Unlocking the potential of adult stem cells

Matthew Dalby

We now expect to live longer and hope to achieve this along with a good quality of life. However, we are starting to outlive the useful life of many of our tissues and organs. This article shows how the ability of stem cells to grow on novel materials could help us to develop replacement tissues.

Key words

Nanoscience
Stem cells
Orthopaedics
Biomaterials
Tissue engineering

Supportive tissues, such as bone and cartilage, may become damaged or diseased with age. Orthopaedic surgeons can use replacement parts but these have a limited lifespan and repeat replacement surgery is complex and risky. For degenerative neurological diseases, such as Parkinson's and Alzheimer's, there is no replacement option. One solution to these problems may lie with the use of **stem cells**.

Embryonic stem cells have been the headline grabbers in the stem cell world. They are pluripotent, meaning they can make any cell type in the body — so potentially could be a source of replacement tissue. However, their use is ethically and legally challenging. Religious groups are divided on when an embryo becomes a 'person'. Some argue that this happens at conception and thus embryonic stem cells should not be used for research and medicine. Others argue for a later point — for example, when a noticeable nervous system has formed (week 3 of embryonic development) — and that it is fine to use the stem cells before this time. Such debates have limited embryonic stem cell research, stimulating scientists to look for alternative sources of stem cells.

Our adult bodies also have stem cells. These **adult stem cells** respond to damage and disease, becoming activated when needed. They are multipotent — i.e. they can only form a limited range of tissues. For

Fotolia

example, mesenchymal stem cells can form bone, cartilage, ligament and tendon and are found in the bone marrow. When an orthopaedic surgeon does a hip replacement, the bone marrow can be removed and the stem cells isolated. There is another type of stem cell in bone marrow called the haematopoietic stem cell. All blood cells are derived from this multipotent stem cell. The bone marrow is the best-known source of stem cells in the adult, and bone marrow stem cell therapy has been used for decades. Bone marrow transplants are used to introduce haematopoietic stem cells from healthy donors into leukaemia patients after their own diseased stem cells have been irradiated and therefore killed.

Tissue engineering

The presence of multipotent stem cells in our bodies throughout our lives means that they could potentially be used to replace damaged or defective tissues. However, to do this we must find a way of growing these cells outside our body, because there are insufficient numbers of these cells from sources such as the bone marrow to form replacement tissue. The growth or culturing of stem cells is essential if we are to unlock their potential. Culturing cells outside the body is just the start of the process. Once sufficient numbers of cells have been established by culturing, they then need to differentiate into cells that will ultimately form specific tissues. For example, mesenchymal cells can potentially differentiate to form bone, ligament or tendon in the laboratory, just as they do in the body. The process of differentiating cells within material **scaffolds** outside the body — so that they form specific tissues that can be reintroduced into the body — is often referred to as tissue engineering. The ultimate goal of tissue engineers is to grow 'off the shelf' tissue and organs from cells and synthetic materials that can be used as required.

So far, tissue engineering has found success in a small number of applications such as cartilage repair, bladder and trachea replacement. In each of these cases, cells have been isolated from patients and grown on materials in the laboratory before being put back into the patient. However, these are simple tissues where use of differentiated cells is fine. For more complex tissues, stem cells are an attractive alternative to use as replacement cells because they can develop into tissues thanks to their multipotency.

When stem cells are put into the body they are not very good at surviving, and often die because they do not adhere to the existing tissue. This cell death limits their potential use. The support materials used in tissue engineering allow the cells to grow and survive when placed back into the body. The materials used are, ideally, biodegradable so that as the cells start to do their job in the body the material disappears and natural, healthy tissue replaces it.

