Chapter 4

Scaffold Biomaterials in Tissue Regeneration in Surgery

Emma Iddles, Gabija Lazaraviciute,
Shuchi Chaturvedi and Shailesh Chaturvedi

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Abstract

This chapter will focus on the subject of tissue regeneration in a variety of different surgical fields and operations. We will explore the use of acellular dermal matrices, stem cell-based therapies, gene regulation, emerging 3D printing techniques and their potential applications in surgery. Acellular dermal matrices (ADMs) are biological materials derived from human or animal tissue through complicated and expensive decellularisation processes, leading to acellular material that can be used to aid tissue healing. ADMs were first introduced for the treatment of burn injuries, but are now widely used in a variety of surgical fields, including abdominal wall and breast reconstruction. A wide range of materials can be used to produce ADMs, but usually include bovine, porcine or human tissues (e.g., dermis and pericardium). ADMs act as scaffolds onto which human tissue can incorporate, allowing for an innovative, yet a very effective way to aid tissue regeneration. Stem cell therapies also hold promise in aiding tissue regeneration in the coming years and we will also explore techniques that are currently being researched by prominent scientists all across the world. For example, adipose tissue-derived stem cells (ASCs) are a potentially revolutionary therapy in regenerative medicine. We will review the current evidence available and consider the possible clinical applications of ASCs, including their potential to treat ischaemic diseases and their role in healing chronic wounds. ASCs are adult stem cells, which display similar morphology and differentiation properties to adult mesenchymal stem cells (MSCs). The multiple linage pathways displayed by ASCs allows a variety of tissues to be repaired and maintained. Moreover, adipose tissue is abundant, easily accessible and is able to be repeatedly harvested with low morbidity. Previously, autologous fat grafting was more commonly utilised for managing volume defects in reconstructive and plastic surgery; however, recent literature has revealed promising therapeutic effects of ASCs in tissue regeneration. Finally, gene regulation, which holds promise in musculoskeletal diseases, and 3D printed scaffolds that aid neural regeneration will also be discussed in this chapter as emerging, and potentially very promising, tissue regeneration techniques.

Keywords: tissue regeneration, reconstruction, acellular dermal matrix, adipose tissue-derived stem cells, stem cells, gene regulation, 3D printing, bovine pericardium, xenograft, porcine dermal matrix, Veritas, Strattice

1. Introduction

Tissue regeneration is a vast subject, with many different important aspects to consider. From groundbreaking advances in the use of acellular dermal matrices, to the still-evolving stem cell treatments, this chapter provides an overview of the essentials in tissue regeneration science. We will explore the use of acellular dermal matrices, stem cell-based therapies, gene regulation, emerging 3D printing techniques and their potential applications in surgery and provide an overview of wound and tissue healing in general.

2. Acellular dermal matrices

Acellular dermal matrices (ADMs) are biological materials derived from human or animal tissue through complicated and expensive decellularisation processes, leading to acellular material that can be used to aid tissue healing. ADMs were first introduced for the treatment of burn injuries, but are now widely used in a variety of surgical fields, including abdominal wall and breast reconstruction. A wide range of materials can be used to produce ADMs, but usually include bovine, porcine or human tissues (e.g., dermis, pericardium). ADMs act as scaffolds onto which human tissue can incorporate, allowing for an innovative, yet a very effective way to aid tissue regeneration (see **Figure 1**).

First introduced in 1994, a specific acellular dermal matrix (AlloDerm) was used as a dermal substitute in a full thickness burn injury [2]. This overcame the troubling consequences of significant scarring and contracture after the use of split-thickness autografts used for full thickness injuries. A high percentage of 'take' was seen and was assessed using histology and electron microscopy [2]. No specific immune response was seen and this is owing to the processes in which the actual acellular dermal matrices are produced. In addition to the benefits of reduced scarring, contracture and avoidance of immune response, acellular dermal matrices also ensured that any wound of the donor site was avoided—purely due to the fact that the donor site was not necessary! This was particularly important and useful in patients with extensive burns where the donor site availability was limited. All of this led to the increasing popularity of the use of acellular dermal matrices in the treatment of burns and, later on, the introduction of acellular dermal matrices into other surgical fields.

