4 Tissue engineering and regenerative therapies

- Stem cells

Adult tissue resident or somatic stem cells

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Stem cells resident in the di ff erent tissues and organs are responsible for providing replacements for specialised cells that have reached the end of their functional lifespan either through natural attrition or because of damage and disease. In certain tissues and organs, notably the bone marrow and gut, stem cells regularly divide and di ff erentiate into specialised cells to replace senescent or damaged cells in the blood and the gastrointestinal mucosa, respectively . Stem cells in other organs, such as the heart or central nervous system, are less able to e ff ect repair or replacement. SSCs have the capacity to di ff erentiate into a limited number of specialised cell types (multipotent); among the best characterised types are haemato poietic stem cells. In tissue engineering and regenerative medi cine, mesenchymal stem or stromal cell (MSC) populations are widely described but have been more di ffi cult to characterise, particularly in terms of stem cell attrib utes relating to clinical use. Mesenchymal stem and stromal cells 1 Building on earlier observations in the 1960s relating to bone marrow-derived cell populations, in the 1990s the term ‘mesenchymal stem cell’ (MSC) was used in relation to therapy , based on observations that some of these cells, under the right conditions, could di ff erentiate into cell types relating to muscu 2 loskeletal, adipose and other tissues. In 2005 the International Society for Cellular Therapy (now the International Society for Cell and Gene Therapy; ISCT) proposed that these cells be termed multipotent ‘mesenchymal stromal cells’ with the same abbreviation MSC, and that the term mesenchymal stem demonstrate stem cell activity by clearly stated criteria’. They 4 went on to describe minimum criteria in 2006 : adherence to plastic, expression of certain surface markers (CD105, CD73 and CD90) but a lack of expression of others (CD45, CD34, CD14 or CD11b, CD79 α or CD19 and HLA-DR) and, finally , the ability to di ff erentiate into osteoblasts, adipocytes and chondroblasts in vitro , often described by authors as trilineage di ff erentiation. The importance of nomenclature relates to the mechanism by which such cells might achieve a clinical e ff ect. The earlier term mesenchymal ‘stem’ cell implies that cells directly con - tribute to re pair and regeneration by di ff erentiation, whereas using the term ‘stromal’ can encompass paracrine and secre - tory behaviour, in which cells are envisaged to work with other cells to influence the outcome of repair and regenera tion (Figure 4.3) . As a consequence, the term mesenchymal ‘stem’ cell has been highlighted as a cause of potential confusion, - whereby pa tients might wrongly infer that the cell constitutes 5,6 - a ‘stem cell therapy’. In 2019, the ISCT gave continued sup - port for the term mesenchymal stromal cell but recommended that it be: supplemented with the tissue source of the cell; intended unless rigorous evidence for stemness exits; associ - 7 ated with robust functional assays demonstrating properties. A further consideration is the manufacture and delivery of such cells. MSCs can be isolated from bone marrow (iliac crest aspiration) or from subcutaneous fat (liposuction/lipoaspira - tion). Cells can be delivered at the point of care, using bedside systems, or isolated in vitro on the basis of their adherence to plastic and subsequently

further characterised. Therefore, they - can be used shortly after extraction or after expansion of their numbers by in vitro culture. Furthermore, MSCs can be di ff er - entiated into the desired lineage in vitro by addition of suitable growth factors and chemicals. The wide variety of cell type, source and manufacturing process represent important opportunities for treatment.

Cell culture Osteoblast Chondrocyte Adipocyte In vitro trilineage differentiation Figure 4.3 Proposed characteristics of mesenchymal stromal cells relevant to tissue engineering and regenerative medicine. Mesenchymal stromal cell Interaction with in /f_l ammatory and immune processes B-cell Macrophage Natural killer cell Dendritic cell T cell

the understanding of which will be greatly improved by molecular biology techniques and functional assay . In terms of agreed nomenclature, a report on consensus has described key parameters in the abbreviation DOSES: D /uni00A0 – /uni00A0 donor, O /uni00A0 – /uni00A0 origin tissue, S /uni00A0 – /uni00A0 separation method, E /uni00A0 – /uni00A0 exhibited characteristics, 8 S /uni00A0 – /uni00A0 site of delivery . The relative ease of cell acquisition has meant that autologous MSCs have been used in clinical settings and they represent a great opportunity for new treatment development. Before widespread adoption, more translational research is required to understand and refine the therapeutic mechanism of action and conduct well-designed clinical trials to establish the evidence of e ff ectiveness. Adult tissue resident or somatic stem cells