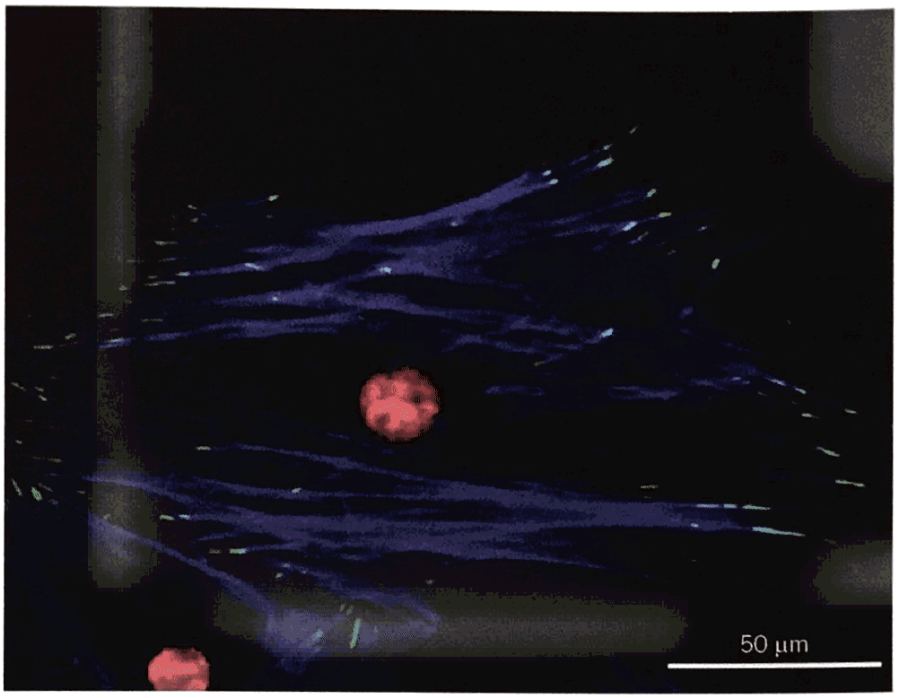

Figure 1 Cells use adhesions (green in this image) to connect and attach to the outside world (tissues or materials). The cell cytoskeleton (actin/myosin) is shown in blue — all animal cells use the cytoskeleton to spread and move. Nuclei are shown in red. Image by fluorescence microscopy.

Stem cells are hard to **culture** outside the body because they tend to differentiate quickly into different cell types. So, as well as being able to discover materials that support growth and allow viable implantation (the scaffolds), we also need to find materials that will allow us to grow enough high-quality (multipotent) stem cells to populate the scaffold.

Novel materials for stem cell culturing

To culture and grow stem cells we need to understand what normally triggers differentiation and prevent this from happening. How cells interact with their environment is a key factor to take into consideration. In the body, proteins on the surface of stem cells will attach to other cells or to a protein scaffold to maintain their undifferentiated status (see Figure 1). We don't know exactly how these interactions maintain stem cell multipotency but we do know that we can prevent stem cells from differentiating by culturing them on specialised materials. These materials are manufactured to have specialised patterns on their surface. Certain patterns have been found to prevent the differentiation of stem cells, enabling culturing and growth of large numbers of mesenchymal stem cells. The patterns are extremely small, even smaller than the stem cells. This **nanotopography** is thought to mimic the natural environment of the stem cells in the body.

Our ability to design patterns on material surfaces comes from the computer industry. The latest

