Stem cells – can blank slates become blank cheques?

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The blank slate

As we all know, the adult body is made up of a number of discrete tissues typified by distinct cell types such as muscle cells, blood cells, neural cells, and so forth. However, we were not always thus – the early embryo is largely composed of undifferentiated cells, or stem cells, which have the potential to develop into any one of the over two hundred specialised cells found in the adult. Embryonic development involves progressive cell proliferation and differentiation as these Ur-cells give rise to progeny that form bones, lungs, skin and other specialised tissues. Thus the later embryo contains the rudiments of adult tissues, and also, within those tissues, a base population of undifferentiated stem cells from which further cells typical of the tissue in question are generated. In the adult, such residual stem cells comprise only a very small proportion of any tissue.

The developmental process therefore witnesses 'blank slate' embryonic stem cells, with the ability to develop into any adult tissue (totipotency), change into adult stem cells with reduced developmental potential (or into adult tissues with no further development potential). The blank slate thus is written over with directions that restrict the adult stem cell's differentiation pathways to only a few cell types (pluripotency), usually specific to the adult tissue in which they are found. (In fact it would be more accurate to say that the slate is not originally blank, but rather contains a complete map of all possible pathways, and that various pathways on the map are progressively erased during development until eventually the cell has but one path to follow. But let's not spoil the analogy).

This multifarious developmental potential has resulted in intense interest in the use of stem cells as the basis for therapeutic treatments. In particular, stem cells are seen as offering a means to correct degenerative diseases and injuries at the cellular level, for example where tissues which have limited capacity for self-repair are compromised through injury (eg myocardial infarction) or disease (eg Type I diabetes). This article is intended to briefly summarise aspects of stem cell biology and their possible utility. Limitations of space of course do not permit us to explore all of the issues pertinent to this complex topic.

My slate or yours?

It is probably not too much of an oversimplification to say that stem cell proponents fall into two camps, those that champion the use of embryonic stem cells for human therapy and those that support the use of adult stem cells. Each of these approaches has particular advantages and disadvantages.

For example, the totipotency of embryonic stem cells would suggest that they are more versatile than adult stem cells, which have a developmental repertoire that may be limited to one or two cell types. Furthermore, the decreased developmental potential of adult stem cells usually is accompanied by a reduced 'life-time'. Thus embryonic stem cells can continue to divide and proliferate for

months in the laboratory, so that a very small starting population can give rise to many millions of cells, whereas adult stem cells survive and proliferate only over significantly shorter time scales. This limits the number of cells that can be produced from a given starter population of primary adult stem cells, and may be an important limitation as many clinical cell transplant procedures will need large numbers of cells.

However, embryonic stem cells may suffer from a serious drawback, namely immunogenicity causing transplant rejection, due to the fact that the cells from which they are derived are different from the patient's cells (allogeneic). Cell therapies based on embryonic cells therefore might have to be used with immunosuppressive drugs, if they are to be used at all. Adult stem cells harvested from a patient by contrast could be reintroduced into the same patient (autologous transplantation) with much less likelihood of rejection. Unfortunately, autologous techniques are by definition patient-specific and cannot be scaled up into the kinds of high volume products beloved of big pharma.

However, life is not simple, and it has to be said that the relative advantages and disadvantages of the two approaches are not quite as clear-cut as the above summary implies. For example, some workers claim to have developed techniques for expanding at least some types of adult stem cell in very large numbers. This might nullify the problem of insufficient supply of adult stem cells. Furthermore, recent data has suggested that adult stem cells in fact sometimes can develop into cells which are not typical of the tissue from which the stem cells were derived ('transdifferentiation'). Thus, it seems that haematopoietic stem cells can develop into all three lineages of brain tissue (neurons, astrocytes, oligodendrocytes), skeletal muscle cells, hepatocytes, and cardiac muscle cells. Conversely, adult brain stem cells appear to be able to develop into blood cells.