Complex engineering procedures are involved in producing acellular dermal matrices and will also depend on the original type of tissue used. Decellularisation is an essential process and ensures there is no immune reaction once the acellular dermal matrix is introduced into

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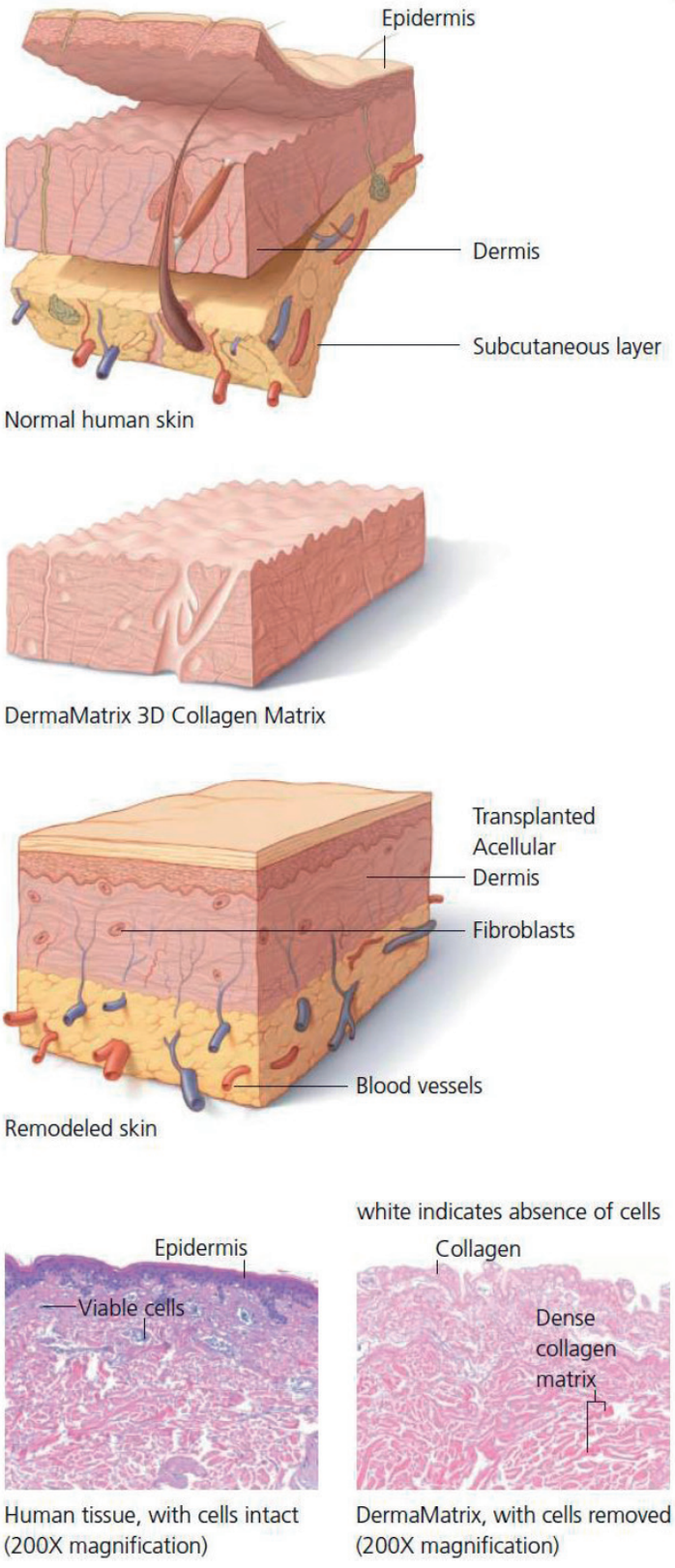

Figure 1. Comparison of DermaMatrix to normal human skin (courtesy of Synthes® [1]).

the recipient's body. All donor cells and antigenic epitopes that have a potential to induce an immune response are removed using a variety of detergents (dependent on a particular type of acellular dermal matrix)—this essentially leaves a scaffold, consisting of collagen, growth factor receptors and vascular channels [3]. Dehydration of the matrix also allows for easier tissue handling and prolonged shelf life [4]. Certain acellular dermal matrices are also terminally sterilised; however, there is no clear evidence whether this provides an advantage [5].