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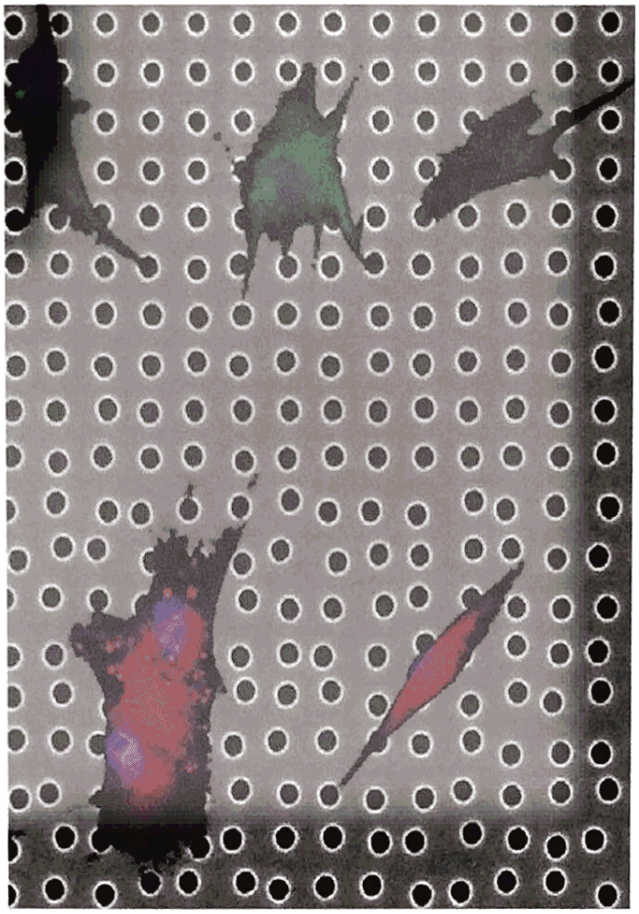
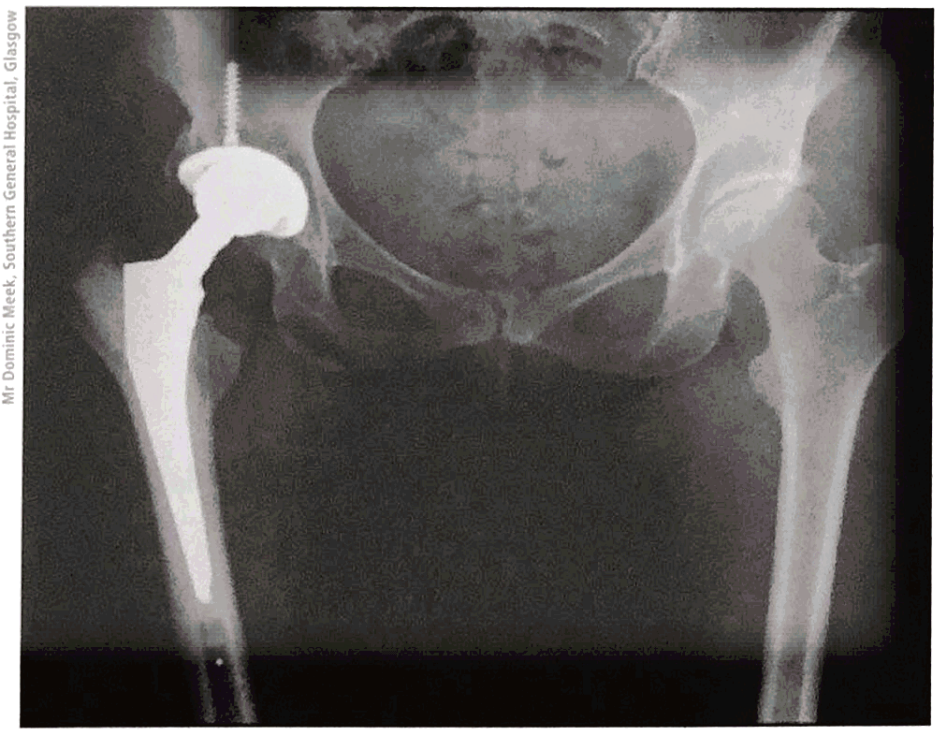


Figure 2 Composite image of mesenchymal stem cells growing on material with nanoscale patterns. On the highly ordered pattern towards the top, the stem cells do not differentiate. On the disordered pattern towards the bottom, the cells differentiate into osteoblasts. Nuclei are stained blue. Cell images by light microscopy, material image by scanning electron microscopy. If the pattern and cells were in the correct scale, the cells would actually cover thousands of pits. Mesenchymal stem cells can spread up to approximately 300 μm long (around 1000 pits long).



