Bone-marrow-derived stem cells – our key to longevity?

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Abstract. Bone marrow (BM) was for many years primarily regarded as the source of hematopoietic stem cells. In this review we discuss current views of the BM stem cell compartment and present data showing that BM contains not only hematopoietic but also heterogeneous non-hematopoietic stem cells. It is likely that similar or overlapping populations of primitive non-hematopoietic stem cells in BM were detected by different investigators using different experimental strategies and hence were assigned different names (e.g., mesenchymal stem cells, multipotent adult progenitor cells, or marrow-isolated adult multilineage inducible cells). However, the search still continues for true pluripotent stem cells in adult BM, which would fulfill the required criteria (e.g., complementation of blastocyst development). Recently our group has identified in BM a population of very small embryonic-like stem cells (VSELs), which express several markers characteristic for pluripotent stem cells and are found during early embryogenesis in the epiblast of the cylinder-stage embryo.

Keywords: CXCR4, embryonic stem cells, Nanog, Oct-4, SSEA, very small embryonic-like stem cells.

Introduction

Several types of non-hematopoietic stem cells (non-HSCs) have been described in adult bone marrow (BM). We postulate that the presence of these various populations of stem cells in BM is a result of the “developmental migration” of stem cells during ontogenesis and the presence of the permissive environment that attracts these cells to BM tissue. HSCs and non-HSCs are actively chemoattracted by factors secreted by BM stroma cells and osteoblasts (e.g., stromal derived factor-1, SDF-1; hepatocyte growth factor, HGF), and colonize BM by the end of the second and the beginning of the third trimester of gestation (Kucia et al. 2004; Kucia et al. 2005a; Kucia et al. 2005b; Kucia et al. 2005c; Kucia et al. 2006a; Kucia et al. 2006b; Kucia et al. 2006d; Ratajczak et al. 2003; Ratajczak et al. 2004). Accumulating evidence suggests that these non- HSCs residing in BM play some role in the homeostasis/turndover of peripheral tissues and, if needed, could be released/mobilized from BM into circulation during tissue injury and stress, facilitating the regeneration of damaged organs (Abbott et al. 2004; Gomperts et al. 2006; Kale et al. 2003; Kollet et al. 2003; Kucia et al. 2004; Kucia et al. 2006c; LaBarge et al. 2002; Long et al. 2005; Wojakowski et al. 2004).

These cells have been variously described in the literature, as: (i) endothelial progenitor cells (EPCs) (Asahara et al. 1997; Shi et al. 1998), (ii) mesenchymal stem cells (MSCs) (Peister et al. 2004; Prockop et al. 1997), (iii) multipotent adult progenitor cells (MAPCs) (Jiang et al. 2002), and (iv) marrow-isolated adult multilineage inducible (MIAMI) cells (D’Ippolito et al. 2004). It is likely that in many cases similar or overlapping populations of primitive stem cells in BM were detected by using different experimental strategies and hence were assigned different names. Unexpectedly, it has also been found that BM could be a potential source of precursors of germ cells (oocytes and spermatogonial cells) (Johnson et al. 2004).
It is still unclear whether BM contains any pluripotent stem cells (PSCs). Several attempts have been made to identify in BM such cells, which at the single-cell level in vitro could give rise to cells from all 3 germ layers (meso-, ecto- and endoderm). Recently our group has purified from BM a population of developmentally primitive stem cells, which we named very small embryonic-like stem cells (VSELs) (Kucia et al. 2006a). These cells express several markers characteristic for the embryonic stem cells that are present in the developing epiblast and differentiate into cells from all 3 germ layers. However, the most valuable evidence for pluripotentiality of the stem cell is its contribution to the development of multiple organs and tissues in vivo after injection into the developing blastocyst, but this was so far not demonstrated in a reproducible manner for any type of stem cells isolated from the adult body.

**Developmental hierarchy of the stem cell compartment – from the totipotent zygote to BM-residing stem cells**

Stem cells have a potential for self-renewal and an ability to differentiate into cells that are committed to particular developmental pathways. The compartment of stem cells is organized in a hierarchical way, from the most primitive (totipotent) to already differentiated tissue-committed (monopotent) stem cells. In this context, HSCs are an example of monopotent stem cells already committed to lympho/hematopoiesis.

Figure 1 and Table 1 summarize the developmental hierarchy of the stem cell compartment. The most primitive totipotent stem cell is the zygote, which is the result of the fusion of 2 germ cells (oocyte and sperm) during fertilization. As a totipotent stem cell, the zygote is able to give rise to both the embryo and the placenta. The “artificial” counterpart of the totipotent zygote is referred to as a clonote and can be created in the laboratory with an experimental approach known as somatic nuclear transfer, involving removal of the nucleus from a somatic cell and its insertion/transfer into an enucleated oocyte (Hochedlinger et al. 2003; Rideout et al. 2001). The first blastomeres are totipotent stem cells that derive from the first divisions of the zygote or clonote. This is supported by the well-known fact that the first blastomeres, if separated from each other, can give rise to 2 or even more independent embryos (Tarkowski et al. 1959), as seen in the case of monozygotic siblings.

When the blastomeres have divided into the 32-cell stage, the embryo is known as a morula. The cells that form the morula have already lost...