Tissue engineering for urologists

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Tissue engineering and stem-cell technologies are now at the forefront of scientific advances and offer novel methods for regenerating and recreating tissue. There is cautious optimism that tissue engineering will play an increasing role in the management of a spectrum of urological disease in the future.

The fascination for young lads to collect earthworms and watch them survive after being cut in half has been written about for centuries. Despite being a hobby of horror for most parents, the endeavours of these budding young scientists would have ignited the subsequent interest for novel experimental studies in the early 18th century on tissue regeneration.

RUDIMENTARY CONCEPTS
Nature provides a fascinating array of organisms that are capable of regenerating entire body parts. Although the human body does not face such demands, it is constantly replacing lost cells. For example, blood replenishes itself, wounds heal, and the lining of the gut sloughs off and is restored.

However, the process of regeneration is more dramatic in freshwater flatworm planaria. Cut one of these animals in half, and a week later, two fully functional worms will have developed from the pieces. Alternatively, cut a piece that is 1/279th the size of the original animal and it, too, will regrow into a complete worm.

Decapitated snails can generate new heads and tadpoles treated with vitamin A will develop abnormally long limbs. Another organism basking in the ‘regeneration limelight’ is the salamander. Scientists have reported on their ability to regenerate a lost arm or leg over a lifetime.

A combination of cellular dedifferentiation to adult stem cells followed by cellular proliferation and tissue differentiation lies under the control of specific developmental genes. Following injury, a blastema (a mass of cells capable of growth and regeneration) will form at the site of injury and then differentiate into particular cell types in order to regenerate lost tissue. Clearly, complex regenerative feats are attainable and recent advances in the field of tissue bioengineering have taken scientists closer to growing organs in the laboratory, thus offering an unprecedented level of personalised medicine that previously was only read about in science fiction novels.

TISSUE ENGINEERING IN UROLOGY
Congenital disorders, cancer, trauma and inflammatory conditions of the genitourinary tract can lead to significant organ damage or loss of function. The aims for tissue engineering and regenerative medicine encompass the restoration and maintenance of normal function.
Current estimates suggest that 7000 patients remain on the renal transplant waiting list in the UK and that the risk of death prior to receiving a kidney transplant may be as high as 10 per cent. An additional 14000 patients may benefit from a renal transplant. Hence, there is a desperate plea for alternative solutions and the search could include renal regeneration alongside newer transplant techniques (Figure 1). End-organ damage in these patients is often an anticipated event and organ replacement using the patient’s own cellular matrix would help to circumnavigate the common problems associated with renal transplantation: rejection, failed organs, immunosuppression issues (infection, secondary cancers) and drug-related complications. Furthermore, new, robust biomaterials are crucially required to help improve outcomes in bladder augmentation surgery, urethroplasty, incontinence surgery, erectile dysfunction treatments and penile reconstruction.

Tissue engineering and stem-cell technologies are now at the forefront of scientific advances and offer novel methods for regenerating and recreating tissue. Current techniques utilise either the acellular or the cellular approach. The acellular method involves the implantation of a scaffold onto which human cells seed, with subsequent differentiation into a specific tissue type. The scaffold can be either a collagen-rich material (eg polyglycolic acid, PGA) that is eventually replaced by the host tissue or an autologous, allogenic or even xenogenic tissue, which is modified to remove the cellular components and then implanted. These scaffolds allow cells to grow into the three-dimensional tissue structure required for organ construction.

The cellular approach involves the use of donor cells, which are then either used alone (stem-cell approach) or seeded onto a scaffold (cell-seeded scaffold approach). The multilineage quality of stem cells enables them to differentiate into potentially any desired tissue type. They can be totipotent (able to differentiate into all types of cells), pluripotent (able to differentiate into all three germ layers) or multipotent (able to differentiate into only closely related cells).

There are three potential cellular sources:
- Embryonic stem cells: raise ethical concerns and retain allogenic potential
- Germline cells: obtained from the umbilical cord, placenta and amnion; these cells are more easily sourced and have fewer ethical issues
- Adult stem cells: obtained from bone marrow, blood samples, adipose/connective tissue and skeletal muscle; unlike other stem cells they appear to have low oncogenic potential.

Advances in laboratory techniques and improved funding have produced effective methods for generating larger amounts of tissue in relatively shorter time periods while eliminating the risk of rejection. The translational impact of this research in urology is certain to improve the treatment of a number of clinical conditions in the future.