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In the embryo, stem cells are able to give rise to all of the di ff er ent cell types of the body at the gamete stage (totipotent) and nearly all cell types (pluripotent) when at the blastocyst stage (Figure 4.1). ESCs can be obtained from the inner cell mass of the early human blastocyst (days 4–5), using embryos that have been cr eated through in vitro treatment of infertility and are surplus to those needed for reimplantation. The technique for isolating and growing human ESCs in culture was developed 9 by James Thomson in 1998. ESCs have proliferative ability and possess key character istics of self-renewal and pluripotency . However, their use in the clinic has major limitations, one of which is ethical. The surplus embryos used for derivation of ESCs would otherwise be discarded but, because they need to be destr oyed to obtain ESCs, the approach has raised major ethical and political debate. The dominant view in many countries, including the UK, is that the potential therapeutic benefits of ESCs justify their use but there are very strict guidelines for their derivation; to date their clinical use has been limited. Cells from ESCs would be allogeneic and therefore be at risk of immunological rejection. Embryonic stem cells

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Exemplars cells as a therapy

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as The delivery of cells into damaged tissues has long been used to facilitate enhanced regeneration. The first modern example of successful cell therapy was bone marrow transplantation for the treatment of leukaemia, which was successfully performed in 1956. Since then, cells have been used for the regeneration of a range of di ff erent tissues. The following section details exemplars of the use of cells as therapeutic agents, for the regeneration of skin and cartilage (articular and auricular). Skin The tissue that was one of the first regenerated using human cells was skin. The pioneering work of Rheinwald and Green in this area led to the identification of optimal conditions for the growth and maintenance of keratinocytes harvested from skin in culture. The first tissue engineered skin consisted of a layer of keratinocytes grown on a collagenous membrane, which could be directly applied to a healing wound. In the original skin tissue engineering process, the keratinocytes were grown onto a membrane and were cultured in the same system as a layer of confluent but (unable to divide) fibroblasts. The fibroblasts are required in this culture because they provide a series of paracrine factors that allow for the keratinocytes to maintain their phenotype and also mature when lifted to the air–liquid interface. The fibroblasts had to be mitotically inhibited because they tend to proliferate at a greater rate than the keratinocytes and can consequently overtake the complex culture. As a consequence of the need for multiple steps and cell types, in addition to the air-lift required for stratification James George Rheinwald , b. 1948, American research scientist. Howard Green , 1925–2015, George Higginson Professor of Cell Biology , Harvard Medical School, Boston, MA, USA, pioneer in the science of skin regeneration. of the epidermal keratinocyte layer to occur, the process is relatively slow (requiring up to a month). This means that the burn wound to be resurfaced using this process needs to be closed and protected prior to application. This process has been r efined over the years and has resulted in the develop - ment of a range of technologies, some of which are still on the market. Despite a reasonable level of integration, the skin itself lacks many of the features of normal human skin, for example colora tion, and is not in widespread use in the clinic. Articular cartilage regeneration Microfracture or microdrilling (Figure 4.5) into subchondral bone at the base of a chondral defect creates a communication between the intra-articular and subchondral spaces, allowing blood, containing bone marrow stromal cells, to arrive at the defect. Used clinically for more than 30 year s, the formation of the clot creates an environment that allows for the reformation of cartilage within the defect, which subsequently provides a level of mechanical function. Although widely used in the clinic with success, the cartilage formed is typically fibrocartilage, which is mechanically inferior to the native articular cartilage and lacks longer term durability .