As mentioned above, a variety of different donor tissues can be used in the production of acellular dermal matrices. Commonly, bovine, porcine or human tissues are used, with dermis and pericardium being the most usual types of tissue utilised. A variety of acellular dermal matrices exist at present, some more commonly used examples are listed in **Table 1** [6]:

One of the authors (Chaturvedi) of this chapter has long experience of using the Veritas® acellular dermal matrix, made from bovine pericardium, and has presented this experience in one of the largest series for breast reconstruction [12]. They have found that the advantages of Veritas® included the easy handling and reduction in the incidence of red breast syndrome, as compared to porcine allografts [12].

Acellular dermal matrices act as scaffolds for the recipients' tissues to grow and revascularise upon [2]. Whilst providing nutritional and structural support, acellular dermal matrix integrates into the surrounding tissues and is eventually replaced by functional autologous tissue (see **Figure 2**) [2].

Acellular dermal matrices are used widely in abdominal wall, burn and breast reconstruction. The management of burns with acellular dermal matrices has already been mentioned, with significant benefits of ADM over split thickness skin grafts in terms of donor site sparing, less contracture, scarring and avoidance of immune response. In addition to burns management, acellular dermal matrices were also initially used for tympanic membrane replacement, dural repairs, gingival grafting and, as already mentioned, abdominal wall repair. The use of acellular dermal matrices in these areas gave a start to what is now an increasingly important and prevalent component of both reconstructive and aesthetic surgery.

Breast and plastic surgeons currently actively utilise acellular dermal matrices in a variety of procedures, in particular, implant-based breast reconstruction [5]. Acellular dermal matrices

Name of acellular dermal matrix	Type of acellular dermal matrix
FlexHD® (Ethicon, Somerville, NJ) [7]	Donated human allograft skin
AlloDerm® (LifeCell, Branchburg, NJ) [8]	Donated human allograft skin
Neoform™ (Mentor, Santa Barbara, CA) [9]	Donated human allograft skin
DermaMatrix™ (Synthes, West Chester, PA) [1]	Donated human allograft skin
Permacol™ (Covidien, Boulder, CO) [10]	Porcine dermal implant
Strattice® (LifeCell, Branchburg, NJ) [11]	Porcine dermal implant
Veritas (Baxter, Deerfield, IL) [12]	Bovine pericardium

Table 1. Examples of currently available acellular dermal matrices.

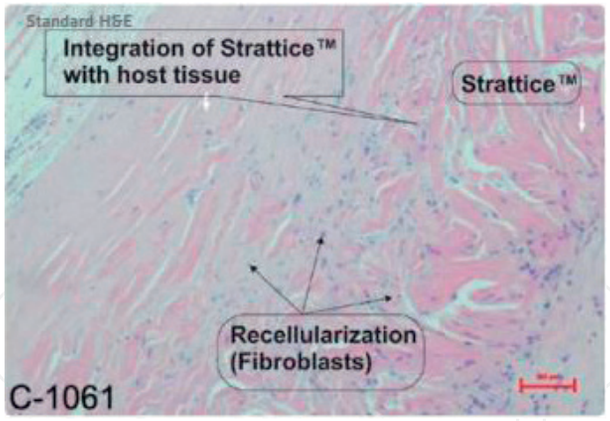

Figure 2. Patient X—Robust recellularisation and remnants of Strattice™ tissue matrix, 31 months post-implantation (courtesy of LifeCell [11]).

have been used in breast surgery since 2001, with many benefits gleaned from their use [5]. Acellular dermal matrices have allowed for immediate breast reconstruction with implants by avoiding the stage of tissue expanders. Mastectomy can be performed with immediate implant based, acellular dermal matrix reconstruction, allowing for immediate results and avoiding a second operation at a later date. Not only do acellular dermal matrices act as scaffolds for tissue regeneration in this case, but also add an additional layer of tissue protection for the foreign body, that is, the implant (see **Figure 3**) [13]. Other examples of applications of acellular dermal matrices in breast surgery include correction of symmastia, incorporation into the upper pole (to decrease surface rippling) and correction of inframammary fold malposition [5]. In addition, acellular dermal matrices are also used in two-stage breast reconstruction procedures with tissue expanders; however, despite advantages, such as faster expansion, improved lower pole projection and better aesthetic shape, the costs are high and need considered prior to individual patient use [5].