Mr Dominic Meek, Southern General Hospital, Glasgow

Figure 3 X-ray of a total hip replacement. A long metal rod into the bone marrow of the femora supports the new femoral head (the 'ball'). In this image, the 'socket' has also been replaced with a synthetic cup.

computer microchips have been created through electron beam lithography. This uses focused electrons to write patterns on silicon. Engineers can write patterns down to 10 nanometres in size, enabling the growth of cells on differently patterned surfaces to be analysed. In Glasgow, cell biologists and electronic engineers have joined forces to make these nanoscale patterns for stem cells.

An example of a pattern that controls mesenchymal stem cell self-renewal is shown in Figure 2 (top). The patterns promote symmetrical cell division — so we can now grow large numbers of multipotent stem cells. This allows new possibilities for clinical stem cell use, such as in **osteoporosis**. Here stem cells capable of forming bone could compete with the bone-absorbing activity of osteoclasts that in osteoporosis are overactive and weaken bones.

These novel patterned material surfaces can also be used to direct stem cell fate. As well as controlling non-differentiated cell growth, targeted differentiation of stem cells is desirable if you want to engineer a particular tissue. By altering the degree of order in which we arrange patterns, we can control the differentiation of mesenchymal stem cells to form bone (see Figure 2, bottom). Intriguingly, the optimal pattern resembles a type of collagen produced by cells turning from cartilage to

Terms explained

Adult stem cells Stem cells found in adults. They have limited differentiation potential and are termed multipotent.

Biomimetic Mimicking nature to get a positive biological response.

Culture A technique used for growing human cells outside the body in laboratory conditions.

Embryonic stem cells Early stage stem cells that can form any tissue of the body. They are pluripotent.

Nanotopography Shapes less than 200 nm in size ($1\ nm = 10^{-9}\ m$).

Osteoporosis Degenerative condition where bone resorption is higher than bone formation.

Scaffold In tissue engineering a scaffold is a material used to support cell growth.

Stem cells Immature cells that can form functional cell types.

Further reading

Oldershaw, R. (2011) 'Stem cells: new cells for old', Biological Science Review, Vol. 23, No. 4, pp. 22–25

http://en.wikipedia.org/wiki/Tissue_engineering

www.nano.org.uk/

www.stemcells.cam.ac.uk

www.ukscf.org/

www.stemcells.org.uk

bone. So there seems to be a **biomimetic** rationale for this response. Stem cells on this surface also have increased adhesion and this appears to be the first step in the bone formation process.

Engineers at Glasgow are now striving to put these patterns onto orthopaedic implant materials. When a surgeon replaces a load-bearing joint such as a hip, they place a metal rod into your bone marrow to secure the new joint (see Figure 3). However, the rod does not stimulate your bone marrow mesenchymal stem cells to form bone — and, instead, soft, fibrous tissue forms. This leads to movement of the implant as the patient walks. This movement increases with time and this is one reason why such implants last only 10–15 years. If we can pattern the materials to stimulate the stem cells to form bone, we could make implants that could last a lifetime.

We can now envisage making complex tissue engineering scaffolds containing regions for self-renewal and areas of targeted differentiation. Challenges remain for engineers to make these patterns in three-dimensional materials for biologists to fill with cells in the laboratory, and clinicians to introduce to areas in need of regeneration. We know that implanted neural stem cells survive much better if delivered in tissue engineering scaffolds than if just injected into a damaged area, so it also appears that materials can offer a supporting role in stem cell survival. One day the current research on novel materials for culturing stem cells may result in new replacement tissues that will improve our quality of life during old age.

Dr Matthew Dalby has a BSc (Hons) degree in biomedical chemistry from Sheffield Hallam University and a PhD in biomedical materials from Queen Mary, University of London. He is a reader in cell engineering at the University of Glasgow. His research focuses on signalling in mesenchymal stem cells.

Key points

- Stem cells can be manipulated to give desired responses of prolonged growth and targeted bone formation by nanoscale topography.
- Nanoscale topography could be used to make new implants where bone growth is desirable.
- New materials could be used in tissue engineering where patient-derived cells are required for engineering of tissues in the laboratory before replacing diseased or damaged tissues.
- The technology could also be used to scale up cell production to grow large numbers of stem cells for use in tissue engineering.