Skin biopsy – keratinocytes Figure 4.4 Schematic diagram showing the principles of induced pluripotent stem cell (iPSC) therapy. Mononuclear cells from peripheral blood or keratinocytes from a skin biopsy ar e cultured in vitro and then reprogrammed to become iPSCs by addition of reprogramming factors. The iPSCs are then expanded and selected differ entiation factors added to

promote differentiation of iPSCs into the desired specialised cell type for use as therapy. Reprogramming factors Induced pluripotent stem cells Differentiation factors Cell therapy Differentiated cells Examples include: chondrocytes Disease neurones modelling myocytes pancreatic islet cells

To overcome these limitations, research has focused on ways to create an environment in the chondral defect that is more conducive to the formation of articular or hyaline carti lage. Autologous chondrocyte implantation (ACI) is one such method (Figure 4.5). In the first step a small number of are harvested from healthy cartilage within a patient's joint, for example the knee. The cells are then expanded, to increase the cell number, in a laborator y (with good manufacturing practice [GMP] quality standards). In a second procedural step, cells are reintroduced into the defect, classically with a surgically positioned 'roof ' or patch over the defect, prior to injection of the cells below . In 2017, following the evaluation of evidence, the UK's National Institute for Health and Care Excellence (NICE) recommended ACI for use in the National Health Service (NHS). The recommendation was for defined patients who have symptomatic articular cartilage defects of the knee, with a cost-e ff ectiveness estimate thought likely to be less than £20 /uni00A0 000 per quality-adjusted life year (QALY) gained.

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Exemplars materials in development

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Synthetic and engineered polymers Synthetic polymers are those made from chemical processing of natural components or from complex synthesis from precursors such as fossil fuels. There are a great many synthetic polymers that are used in the body , including polymethyl methacrylate - cells (PMMA), which is used to make intraocular lenses and as a cement in joint replacement; Dacron™ (Terylene™), used in vascular grafts; and a range of resorbable materials, including poly(caprolactone) (PCL), poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and copolymers thereof (PLGA). These resorbable polymers have been used in the body for some time as sutures and in other degradable structures. Moreover, they have become widely used in regenerative medicine for the produc - tion of sca ff olds, on which cells can be seeded and grown prior to, during or after implantation into the body . Synthetic mate - rials can be processed in a range of di ff erent ways in order to provide a structure optimised to the intended purpose. P orous monoliths can be produced by foaming processes, whic h can - include but are not limited to infiltration and then expansion of supercritical carbon dioxide in order to create a foamed structure. The pore sizes of such structures may be tailored by modifying process conditions or material compositions (Figure 4.6). Such polymers can also be formed as spheres by using emul - sion processing or they can be processed into a mat of fibres using a process known as electrospinning, whereby charged threads of polymer are drawn using an electric field and sub - sequently deposited onto a surface (Figur e 4.7). Manufactured in this way , the materials tend to have a very high surface area and can exhibit structural features across the same length scales as the fibrous components of the extracellular matrix. As a consequence, electrospun patches have been designed for the re pair of anatomical structures such as the rotator cu ff and have even been used to explore how modifications in matrix geometry may result in pathology . Bioceramics A range of ceramics have been used for the delivery of com - pounds that can trigger the regeneration of mineralised tissues.

(b) Figure 4.6 Electron micrograph of a poly(lactic acid) scaffold foamed using supercritical carbon dioxide (a) with pore structure assessed using micro-computed tomography (b) . (Adapted with permission from Collins NJ, Leeke GA, Bridson RH et al . The in /f_l uence of silica on pore diameter and distribution in PLA scaffolds produced using supercritical CO . J Mater Sci: Mater Med 2008; 19 : 1497–502.) 2

® The most widely used such material is Bioglass , a glassy material (a ceramic with no crystal structure) containing calcium, silicate and phosphate ions (Na O–CaO–P O 2 2 5 When placed into an aqueous environment, such as within body fluids, the surface of the ceramic material can break down, releasing the component ions into the surrounding liquid. This can result in the deposition of a bone-like mineral across the surface of the material itself, which can encourage the mate rial to

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Exemplars: materials in development

