Translational hurdles for tissue engineering

Tissue engineering is a subject of intense research activity worldwide. Despite the high level of activity, most of this research has, so far, had a fairly low impact on surgical practice. In part, this is because of the problems associated with maintaining cell viability; for example, a potential challenge in repairing or replacing the intervertebral disc by tissue-engineered material is the difficulty of supplying nutrients and removing waste products from largely avascular tissues. Another reason for the limited application may be that many of the laboratory-based studies tend to focus on topics such as cell culture, design of scaffolds to support cells and development of scaffold materials rather than integrating clinical and experimental expertise to directly address specific problems. Related to this reason is that many studies do not select applications that are likely to bring benefit in the short to medium term. Selection of applications is important because it is likely that conventional synthetic materials will be preferable to tissue-engineered constructs in the foreseeable future for very many applications.

The paper discussed here addresses a further problem: that surgical practice may compromise the ability of cells to make replacement tissues. These procedures may involve the use of antibiotics or local anaesthetics or wound cleansing and may also lead to infection or (temporarily) affect local temperature. The study involves undifferentiated human skeletal stem cells (also called mesenchymal stem cells) and, therefore, is directly relevant to a feasible target application of tissue engineering scaffold and subsequent tissue regeneration involve many facets of procedure. This includes practical surgical procedures as well as the basic cell biology involved in tissue regeneration. The survival of cells on a tissue engineering scaffold needs to consider all aspects of procedure. This study, the effects of these anaesthetics on cell viability and proliferation in culture were measured. In addition, their ability to affect the differentiation of the cells into osteoblasts was monitored by determining their ability to make alkaline phosphatase seven days after exposure to anaesthetic.

All three anaesthetics had some toxic effect on the cells; they also affected the production of alkaline phosphatase. Both lidocaine and bupivacaine had a toxic effect, except at very low concentrations, which was dose dependent. This result is of concern because bupivacaine is the most widely used post-operative intra-articular local anaesthetic. Inhibition of cell proliferation persisted for seven days after exposure to lidocaine. The toxic effects of levobupivacaine were less serious and, seven days after its administration, the level of cell proliferation had enabled the number of cells to recover to the same level as if it had not been administered. At the higher concentrations used in this study, lidocaine reduced the alkaline phosphatase activity in the cell cultures. Cells were also stained to monitor alkaline phosphatase activity. Staining demonstrated a concentration dependent decrease in alkaline phosphatase expression one week after exposure to local anaesthetics, although the effect was less marked with levobupivacaine.

The immediate implication of this work is that the choice of local anaesthetic is very important in any surgical procedure using skeletal stem cells. Bupivacaine, despite its frequent use, and lidocaine should be avoided because of their toxicity. Indeed, lidocaine has been shown to have similar toxic effects on differentiated cells, such as chondrocytes. Of the local anaesthetics studied, only levobupivacaine did not show appreciable toxic effects. These results are unlikely to be restricted to bone healing; it is likely that they have implications for other orthopaedic procedures using skeletal stem cells, such as cartilage regeneration. The mechanism for the toxicity of bupivacaine and lidocaine is not clear but several possible contributory factors have been identified. These include: damage to mitochondria, inhibition or activation of certain enzymes, blockage of sodium channels, damage cause by free radicals and changes in membrane fluidity.

The more general implication is that development of tissue engineering applications needs to consider all aspects of procedure. This includes practical surgical procedures as well as the basic cell biology involved in tissue regeneration. The survival of cells on a tissue engineering scaffold and subsequent tissue regeneration involve many factors that are currently not investigated in most experimental studies.

David W. L. Hukins,
Professor of Biomedical Engineering,
University of Birmingham, UK.
d.w.hukins@bham.ac.uk

References

©2012 British Editorial Society of Bone and Joint Surgery