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No Identical "Mesenchymal Stem Cells" at Different Times and Sites: Human Committed Progenitors of Distinct Origin and Differentiation Potential Are Incorporated as Adventitial Cells in Microvessels

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SUMMARY

A widely shared view reads that mesenchymal stem/stromal cells ("MSCs") are ubiquitous in human connective tissues, can be defined by a common in vitro phenotype, share a skeletogenic potential as assessed by in vitro differentiation assays, and coincide with ubiquitous pericytes. Using stringent in vivo differentiation assays and transcriptome analysis, we show that human cell populations from different anatomical sources, regarded as "MSCs" based on these criteria and assumptions, actually differ widely in their transcriptomic signature and in vivo differentiation potential. In contrast, they share the capacity to guide the assembly of functional microvessels in vivo, regardless of their anatomical source, or in situ identity as perivascular or circulating cells. This analysis reveals that muscle pericytes, which are not spontaneously osteochondrogenic as previously claimed, may indeed coincide with an ectopic perivascular subset of committed myogenic cells similar to satellite cells. Cord blood-derived stromal cells, on the other hand, display the unique capacity to form cartilage in vivo spontaneously, in addition to an assayable osteogenic capacity. These data suggest the need to revise current misconceptions on the origin and function of so-called "MSCs," with important applicative implications. The data also support the view that rather than a uniform class of "MSCs," different mesoderm derivatives include distinct classes of tissue-specific committed progenitors, possibly of different developmental origin.

INTRODUCTION

The anatomical identity of mesenchymal stem/stromal cells ("MSCs," the current "jargon"), their phenotype, distribution in different tissues, lineage, physiological functions, and biological properties represent one of the most controversial and confusing areas in stem cell biology. At this time, two quite distinct descriptions of "MSCs" are found in the literature. One, which emanates from ~50 years of widely reproduced experimental work in vivo, sees "MSCs" as the same biological object previously known as cultured bone marrow stromal cells (BMSCs); these cells are unique to bone marrow (BM), and include a subset of physically identifiable clonogenic, multipotent, self-renewing progenitors of skeletal tissues, and skeletal tissues only (Bianco et al., 2013). This progenitor is endowed with the unique capacity to organize the hematopoietic microenvironment and the hematopoietic stem cell niche (Bianco, 2011; Friedenstein et al., 1982). The other view sees "MSCs" as progenitors of multiple tissues beyond the range of skeletal tissues, such as skeletal muscle (Caplan, 1991, 2008; Crisan et al., 2008). The demonstration that "MSCs" are perivascular cells in BM (Sacchetti et al., 2007) was later extrapolated to claim that in virtually all tissues, pericytes (identified as $CD34^{-}/CD45^{-}/CD146^{+}$ cells) would represent "MSCs" (Caplan, 2008; Crisan et al., 2008). Hence, these broadly multipotent progenitors, essentially defined by in vitro assays (Dominici et al., 2006; Pittenger et al., 1999) that are neither specific nor stringent, would be found in multiple tissues well beyond BM (e.g., skeletal muscle, fat, placenta, umbilical cord) (Caplan, 2008; da Silva Meirelles et al., 2006).

Definition of the origin, anatomy, biological properties, and function of so-called "MSCs" has obvious implications, both for understanding their biology and for their use in potential therapies. Notably, assuming that "MSCs" with identical differentiation properties can be isolated from virtually every tissue would imply that multiple tissues are equally suitable cell sources for the regeneration of multiple tissues. On the other hand, the assumption that

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"MSCs" are the ex vivo counterpart of pericytes would lend support to the view that a number of non-progenitor functions (Bianco et al., 2013) of "MSCs" (anti-inflammatory, immunomodulatory, trophic), claimed to be of major import for therapy of a number of unrelated disorders (Caplan and Correa, 2011), are traceable to an identifiable and ubiquitous in vivo cell type. Nonetheless, pericytes are only defined by anatomy, and currently no experimental data support the notion that they represent a distinct lineage (Armulik et al., 2011; Diaz-Flores et al., 2009). In addition, their role in tissue injury and repair is pleiotropic and spans multiple distinct processes including inflammation; furthermore, their participation in the repair of tissues (e.g., through the formation of scar tissue) does not necessarily coincide with a regenerative function.