Synthetic and engineered polymers Synthetic polymers are those made from chemical processing of natural components or from complex synthesis from precursors such as fossil fuels. There are a great many synthetic polymers that are used in the body , including polymethyl methacrylate - cells (PMMA), which is used to make intraocular lenses and as a cement in joint replacement; Dacron™ (Terylene™), used in vascular grafts; and a range of resorbable materials, including poly(caprolactone) (PCL), poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and copolymers thereof (PLGA). These resorbable polymers have been used in the body for some time as sutures and in other degradable structures. Moreover, they have become widely used in regenerative medicine for the produc - tion of sca ff olds, on which cells can be seeded and grown prior to, during or after implantation into the body . Synthetic mate - rials can be processed in a range of di ff erent ways in order to provide a structure optimised to the intended purpose. P orous monoliths can be produced by foaming processes, whic h can - include but are not limited to infiltration and then expansion of supercritical carbon dioxide in order to create a foamed structure. The pore sizes of such structures may be tailored by modifying process conditions or material compositions (Figure 4.6). Such polymers can also be formed as spheres by using emul - sion processing or they can be processed into a mat of fibres using a process known as electrospinning, whereby charged threads of polymer are drawn using an electric field and sub - sequently deposited onto a surface (Figur e 4.7). Manufactured in this way , the materials tend to have a very high surface area and can exhibit structural features across the same length scales as the fibrous components of the extracellular matrix. As a consequence, electrospun patches have been designed for the re pair of anatomical

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Exemplars molecules in action

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Healing skin without scarring All tissues in the body , when damaged, are subject to a conserved process by which cells are recruited to the wound to remove damaged tissue fragments and then deposit and subsequently remodel the tissue (see Chapter 3). In the case of the skin, the initial damage results in bleeding into the wound followed by haemostasis and, when the platelets within the clot degranulate, the secretion of proinflammatory factors. The tumour necrosis factor alpha (TNF α), interleukin (IL) 1 and IL-6, platelet- derived growth factor (PDGF), fibroblast growth factor (FGF), insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF) recruit monocytes and endothelial cells into the wound bed to begin the wound-healing process. These cells release further cytokines, such as transforming growth factor beta 1 (TGF β 1), that mediate the formation of new extracellular matrix (normally initially collagen III in skin). Over time, the collagen III is remodelled and replaced with collagen I, which is normally deposited in a basket weave pattern. This process very e ffi ciently closes wounds and, when not too severe, healing can be with minimal scar formation. In the case of severe damage or infection, the inflammatory response can ‘overshoot’, resulting in the overproduction of cytokines such as TGF β 1, which drive the recruitment of excess myofibroblasts to the wound site. This leads to the deposition and subsequent overcontraction of collagen matrix, which can result in the classic appearance of a scar. A number of interventions have targeted this process with the aim of preventing the formation of a scar on the skin. Of note was the identification and isolation of TGF β 3, which plays a role in regulating extracellular matrix formation. This molecule was shown to regulate wound healing by blocking the TGF β 1 and -2 receptors on the cell surface and by modulating the penetration of cells in a newly forming tissue. TGF subsequently developed as a therapeutic agent for use within the skin, with the aim of preventing scar formation. As TGF is a large, protein-based drug it was challenging to manufacture and purify and so was expensive in comparison with small-molecule drugs. Although this molecule had significant poten tial as an antiscarring agent in phase I and II trials, ultimately it was not adopted. This is an exemplar of a translational approach, working from a proposed mechanism through to stepwise clinical trials to test e ff ectiveness. Molecular delivery to prevent ocular fibrosis Another example of the function of a tissue being significantly impaired by fibrosis is the eye. When the cornea is damaged, as long as the wound is kept clean, re-epithelialisation of the surface can occur relatively quickly with full restoration of the corneal surface within 7 days or so. However, if there is an infection on the surface of the eye there can be a potent inflammatory response that results in the rapid and disordered deposition of collagenous tissue across the ocular surface. patient can become blind. Recent work to create a therapeutic - agent to prevent ocular scarring has focused on the localised delivery of a TGF β 1 antagonist called decorin. Decorin is a proteoglycan with a high a ffi nity for collagen I, which it decorates the surface of in normal extracellular matrix. When free in solution, decorin also has an a

