Rethinking somatic stem cell plasticity

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The word very much on the minds of the stem cell community during the past several years has been "plasticity." Several publications have appeared with provocative "alchemical" titles such as "Turning [your favorite tissue] into [some other tissue]." Many of these reports claim that somatic stem cells previously thought to be restricted to producing mature cells specific to their tissue of origin may in fact be capable of a much wider spectrum of differentiation. Collectively, these reports have led many investigators to rethink traditional somatic stem cell dogmas, and a minority to claim that these dogmas are outdated and should be revised. In addition to biological interest, reports of stem cell plasticity also raise numerous new and exciting therapeutic possibilities. For example, it has been suggested that the bone marrow may be a source of transplantable muscle, liver, and even neuronal tissues. Traditionally, it has been considered to be a source of stem cells restricted to the production of blood cells or hematopoietic populations. In the extreme, some have begun to consider the bone marrow as a source of stem cells that resemble embryonic stem (ES) cells in their developmental capacities. Such arguments are being employed by groups opposed to human embryonic stem cell research.

So what is the real situation regarding somatic stem cell plasticity? In my opinion, while the numerous studies are intriguing and certainly interesting, it is not yet time to abandon traditional notions established (at least in the most extensively analyzed hematopoietic system) by four decades of research. In fact, it may be argued that setting up an oppositional situation—"Is it or is it not plastic?"—is overly narrow and not constructive. The main reason I argue these points stems from the definition of the word "plastic," which implies the ability of one entity to change into another. In the case of somatic stem cells, this could be, for example, the ability of a hematopoietic stem cell to change its fate to become capable of producing liver cells. The lesson to be learned from the field of hematopoiesis is the value of clonal analysis. It was just such an emphasis on clonal analysis that led to the establishment of the basic properties of stem cells in the mid-1960s[1]. That is, it was clearly shown that a single stem cell can both self-renew and give rise to robust populations of different blood cell types. Thus, to establish plasticity, it must be clearly and directly demonstrated that a single somatic stem cell can give rise to both its "expected" tissue and to an "unexpected" tissue.

Given that early hematopoietic studies were performed by combining considerable thought and experimental elegance with minimal, "bare bones" technology, surely the same degree of clonal precision should be insisted on in this technologically rich postgenomic era. It is surprising and a little sad how few investigators have stressed this point, which in my opinion is of central importance. A second point involves the ability of a stem cell to give rise to large clones of mature progeny. For example, in a situation where a single, traditionally defined hematopoietic stem cell reconstitutes an entire blood cell system and yields a small number of, say, epithelial cell types, is it fair to claim plasticity? Or is this an aberrant, low-probability phenomenon reflecting the consequences of the extreme proliferative activity of the transplanted cell? In such a case the alleged "plasticity" may be formally equivalent to a few primary cells escaping senescence during extensive *in vitro* culture, resulting from accumulated genetic or epigenetic alterations.

Several reports have come close to achieving the necessary level of clonal precision and satisfying the robust contribution criteria outlined above. Examples have included the production of hepatic tissue by highly purified hematopoietic stem cells in the bone marrow[2], and the substantial reconstitution of cardiac tissue by similarly purified bone marrow stem cells[3]. Although both studies are extremely interesting and were well performed, it is not yet possible to conclude from them that a hematopoietic stem cell has expanded non-hematopoietic differentiation abilities. It seems clear nonetheless that substantial liver and cardiac differentiation potential can be found in some populations of bone marrow cells. Regardless of whether this reflects stem cell plasticity or not, these observations are certainly of potential interest from a clinical perspective. An interesting report has suggested that a single transplanted bone marrow stem cell can significantly contribute to epithelial cell populations, in addition to all blood cell lineages[4]. All of these studies are extremely promising; as with all sound science, however, they must be independently verified.

Recently, several publications have appeared that highlight the sometimes unexpected complications that can arise in studies of stem cell plasticity. In short, these studies support the notion that extraordinary claims will require an extraordinary degree of experimental rigor. In one case, it has been demonstrated that the hematopoietic activity observed in muscle cell populations results from bone marrow–derived cells that are present in the muscle tissue[5]. Although the biological significance of this is not clear, it seems unlikely that muscle stem cells could "transdifferentiate" into blood-forming cells[5]. Indeed, it has been demonstrated that bone marrow stem cells circulate through the peripheral blood at a surprising rate. Therefore, any reports of blood-forming activity by non-hematopoietic tissues must be carefully evaluated. A second publication reports the failure to reproduce an earlier report that nervous tissue can give rise to blood, raising the possibility that the original observations may have been due to changes accrued during the extensive *in vitro* cultures that were employed[6]. Finally, two studies[7,8] have shown that coculturing nervous tissue or bone marrow cells with ES cells can result in rare fusion events that yield tetraploid cells. These cells can acquire at least some of the undifferentiated potential characteristic of embryonic stem cells. This complicates any interpretations regarding the reprogramming or transdifferentiation of somatic cell nuclei.

The above discussion is not meant to diminish the interest in the possibility of somatic stem cell plasticity. Clearly, interesting results will be obtained from the many ongoing studies in this area. Rather, I wish to stress the need for experimental rigor and caution before old dogmas are ripe for revision. Indeed, the paradigms provided by the experiments of the mid-1960s are still very much alive, and in need of mechanistic explanation.

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