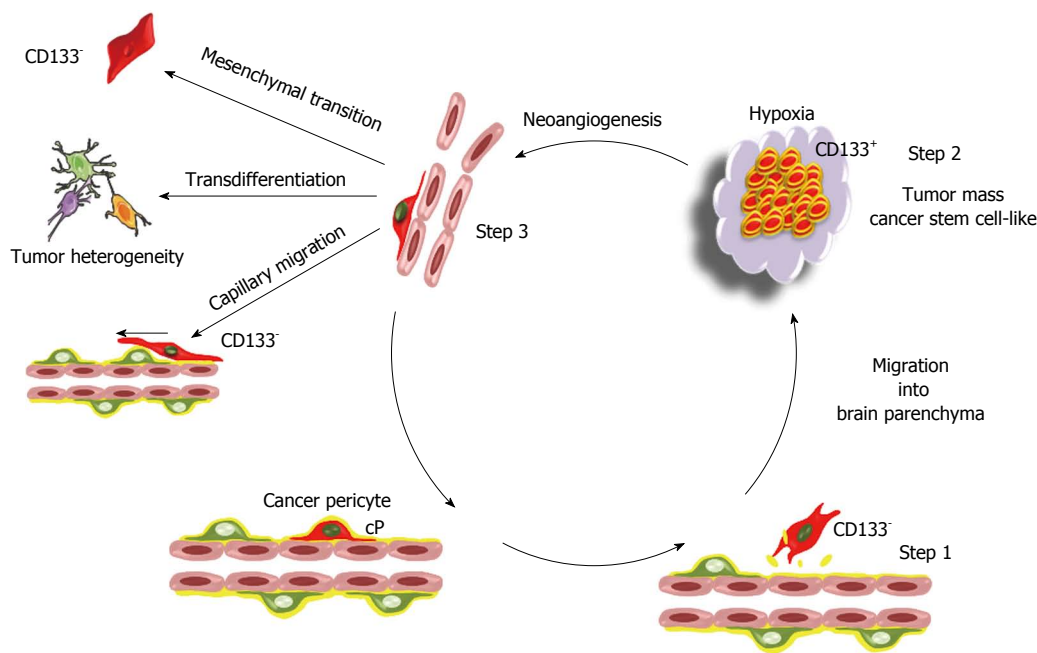


Figure 3 The cancer pericyte model: A perpetuum mobile. The proposed model of brain tumor is based on the mesenchymal stem cell potential of pericytes. In this model, the brain cancer initiating cell is a cancer pericyte (cP) harbouring oncogenic alterations and located on a brain capillary. After disruption of the basement membrane by proteases, it detaches from the vessel wall and migrates into brain parenchyma as normal pericytes do following injury^[76] (step 1). During the passage from a vascular to a neural environment the pericyte acquires a CD133⁺ neural stem cell-like phenotype, as observed *in vitro* for non-transformed pericytes^[72]. Such a transition towards a neural stem cell phenotype is already observed for non-transformed pericytes at least *in vitro*. This generates the CD133⁺ cancer stem cell pool (step 2). Amplification of the cancer stem cell pool generates hypoxia that triggers neoangiogenesis and the migration of endothelial cells towards the lesion as well as the migration of cancer stem cells towards endothelial capillaries^[83] (step 3). Cancer stem cells within this new vascular microenvironment reacquire a CD133⁺ pericyte-like phenotype. At this stage, they can either integrate into the tumor neovasculature and reinitiate a new cycle generating a perpetuum mobile, or migrate along capillaries and invade brain as previously described^[116,117]. Alternatively, due to the mesenchymal stem cell potential of pericytes, these pericyte-like cancer cells could in turn participate to the cellular heterogeneity found in glioblastoma multiforme. Since CD133 is not detected in pericytes, the existence of CD133⁺ pericyte-like cancer stem cells provides an issue to the controversy regarding the existence in glioma tumors of both CD133⁺ and CD133⁻ cancer stem cells^[118,119]. Note that this model is not exclusive. The transformation of a glial or neural stem cell might also generate cancer initiating cells.

neurons or indirectly *via* their immunomodulatory properties or the secretion of neurotrophins^[74]. Consistent with this idea is the observation that pericytes migrate away from the vascular wall and could generate neurons in response to injury^[75,76].

THE CANCER PERICYTE MODEL: A PERPETUUM MOBILE

The NVU also plays a critical role in brain cancer since a contingent of brain cancer stem cells is found near the capillaries^[77-79]. Importantly, glioblastoma stem cells are able to transdifferentiate into pericytes^[80]. According to the function of pericytes in vessel formation, these cancer pericytes contribute to the glioblastoma microvasculature^[80,81]. The recent finding that MSCs are pericytes, and that glioblastoma cells generate cancer pericytes, suggests that the stemness potential of pericytes could play a yet unsuspected role in cancer formation and progression. In the synthetic hypothetical model depicted in Figure 3, a transformed dormant pericyte harboring oncogenic mutations and lying in its vascular niche is activated and released from its vascular location as a consequence of the up-regulation of matrix proteases (Figure 3, step 1).

This activation can be triggered by inflammation or can occur following a local injury as observed *in vivo* with normal pericytes^[76,82]. In the proposed model, and in accordance with the similarities between pericytes and MSCs, this *cancer pericyte* behaves as a cancer mesenchymal stem cell. In accordance to the described potential of MSCs to generate neural stem cell-like cells^[30,72], cancer pericyte cells acquire a neural stem cell-like phenotype during their migration in brain parenchyma. This generates the cancer stem cell pool found in the tumor mass (Figure 3, step 2). Proliferation of these cancer stem cells generates hypoxia and triggers the angiogenic switch. Cancer stem cells are then recruited to develop vessels by endothelial cell-secreted cytokines such as CXCL12^[83-85] (Figure 3, step 3). In this novel vascular microenvironment made of chaotic vessels, cancer stem cells reacquire a pericyte-like phenotype as described^[80,81]. These pericyte-like cancer cells not only participate to tumor vascularization^[80,81], but also re-express their mesenchymal potential by undergoing a mesenchymal transition reminiscent to the epithelial mesenchymal transition. This generates the perpetuum mobile described in Figure 3. Indeed, MSCs have already been characterized as cancer initiating cells in gastric cancer^[86].

CONCLUSION

Since the first observation of pericyte cells by Rouget^[87], it has been a long road and winding road to get here. For many years, pericytes have been largely under-recognized and considered only as supportive cells of the vasculature. Their active role in angiogenesis and in cell-cell interactions with endothelial cells and astrocytes, as well as their *in vitro* stem cell functions, has only recently emerged. However, much remains to be done for a better understanding of the *in vivo* pericyte potential. For example, can pericytes/MSCs be considered as mobile “drugstores” migrating and delivering factors at the sites of injury^[88]? Is the pericyte/MSC transdifferentiation potential an *in vitro* artifact or is it physiologically relevant? Is it an ancient feature of more primitive organisms which has been lost during the course of evolution and which is now reactivated *in vitro*? Alternatively, could it be an emerging evolutionary trait already engaged *in vivo* in some regenerative processes? Is the neural transdifferentiation potential of brain pericyte/MSC only efficient for repairing micro-lesions, which could explain why our current experimental paradigms which generate large infarcts might not be adequate to detect this potential? Do brain pericytes/MSCs behave like “sleeping beauties” awaiting the right physiological or pharmaceutical inducers for expressing their transdifferentiating and regenerative potentials? Conversely is the perversion of this potential involved in some brain tumors? The answers to these questions promise to be fascinating.

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