ffi nity to seven di ff erent cytokine molecules, one of which is TGF β 1, and has been shown to modulate fibrosis. A decorin-containing eye drop is able to deliver a sustained dose of decorin to the surface of the cornea following damage and subsequent infection. The drop has been shown to be e ff ective in preclinical models of ocular fibrosis, facilitating the restoration of a transparent ocular surface with a significant reduction in markers that are usually indicative of scar formation (Figure 4.10). Challenges to the delivery of molecules Despite the opportunities a ff orded by molecules in tissue regeneration, major challenges remain that relate to getting the therapeutic agent to the right part of the body at the right time. Small molecules tend to di ff use rapidly through excipient (delivery) materials and so are rapidly released into the tissue environment, meaning that a strategy for sustained delivery is a necessity if repeat administration of the drug molecule is to be avoided. A number of implantable materials exist that allow for the slow localised release of molecules at the desired site of application. The majority of these are dense, degrad - able polymers that can be implanted locally and allowed to degrade, thus enabling sustained release of the therapeutic agent. The issues are potentially even more significant for large biomolecules such as proteins, which tend to be v ery sensitive to local environmental changes, with associated reductions in bioactivity . They can also have extremely high activities at very low concentrations and can be extremely expensive. In addi - tion, excipients for these therapeutic products must be chosen very carefully so that potency is maintained and storage time maximised. Exemplars: molecules in action

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formation of a scar on the skin. Of note was the identification and isolation of TGF β 3, which plays a role in regulating extracellular matrix formation. This molecule was shown to regulate wound healing by blocking the TGF β 1 and -2 receptors on the cell surface and by modulating the penetration of cells in a newly forming tissue. TGF subsequently developed as a therapeutic agent for use within the skin, with the aim of preventing scar formation. As TGF is a large, protein-based drug it was challenging to manufacture and purify and so was expensive in comparison with small-molecule drugs. Although this molecule had significant poten tial as an antiscarring agent in phase I and II trials, ultimately it was not adopted. This is an exemplar of a translational approach, working from a proposed mechanism through to stepwise clinical trials to test e ff ectiveness. Molecular delivery to prevent ocular fibrosis Another example of the function of a tissue being significantly impaired by fibrosis is the eye. When the cornea is damaged, as long as the wound is kept clean, re-epithelialisation of the surface can occur relatively quickly with full restoration of the corneal surface within 7 days or so. However, if there is an infection on the surface of the eye there can be a potent inflammatory response that results in the rapid and disordered deposition of collagenous tissue across the ocular surface. patient can become blind. Recent work to create a therapeutic - agent to prevent ocular scarring has focused on the localised delivery of a TGF β 1 antagonist called decorin. Decorin is a proteoglycan with a high a ffi nity for collagen I, which it decorates the surface of in normal extracellular matrix. When free in solution, decorin also has an a ffi nity to seven di ff erent cytokine molecules, one of which is TGF β 1, and has been shown to modulate fibrosis. A decorin-containing eye drop is able to deliver a sustained dose of decorin to the surface of the cornea following damage and subsequent infection. The drop has been shown to be e ff ective in preclinical models of ocular fibrosis, facilitating the restoration of a transparent ocular surface with a significant reduction in markers that are usually indicative of scar formation (Figure 4.10). Challenges to the delivery of molecules Despite the opportunities a ff orded by molecules in tissue regeneration, major challenges remain that relate to getting the therapeutic agent to the right part of the body at the right time. Small molecules tend to di ff use rapidly through excipient (delivery) materials and so are rapidly released into the tissue environment, meaning that a strategy for sustained delivery is a necessity if repeat administration of the drug molecule is to be avoided. A number of implantable materials exist that allow for the slow localised release of molecules at the desired site of application. The majority of these are dense, degrad - able polymers that can be implanted locally and allowed to degrade, thus enabling sustained release of the therapeutic agent. The issues are potentially even more significant for large biomolecules such as proteins, which tend to be v ery sensitive to local environmental changes, with associated reductions in bioactivity . They can also have extremely high activities at very low concentrations and can be extremely expensive. In addi - tion, excipients for these therapeutic products must be chosen very carefully so that potency is maintained and storage time maximised.