New ways of utilising acellular dermal matrices in breast surgery have also been trialled and include use of meshed and fenestrated acellular dermal matrices [14]. This allows for

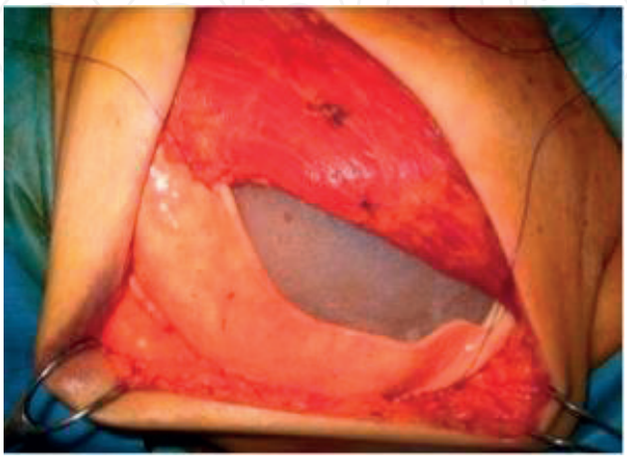

Figure 3. Tissue expander placement into the Pectoralis major and acellular dermal matrix pocket (courtesy of Weichman et al. [12]).

the reduction of costs, with evidence also showing that with fenestrated acellular dermal matrices, the incidence of capsular contractures, infections and seroma formation can be decreased [5].

Complications associated with acellular dermal matrices depend on the type of the acellular dermal matrix used and also the particular procedure it is used for. Breast reconstruction with acellular dermal matrix can cause increased risk of post-operative infection, skin necrosis and post-operative seroma [15]. The correct patient should be identified in order to ensure the risks that are acceptable. Caution needs to be used with obese patients (BMI > 30), simultaneous axillary clearance and smoking history. Radiation will affect any reconstructed breast; however, acellular dermal matrices have, in fact, been shown to reducing the severity of capsular contracture [15].

The use of acellular dermal matrices in abdominal wall reconstruction offers an alternative to a permanent prosthetic mesh and has been in use since mid 2000s [16]. Although some surgeons prefer acellular dermal matrices for abdominal wall reconstructions, concerns have previously been raised regarding the long-term outcomes of acellular dermal matrices as compared to synthetic meshes, with the main worry being the durability. A recent study, however, showed that hernia recurrence rates with acellular dermal matrices were comparable to those done with synthetic mesh—in particular, it was also seen that xenograft acellular dermal matrices led to even lower recurrence rates than human allografts [17]. The question of cost, however, arises again, and synthetic meshes are in fact cheaper than acellular dermal matrices [17].

Outcomes with acellular dermal matrices in breast surgery have already been mentioned (and there is extensive literature for this subject, including a systematic review), but favourable reports have been published on outcomes in pelvic, abdominal, chest wall reconstruction, dural repair, hand surgery, urethral reconstruction and gingival graft procedures, too [6]. Butler et al. successfully used AlloDerm in the reconstruction of large and complex pelvic, chest and abdominal wall defects [18]; however, further studies would be needed in the use of acellular dermal matrices for dural repair (Chaplin et al. successfully used XenoDerm in a porcine model and called it "a nearly ideal dural replacement") [19]. Kim et al. also successfully used acellular dermal matrix for a recurrent first dorsal web space defect, showing excellent cosmetic and functional results [20]. Aichelmann-Reidy et al. showed that acellular dermal matrix could also be a useful substitute in root coverage procedures [21]. Controversies, however, still exist and some studies have shown increased infection rates with ADM-based reconstruction as compared to non-ADM-based reconstruction [22].

