nature neuroscience

Stem cells show their muscle

One of the more surprising discoveries of the last few years has been that adult stem cells are not irreversibly committed to their tissue of origin, and that they can under certain conditions be induced to form other cell types. An exceptionally clear example appears on page 986 of this issue, where an Italian team led by Angelo Vescovi reports that neural stem cells can give rise to skeletal muscle. This finding seems likely to attract considerable attention, and, along with several other recent reports, to provide new fuel for an increasingly strident debate on the ethics of human stem cell research.

The political debate has heated up in recent weeks; both the UK and the US have released guidelines that would permit research on human embryonic stem (ES) cells, but it is already clear that such research faces an uncertain political future in both countries, as legislators find themselves caught between the biomedical research community and a 'pro-life' lobby that opposes any experiments involving human embryos. Critics of human ES cell research have argued that it is not only immoral but also unnecessary, in that adult stem cells can provide all the advantages of ES cells without requiring the destruction of embryos. This argument, however, is based on weak evidence, and it is disturbing—if unsurprising—to see the science misrepresented in this way. It is important, therefore, that the scientific community should do what it can to make the facts clear, and to prevent research results from being distorted for political ends.

The attraction of ES cells is that they can give rise to all cell types of the body, and are thus a potentially universal source of donor cells for transplantation therapy. Adult stem cells, by contrast, appear to be more restricted, and although they are more versatile than was once believed, the evidence for their plasticity still rests on only a handful of studies, some of which are fairly preliminary. Early last year, Vescovi's group reported that neural stem cells (NSCs) could give rise to blood. This was followed by reports that bone marrow cells can contribute to muscle, that muscle cells can contribute to blood, and that bone marrow cells can form astrocytes. NSCs can also integrate into a variety of sites in the early embryo, and at least in some cases express markers appropriate for their new location. Within the last few weeks, it has been reported that bone marrow cells can form hepatocytes in human patients receiving bone marrow transplants, and that they can also give rise to neurons *in vitro*.

The Italian study is thus not without precedents, but it is notable for several reasons. First, the authors used cloned cell lines for most of their experiments, thus avoiding the ambiguities inherent in studies using mixed populations of cells. They also provided a clear demonstration of the altered fate, showing that NSCs form fused myotubes that appear well differentiated as judged by the expression of a variety of muscle-specific markers and by their appearance under the electron microscope. Moreover, the phenomenon is not an artifact of prolonged culture; the capacity to form muscle exists not only in cloned NSCs but also in freshly dissociated brain cells. Perhaps most significantly, no exogenous signals were required, either *in vitro* or *in vivo*; all that was needed to induce muscle formation was to co-culture the NSCs with myoblasts or to inject them into adult muscle.

A key question, for this and other examples of stem cell plasticity, will of course be the molecular identity of the inducing signals. Vescovi and colleagues report that the formation of muscle requires cell contact, suggesting that the inducing signal in this case is membrane-bound rather than secreted. It must also be present in adult muscle; this is particularly encouraging, because one of the major uncertainties facing transplantation therapy is whether adult host tissues contain the necessary information to instruct transplanted cells to adopt a fate appropriate for their new location. Although the identity of the signaling molecule(s) is still unknown, the availability of an *in vitro* model system should facilitate further progress.

What are the limits to plasticity? Are stem cells from different tissues completely interconvertible? It is still too early to say, but they are clearly not naive, in that they preserve a memory of their origin. Vescovi's cells, for instance, seem to act as a group, reinforcing each other's tendency to form neural cell types; it seems that they can only make muscle if the signal is strong enough to override both their intrinsic tendencies and the signals from their like-minded neighbors. It remains unclear whether neural stem cells, or stem cells from other differentiated tissues, can in principle form any cell type if they receive a strong enough signal.

What is clear, however, is that tissue-specific stem cells differ from ES cells, both in their proliferative capacities and in the ease with which they form different cell types. This has important political implications. Opponents of human ES cell research have often cited Vescovi's earlier work, along with other demonstrations of plasticity, as evidence that ES cell research is unnecessary, and that all the benefits could be obtained instead through research on adult stem cells. Although this may eventually prove to be the case, there is simply not enough data at present to support this assertion. Vescovi says that he "completely disagree[s]" with this interpretation of his findings, and believes—as do the British government and the US National Institutes of Health—that both lines should be pursued. Common sense dictates that it is not possible to decide which approach is more promising until both have been explored. Given that the field is still so young, it is far to early to make that call.