FURTHER READING

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Induced pluripotent stem cells

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Introduction

INTRODUCTION

Tissue engineering and regenerative medicine are relatively new but rapidly expanding multidisciplinary fields relevant to surgery that have the potential to transform the treatment of a wide range of human diseases. The ability of tissues to undergo spontaneous repair and regeneration is highly variable and, in most cases, limited. This has driven the devel opment of approaches that harness the biology at the site of tissue damage to mediate regeneration through the localised delivery of cells, materials and molecules. The continuing impro vement in our understanding of how tissues are formed and how they heal underpins the continuous development of novel approaches. As these technologies improve, translate and build up clinical evidence of e ff ectiveness, the prospect of actual tissue regeneration, not just repair, will establish clinical utility . In this chapter, we explore the development of the tissue engineering paradigm (Figure 4.1) and the constituent processes that have been used to enhance tissue healing by considering cells, materials and molecules and the interplay between them, alongside key exemplars. We further highlight the opportunities, challenges and likely future directions for the field.

KEY AREAS OF UNDERPINNING SCIENCE

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Advances in tissue engineering and more broadly regenera tive medicine are underpinned by developments in both the physical and biological sciences, building on the classical tissue engineering paradigm (Figure 4.1). An improved understand ing of developmental biology and the cues that direct stem cell fa te have been key to advancement of the field. A better understanding of the stem cell niche has enabled scientists to propose changes to molecular and mechanical properties that could bring about modifi ed cell behaviour . This has been realised by advances in materials science, which have been crit ical in the development of structures (sca ff olds), onto and into used to localise cells and molecules to a specific site within the body . Notwithstanding the potential o ff ered by these therapies, it should be emphasised that the whole field is still at a relatively early stage of development. Although there are examples where tissue engineering and regenerative therapies have already been introduced into clinical practice, for example the repair of damaged cartilage, most potential regenerative ther - apies have not yet entered routine surgical practice as there are considerable barriers to be overcome before this translational step can be achieved. We have divided the chapter into sections r elating to cells, materials and molecules, while recognising the interplay and composite therapeutic solutions that ultimately arise.

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Learning objectives

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To understand: The potential opportunities afforded by tissue engineering • and regenerative therapy The nature of stem cells, including somatic and adult stem • cells, embryonic stem cells and induced pluripotent stem cells Learning objectives

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A large number of materials have been used in tissue engineer ing and regenerative medicine, either as delivery vehicles or as sca ff olds; it is beyond the scope of this chapter to describe them extensively (see Further reading). In simple terms, materials can be either natural or synthetic and further characterised by their mechanical properties, which will often need to take account of porosity . A further layer of complexity relates to specific molecules within and upon the material and the intended targeting or seeding with cells. In this section, we will focus on synthetic polymers, hydrogels and osteoinductive ® ceramics such as Bioglass . These materials have been selected because of their broad relevance in tissue engineering and regenerative medicine.
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Modification of the tissue environment during healing can be achieved by the delivery of molecules that are selected and able to specifically modify biological responses at the site of injury . In terms of tissue regeneration, these molecules can modulate the inflammatory environment, either by enhancement or by angiogenesis. This approach has been used to optimise tissue regeneration across several applications, with specific exam ples, for the skin and the eye, described below .
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OPPORTUNITIES

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The potential impact of tissue engineering and regenerative therapies is so far-reaching that practising surgeons should be aware of the resulting opportunities to improve patient management. Several conditions that could benefit from this approach are of particular relevance to surgeons because they are closely involved in assessment and treatment (Table 4.1 Selected examples include the repair or replacement of injured or diseased cartilage, skin, pancreatic islets, bladder, intestine, heart tissue, arteries, larynx and bronchus. A longer term goal Burrill Bernard Crohn , 1884–1983, gastroenterologist, Mount Sinai Hospital, New Y ork, NY , USA, described regional ileitis in 1932. - in tissue engineering is the replacement of diseased whole organs such as the liver and kidney , although the technical challenges here are enormous.). Surgeons are integral to many of the multidisciplinary research teams currently undertaking translational research in this field and will play a vital role in the future delivery and