Evolution of tissue engineering: the bladder

The cell damage caused by inflammatory, neurological and oncological conditions of the human bladder may lead to a variety of symptoms, including dysfunctional bladder emptying, recurrent infections, stone formation and pain. These symptoms are often recurrent, resistant to conservative treatment and impact on patients’ quality of life.

Contemporary reconstructive, surgical techniques using gastrointestinal segments are associated with specific limitations, including infection, stones, mucus production and malignant transformation. Furthermore, as long-term catheterisation and/or intermittent self-catheterisation are universally loathed by patients, a potential solution may reside in the form of tissue engineering.

The search for an alternative reservoir to replace the native bladder has proved elusive. Synthetic, non-biodegradable materials, such as silicone, rubber, polytetrafluoroethylene and polypropylene were initially used. However, these grafts quickly encrusted, were prone to infection and subject to host–foreign body reactions.

Various studies have attempted to use acellular techniques to augment bladder tissue, but in spite of evidence for a trilayered structure consisting of urothelial-lined lumen, submucosa and smooth muscle, these grafts have met with mixed results. Initial biological and functional gains are offset by graft shrinkage and diminishing function over time. This is likely to be secondary to ineffective neovascularisation.

In addition, techniques trying to induce stem cells to differentiate into urothelium and grafts to encourage cells to grow into the desired morphology are currently being explored. This work provided the foundation for a landmark clinical trial that used autologous-engineered bladder tissue as an alternative for conventional enterocystoplasty.

Professor Anthony Atala’s group currently lead the world in basic scientific and clinical experience regarding tissue engineering in the genitourinary tract. They performed augmentation cystoplasty on seven patients with spina bifida and end-stage bladder disease. PGA composite grafts seeded with autologous urothelial and smooth muscle cells were successfully implanted using an omental wrap to aid in vascularisation. Although histological data at five-year follow-up displayed a trilayered architecture comprising urothelium, submucosa and muscle, there was significant variability seen in the functional parameters of capacity, compliance and leak point pressure. Only
one of seven patients achieved the increase in bladder capacity and improvement in compliance that is routinely observed with conventional enterocystoplasty. In addition, patients were unable to void spontaneously and continued to require intermittent catheterisation.

Evolution of tissue engineering: the urethra

Urethral stricture disease is a common phenomenon but associated with high rates of recurrence and the need for repeated treatments. Substitution urethroplasty involves grafting healthy tissue (eg buccal mucosa) in order to improve outcomes. However, limited tissue resources and associated donor-site problems impact overall success rates.

Raya-Rivera et al. harvested bladder tissue from five boys (median age 11 years) who had sustained urethral defects as a result of injury and seeded them onto a synthetic poly(lactic-co-glycolic)acid (PGLA) meshwork in order to generate tubularised urethras. After three months, all cases had developed a normal urethral anatomy with satisfactory functional outcomes.11

Bhargava et al. demonstrated the development of an autologous tissue-engineered buccal mucosa graft from culturing only a few cells of the buccal mucosa.12 The technique appears promising, although most patients required further surgical modification. Results appear to mirror those achieved with ‘off-the-shelf’ materials; although small patient numbers and short follow-up are obvious limitations in these studies.13

Evolution of tissue engineering: pelvic floor prolapse

Autografts such as rectus fascia and vaginal wall slings can be weak and often require a two-stage operation to harvest and implant. Allografts including cadaveric tissue have less risk of infection and erosion than synthetic analogues but are thought to be weaker. Xenografts, often porcine small intestinal slings, are limited by infection and ethical concerns.14

FUTURE PROSPECTS

Clearly, there has been significant progress in the field of tissue engineering. However, in spite of the advances in technique and methodology, supported by a continued high level of interest, widespread translational clinical impact remains elusive. Currently we are limited by the types of cells that we can manipulate and the technical ability to grow these into a three-dimensional organ structure that is fully functional, safe to use and ethically approved.

Understanding how cells participate in the regenerative process, as well as the mechanisms that influence their involvement, is crucial to identifying the key cellular and molecular participants in organogenesis. By achieving these goals, researchers will be able to tailor their advances in materials and biology to match the needs of each system. Continual development and additional innovation are necessary before broader clinical applications are realised. However, there is cautious optimism that tissue engineering will play an increasing role in the management of a spectrum of urological disease in the future.

Declaration of interests: none declared.

REFERENCES