This unanticipated plasticity fosters the hope that some of the disadvantages of adult stem cells – the small numbers in which they can be found in most adult tissues, and their limited proliferation capacity resulting in low final numbers – may be overcome by using cells from the most abundant adult source (probably blood) in conjunction with an appropriate differentiation process. However, other workers question the significance of transdifferentiation, suggesting that it only occurs in a small proportion of cells. Transdifferentiation has also been suggested to be due at least in some cases to fusion of the stem cell with another cell, ie not really a differentiation step.

It is also relevant that some groups appear to have developed technology which may allow stem cells to be modified so as to be non-immunogenic. Possibly this type of technique will be applicable both to adult and embryonic stem cells, allowing broad allogeneic application of stem cell technology.

It should also be said that cell transplantation may not always be necessary to exploit the regenerative potential of stem cells. One can envisage using small molecules to induce the existing population of adult stem cells in the patient's tissues to proliferate and differentiate into the appropriate cell types to accommodate for the pathology in question. This requires understanding of the cell signalling pathways and factors that control and trigger differentiation, and presupposes the ability to turn such factors into safe drugs with minimal side-effects. The use of small molecules or proteins in this way would not suffer from the immune rejection problems that may hamper broad use of allogeneic transplantation, nor from the problems of supply that may restrict the use of adult stem cells.

Scrips on the slate

The therapeutic potential of stem cells is most clearly applicable to diseases of degeneration, such as ageing diseases in which vital tissues become progressively less viable over time, and to cases of injury in tissues which do not easily repair themselves. In addition, some genetic diseases in which a particular cell type is suboptimal or non-viable due to a DNA mutation may also be amenable to stem cell therapy.

Neurodegenerative disorders, such as Parkinson's and Alzheimer's, are classic ageing diseases which may be susceptible to stem cell therapy. Parkinson's, for example, is typified by progressive loss of dopaminergic neurons over time resulting in various behavioural and motor problems. Replacement of dopaminergic neurons is believed to be sufficient to significantly ameliorate the symptoms of the disease. Various stem cell approaches for Parkinson's may be possible, including the use of appropriate inducers to trigger differentiation of existing stem cells into dopaminergic neurons in the appropriate areas of the brain; or harvesting stem cells with dopaminergic neuron potential from the patient, amplifying them ex vivo, inducing them to follow the dopaminergic neuron differentiation pathway, and reinfusing them in autologous transplantation; or using foreign cells such as human embryonic stem cells in a similar, but allogeneic, process.

Tissue injuries which have been suggested to be targets for stem cell therapy include burns, myocardial infarction, spinal cord injury and stroke. Both of the latter conditions leave many patients with significant, life-long motor problems. Genetic disorders of relevance to stem cell technology include Type I diabetes, which represents a significant market, and muscular dystrophy. In short, the applicability of the stem cell to disease may be as broad as its developmental repertoire, giving rise to speculation that companies with dominant stem cell technology might be in possession of a book of blank cheques.

Who signed the cheques?

However, routine therapeutic use of stem cells outside the haematopoietic context is by no means incipient, and a number of technical issues remain unresolved. For example, critical to all stem cell therapy approaches is the ability to control differentiation – both to maintain the non-differentiated state during amplification of cells, and to trigger at will a specific differentiation pathway. The latter in particular remains a significant challenge. Without a clear understanding of the mechanisms that control stem cell differentiation, we cannot accurately predict how they will behave after transplantation in the human patient. We do not know if they will behave appropriately over the long term, nor if they will exhibit inappropriate proliferation, differentiation or dedifferentiation. We do not know if they will integrate appropriately into the injured tissue, nor if they will further disrupt the tissue, nor indeed if they will function correctly and survive over the long term.

It is also not clear whether transdifferentiation of adult stem cells is normal or an artefact of laboratory conditions. It is not known in all cases what signals trigger transdifferentiation, nor which tissues contain adult stem cells, how many adult stem cells there are in a given tissue, where in the tissue they normally reside, and what factors cause adult stem cells to relocate to sites of injury. Until these types of questions are satisfactorily resolved, any hasty rush into product development might leave companies and their investors with the impression that in fact the only blank cheques they had were signed by themselves and drawn on

their own accounts. This is not to deny the promise of stem cells – simply to urge caution during the current early, and risky, stage of evolution of stem cell therapies.

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