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Self-renewing mesenchymal progenitors in the bone marrow and in other mesodermal tissues

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The original notion that the bone marrow stroma would include a population of multipotent progenitors of skeletal tissues has evolved into the notion of a “mesenchymal stem cells”, which would be found not only in the bone marrow but also in other mesoderm derivatives in the adult organism. Until recently, self-renewal, one of the key defining properties of stem cells, remained undemonstrated, leaving an aura of uncertainty around the very notion of mesenchymal stem cell. Using the Melanoma Cell associated Adhesion Molecule (MCAM, CD146) as a marker suited to follow the fate of explanted clonogenic progenitors through ex vivo expansion and in vivo transplantation, we were able to show that MCAM expressing clonogenic progenitors in the bone marrow stroma do self-renew in vivo, generate multiple skeletal tissues, and regenerate a compartment of subendothelial stromal cells identical to the ones originally explanted as CFU-Fs. A unique feature of bone marrow stromal clonogenic progenitors is their ability to establish the hematopoietic microenvironment (HME) at heterotopic sites, which makes skeletal progenitors in the bone marrow stroma a key component of the

hematopoietic stem cell “niche”. MCAM-expressing clonogenic progenitors (CFU-Fs) are found in, and can be purified from, a variety of other mesodermal derivatives, including skeletal muscle. Here, MCAM-expressing CFU-Fs represent a non-canonical, self-renewing myogenic progenitor, distinct from satellite cells, and endowed with an amazing capacity for spontaneous myogenic differentiation. Both in the bone marrow stroma and in skeletal muscle, cells that express MCAM in situ are located to the abluminal side of microvessels (sinusoids in the bone marrow). From all these data, a novel picture emerges in which a system of clonogenic progenitors endowed with tissue specific differentiation potential and self-renewal capacity exist in different tissues, with the same anatomical location and a closely similar surface phenotype. Their nature as microvascular subendothelial cells provides a novel clue as to the developmental mechanisms that lead to the establishment of progenitor/stem cells in post-natal tissues.

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