Significant costs are also involved when using acellular dermal matrices and remain a topical issue in all fields of surgery. Some situations where costs may be unacceptable have already been considered, for example, with some general surgeons preferencing synthetic meshes in abdominal wall reconstruction due to decreased costs [17]. However, in cases where acellular dermal matrix allows for a two-stage procedure (e.g., implant-based reconstruction with tissue expanders placed during the primary procedure) to be converted into a single-stage procedure (i.e., implant-based ADM reconstruction without the need of tissue expanders), significant savings will be made and this needs to be considered on an individual patient basis.

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3. Mesenchymal stem cells

The exciting field of stem cell therapies has rapidly evolved in order to provide a potential alternative treatment for tissue repair and to enable the regeneration of injured organs. New developments are continually arising from this promising topic of research.

Stem cells are unique in that they are undifferentiated cells that can renew themselves throughout the entire lifespan of an organism. They develop from one common precursor and have the ability to differentiate into multiple cell types with specific functions (see **Figure 4**). Stem cells are characterised by their ability to self-renew over prolonged periods of time [23]. Stem cells that have the potential to repair surgical wounds include mesenchymal stem cells (MSC), embryonic stem cells (ESC) and induced pluripotent stem cells (iPS) [24].

The most commonly utilised stem cells are MSCs, which are derived from adult patients. Autologous mesenchymal stem cells are present in almost all adult tissues including the dermis, periosteum and adipose tissue, solid organs, such as the liver, lungs and spleen and within bone marrow and blood, including from the peripheries, menstruation and the umbilical cord [25].

There has been great enthusiasm within the literature regarding the potential use of stem cells in tissue regeneration over the last decade. The initial focus of research surrounded the clinical applications of embryonic stem cells. However, over the past decade, there has been a move within the scientific community to research the potential applications of mesenchymal