We previously identified a minimal surface phenotype suited not only to enrich the archetypal human "MSCs" in uncultured BM cell suspensions, but also to correlate their ex vivo-assayed clonogenic capacity with their in situ identity and in vivo fate following transplantation (Sacchetti et al., 2007). As applied to the study of BMSCs, this led to identification of "MSCs" as subendothelial, perivascular CD146^{+} cells on BM sinusoids, and also provided evidence for their self-renewal in vivo, which had long been the missing evidence to support the claim that BMSCs indeed include a subset of bona fide stem cells, rather than multipotent progenitors (Bianco et al., 2013; Sacchetti et al., 2007). Using an identical approach to prospectively isolate "MSCs" from a variety of non-BM tissues, Crisan and co-workers later reported that a ubiquitous population of highly myogenic and skeletogenic CD146^{+} cells, coinciding with "MSCs," is found in association with microvessels of skeletal muscle and other tissues, lending support to the view of pericytes as a uniform, widely distributed population of cells that can be explanted and cultured as "MSCs" (Caplan, 2008; Caplan and Correa, 2011; Crisan et al., 2008). However, striated muscle and skeletal lineages such as bone, cartilage, and marrow fat diverge early in development, and no common progenitor of bone and muscle is found in prenatal life past the time of sclero-myotome specification in somites (Applebaum and Kalcheim, 2015). The notion of a common postnatal progenitor of bone and muscle, therefore, would be at odds with established tenets in developmental biology (Bianco and Robey, 2015).

We show here that MCAM/CD146-expressing stromal cells from different human tissues diverge radically from their BM counterparts in differentiation potency and transcriptional profile, reflective of their different developmental origin. While BM-derived "MSCs"/pericytes are natively skeletogenic but not myogenic, muscle-derived "MSCs"/pericytes are inherently myogenic but not natively skeletogenic, and appear to represent a subset of cells with functional features of satellite cells, but not their characteristic anatomical location. We further show that prenatal, cord blood-borne "MSCs" in turn exhibit a distinct transcriptional and potency profile, and an inherent cartilage commitment, which diverge markedly from that of postnatal BM-derived "MSCs." Finally we show that, irrespective of the postnatal tissue source of these perivascular cells or from fetal blood, these committed progenitors of mesoderm derivatives can associate with nascent blood vessels (BVs) in vivo and be recruited to a mural cell fate. However, a system of committed and self-renewing progenitors with distinct native potency, and not a uniform, equipotent class of "MSCs" is associated with microvascular walls in postnatal mesoderm-derived tissues as reported previously for bone/marrow (Sacchetti et al., 2007), and as shown herein for muscle. Pericyte recruitment from preexisting local progenitors is a simple developmental process that explains the very existence of such progenitors in postnatal life and their tissue-specific properties.

RESULTS

The Phenotype of "MSCs" In Vitro Does Not Reflect Cell Identity and Function

Stromal cell strains were established from four different tissue sources: BM, skeletal muscle (MU), periosteum (PE), and perinatal cord blood (CB). For all postnatal tissue sources, clonogenic cells were prospectively isolated based on a minimal surface phenotype as previously described for human BMSCs (CD34^{-}/CD45^{-}/CD146^{+}); colonies of CB stromal cells were established as described previously (Kluth et al., 2010; Kogler et al., 2004). Of note, CD146 identified a clonogenic subset in MU (presented below) and PE (data not shown), as it does in BM. Multiclonal strains derived from growth of the originally explanted cells were then expanded under identical basal culture conditions that do not support the growth of endothelial cells or induce differentiation. All resulting cell strains exhibited the canonical in vitro cell-surface markers regarded as characteristic of "MSCs" (Figure 1A).

To determine the specificity and functional significance of the cell-surface phenotype of "MSCs," widely regarded as a defining feature of "MSCs" across tissues, we performed gene-expression profiling using Affimetrix technology. Both unsupervised hierarchical clustering (Figure 1B) and principal component analysis (Figure 1C) revealed that gene-expression profiles of "MSCs" are clearly separated by an "origin" factor, indicating the lack of specificity and sensitivity of the widely used "minimum" surface phenotype. ANOVA-based supervised analysis selected 1,614 class-specific, differentially expressed genes (Table S1) showing a fold difference >3 and a false discovery rate

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