IS THE SKELETAL MUSCLE TISSUE A SOURCE OF HEMATOPOIETIC STEM CELLS?

Ali Turhan

Poitiers University Hospital, Division of Laboratory Hematology and Oncology, Inserm U935, France

During embryonic development, skeletal muscle and hematopoietic cells originate both from the mesoderm. In both tissues, the existence of stem cells with a hierarchical structure has been demonstrated. During the last decade, several groups have reported the possibility of the persistence of a close relationships between these two tissues in adults. In PAX7 K/O mice, a population of muscle cells isolated on the basis of Hoechst staining, "side-population" (SP) cells, has been shown to generate hematopoietic cells. Conversely, transplantation of SP cells from bone marrow has been shown to give rise to muscle cells in mice. This phenomenon, which has been termed initially under the term of "cell plasticity" has generated a major enthusiasm as several teams have reported that hematopoietic cell transplantation, could generate muscle, liver and even neural cells after transplantation in mice. The mechanism of this phenomenon has been the subject of debates as to whether a "transdifferentiation" or the presence of multipotent stem cells persistence in different adult tissues could have been involved in this process. The presence of multipotent stem cells has been described in several tissues including in murine muscle which harbours a major hematopoietic activity with both self-renewal and expansion potential. It has been shown that these cells can contribute to hematopoietic and muscle tissues after several rounds of transplantation. Interestingly, stem cells with long-term hematopoietic potential isolated from skeletal muscle exhibit a hematopoietic (CD45+, SP) phenotype. Our group studied extensively the characteristics of these cells at the clonal level as compared to the same cells isolated from bone marrow. Muscle-derived cells have been shown to exhibit major expansion and trilineage differentiation (Myeloid, NK, lymphoid) potential. The same potential has been also observed in vivo transplantation experiments. The possibility of isolating hematopoietic stem cells with long-term repopulating ability in mice has prompted us to ask whether the same potential can also be observed in human muscle. Human skeletal muscle has been shown to harbour large numbers of CD34+ cells but these cells appeared to be essentially endothelial cells, although some long-term hematopoietic potential has been observed in vitro experiments. To evaluate the in vivo long-term hematopoietic potential of skeletal muscle tissue, we have performed transplantation experiments in cynomolgous macaques. The results of these experiments will be discussed.

Stem cells: from the Niches to Deep Freeze.

Hematopoietic stem cells (HSC) are defined by their ability to self-renew and to differentiate in the same time allowing maintenance of mature blood cell production during lifetime. These two properties require intrinsic and extrinsic factors. Postulated more than 30 years ago, the stem cell "niche" hypothesis has been explored extensively during the last decade using modern cell biology techniques and animal models, leading to unprecedented progress in understanding the nature of the hematopoietic stem cell niche and the interaction between the microenvironmental signals and cell surface receptors. It has now been shown that the bone marrow niche harbours the extrinsic factors maintaining the stem cells at a very primitive and mostly quiescent state. The most primitive HSC have been shown to reside close to endosteum, the so-called "osteoblastic" niche. A second type of "'niche" has been identified, which is now called

"vascular' niche, in contact with marrow sinusoids, where the transit of cells occurs from bone marrow to peripheral blood. Both types of niches co-exist in the normal marrow, but it remains to be determined if they harbour HSC with the same potentiality. More recently, mesenchymal stem cells (MSC) have been shown to be the potential precursors of these two cell components in experimental systems. reported to play a major role the marrow niche for HSC. The study of individual components of the niche has shown that all interactions might not be equal in terms of biological effects, some interactions stimulating more than others, HSC quiescence. Similarly, factors allowing mobilisation of the stem cells from their niches to peripheral blood have been studied. The interactions between CXCR4, expressed on the surface of HSC and the CXCL12 (or SDF-1) has been shown to be crucial for the maintaining HSC in their niches. The abrogation of this interaction leads to mobilization of the HSC from bone marrow to peripheral blood. The understanding of these interactions led to the development of cell mobilization strategies for auto- and allografting, using G-CSF, and more recently AMD3100, a drug which reversibly disrupts the CXCR4 and CXCL12 interaction. Recent data suggest that stem cell niches might be also involved in the pathogenesis of hematopoietic malignancies, in myelodysplastic syndromes (MDS) or chronic myeloid leukemia (CML). The understanding of these abnormalities might lead in the future, to the development of niche-based therapies for hematopoietic and non-hematopoietic malignancies. Overall, hematopoietic stem cells can now be manipulated starting from their niches up to their migration and collection in peripheral blood, these techniques paving the way for future innovative cell therapy strategies.