The role and range of materials and scaffolds for tissue • engineering The role and range of molecules and their delivery • The main challenges, safety issues and future directions • TABLE 4.1 Examples of tissues created by tissue engineering and conditions they may be used to treat. Tissue Conditions treated Skin Burns and skin defects after excision or trauma Eye Retinal and corneal disease Cardiac muscle Heart failure Heart valves Congenital and acquired valvular heart disease Cartilage and bone Degenerative and traumatic bone and joint disorders Trachea and bronchus Congenital and acquired stenosis and resection for malignancy Bladder Congenital bladder malformation and cystectomy Anal/bladder sphincter Incontinence Pancreatic islets Insulin-dependent diabetes Large blood vessels Atheromatous, aneurysmal and traumatic arterial disease Oesophagus Benign stenosis and resection for malignancy Small intestine Intestinal failure after surgical resection for Crohn’s disease, cancer or ischaemia

apeutic application, tissue engineering also has the potential to provide in vitro tissues that can be used to model human disease and to test therapeutic drugs for e ffi cacy and toxicity . However, it is important to emphasise that, while the potential benefit of cell therapy and tissue engineering is undeniable, there are many technical, regulatory and safety issues to be addressed for it to have wide clinical impact. Summary box 4.1 Tissue engineering and regenerative therapies /uni25CF /uni25CF /uni25CF

These have potential to provide: Treatment for a wide range of diseases Clinical applications – underpinned by translational research, delivery strategies and clinical evidence Models to test therapeutic ef /f_i cacy and toxicity

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TABLE 4.3 Risks of cell-based therapy. Tumour formation Genetic and epigenetic abnormalities Transmission of infection Poor viability and loss of function Differentiation to undesired cell types Rejection (allogeneic cells) Side effects of immunosuppression (allogeneic cells)

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Somatic cells

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- Fully di ff erentiated specialised cells (somatic cells) obtained from normal tissues have been used for tissue engineering and regenerative therapy with some degree of success. For example, skin has been engineered using cultured epithelial cells grown in vitro and used to treat patients with burn injuries. Chondrocytes have been isolated, expanded in vitro - and implanted into areas of deficient cartilage in a procedure called autologous chondrocyte implantation. Bladder wall has a

Adult stem and str omal Somatic (differentiated) cells cells Contr olled delivery Cells Materials Molecules Anti-in /f_l ammatory Osteogenic

also been engineered using a combination of smooth muscle cells and uroepithelial cells expanded in vitro and grown on a sca ff old before reimplantation. Such tissues can be grown using cells obtained from the intended recipient by tissue biopsy (autologous cells) or using cells obtained from unrelated donors (allogeneic cells). The major advantage of the former source is that, after implantation, they are not rejected by the recipient’s immune system; hence there is no requirement for immunosuppression (see Chapter 88). For other indications, the use of fully di ff erentiated special ised cells is not practical in most situations because such cells are not readily available in su ffi cient numbers and they have only limited proliferative ability in vitro , which means that their numbers cannot be readily expanded to su ffi cient levels. To overcome these limitations, the major focus in the field of cell therapy has been on the use of stem cells.

Cell type Somatic cells SSCs Ease of availability Limited Good Expansion in vitro Limited Good Potency No Limited Ethical concerns No No Risk of malignancy None Low Autologous Yes Yes Anticipated future use Limited High hESCs, human embryonic stem cells; iPSCs, induced pluripotent stem cells; SSCs, somatic stem cells. ethical issues associated with hESCs. Zygote Totipotent cell Blastocyst ESCs or iPSCs Trophoblast Pluripotent cell Primitive endoderm Epiblast Multipotent cell Nullipotent cell Figure 4.2 Hierarchy of cells according to potency, ranging from stem cells to specialised differentiated cells. ESC, embryonic stem cell; iPSC, induced pluripotent stem cell. (Adapted with permission from Tewary M, Shakiba N, Zandstra PW. Stem cell bioengineering: building from stem cell biology. Nat Rev Genet 2018 ; 19 : 595–614.) hESCs Fetal cells iPSCs Moderate Moderate Good Excellent Good Excellent Excellent Limited Excellent a Yes Yes Yes Moderate Moderate Moderate No No Yes Limited Limited High a Note that iPSCs avoid some of the

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