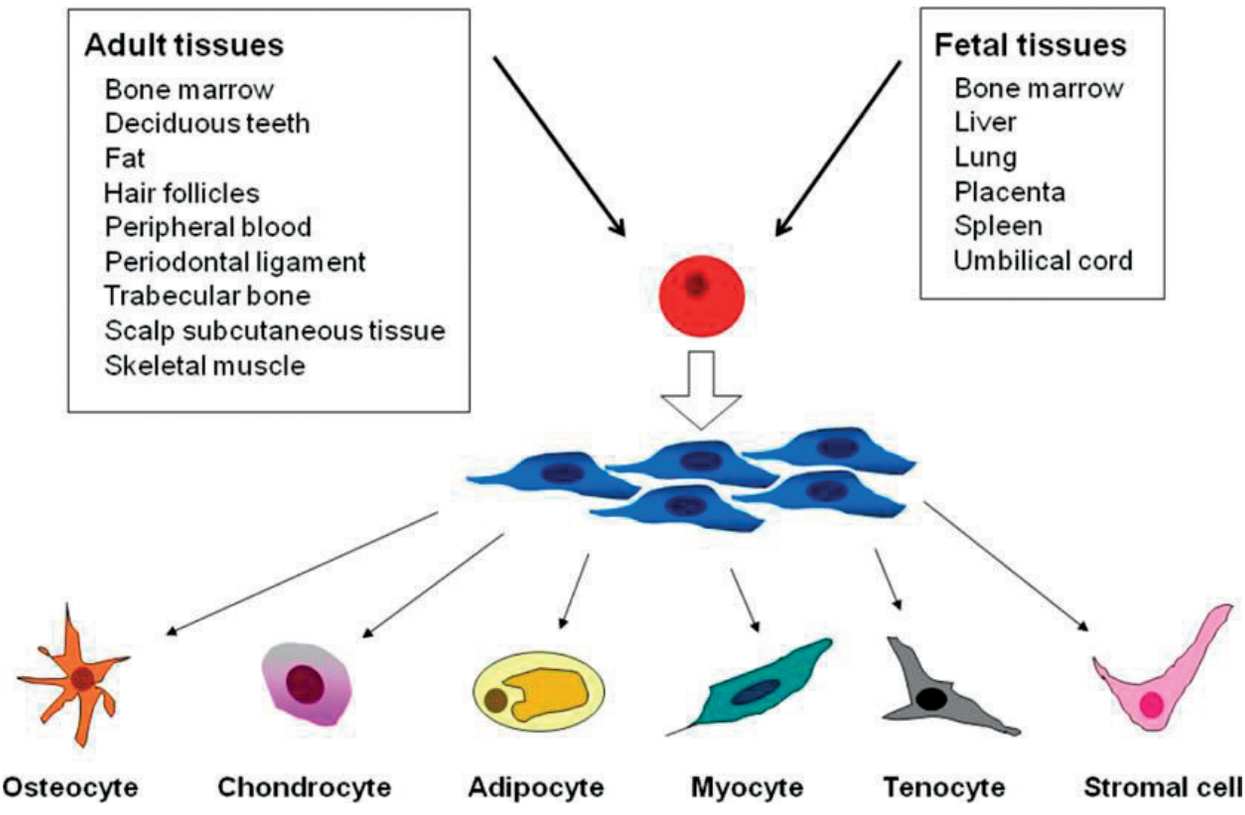

Figure 4. Skeletal regeneration by mesenchymal stem cells: what else (courtesy of Andrades et al. [26]).

stem cells. In comparison to embryonic-derived stem cells, there are less ethical concerns surrounding their cultivation and utilisation [27].

Traditionally MSCs were derived from adult bone marrow using a bone marrow aspirate. However, lately there has been mounting interested in harvesting MSCs from adipose tissue, these are known as adipose-derived stem cells (ASCs). ASCs are of value as they are abundant in supply and easily accessible by means of an excised solid block of tissue or through liposuction techniques [27]. The International Society for Cellular Therapy instituted the following criteria to identify human mesenchymal stem cells (hMSCs) (see **Table 2**) [28].

Adipose tissue is a highly complex tissue derived from mesodermal origin [28]. Its main functions include energy storage, insulation, protection from mechanical injury, endocrine properties and now as a source of multipotent stem cells [29]. It can be classified as brown and white adipose tissue. Thermogenic brown tissue is responsible for energy expenditure and is mostly found in the foetus and new born babies [29]. White adipose tissue is located subcutaneously and intra-abdominally and is responsible for energy storage and insulation (**Figure 5**). White tissue tends to be in abundance and thus renders it a viable long-term option for supply of stem cells [25].

Additionally, subcutaneous adipose tissue can be classified as superficial or deep tissue. The differential potential of ASCs may be altered depending on the location of the harvest. Taranto et el. demonstrated varying stem cell properties within subcutaneous tissues dependant on their location. Adipose tissue yielded from superficial tissues demonstrated increased multipotency [31]. One study has shown that ASCs derived from superficial tissues displayed a slightly higher osteogenic potential than from the deep layer [32]. Previous reports suggest that the yield of ASCs is 100–500 times higher in comparison to bone marrow-derived stem cells [30, 32].

Throughout the literature, there are a number of methods described for the cultivation of MSCs. Naderi et al. describes the isolation and cultivation techniques to obtain ASCs [33]. The adipose tissue is chopped and digested by collagenase and centrifuged in the laboratory. Isolated stem cells are cultivated and subsequently differentiated into a variety of different cell lineages. During pre-clinical trials, ASCs have proven to be very stable under cell culture conditions with a normal haploid karyotype remaining following 100 duplications [34]. ASCs can successfully be cryopreserved whilst maintaining their viability therefore ASCs could be potentially stored prior to use [35].

An extensive volume of research investigating the role and mechanism of action of MSCs in wound healing has been undertaken. Motegi et al. and Fromm-Dornieden et al. recently summarised this into two main categories [28, 34]. These include promoting wound healing through: (I) paracrine actions with nearby cells through the release of growth factors and cytokines and (II) differentiation of cells into resident cells to create a scaffolding to encourage healing. The

1. Proliferation *in vitro* as plastic-adherent cells.

2. Positive expression of CD105, CD73, CD90 and negative expression of the haematopoietic cell surface markers CD45, CD34, and CD14, CD11b and CD79α, or CD19 and HLA-DR.

3. Differentiation into osteoblasts, adipocytes and chondrocytes in culture conditions *in vitro.*

Table 2. Adapted from 'Mesenchymal stem cells: The roles and functions in cutaneous wound healing and tumour growth' [27].

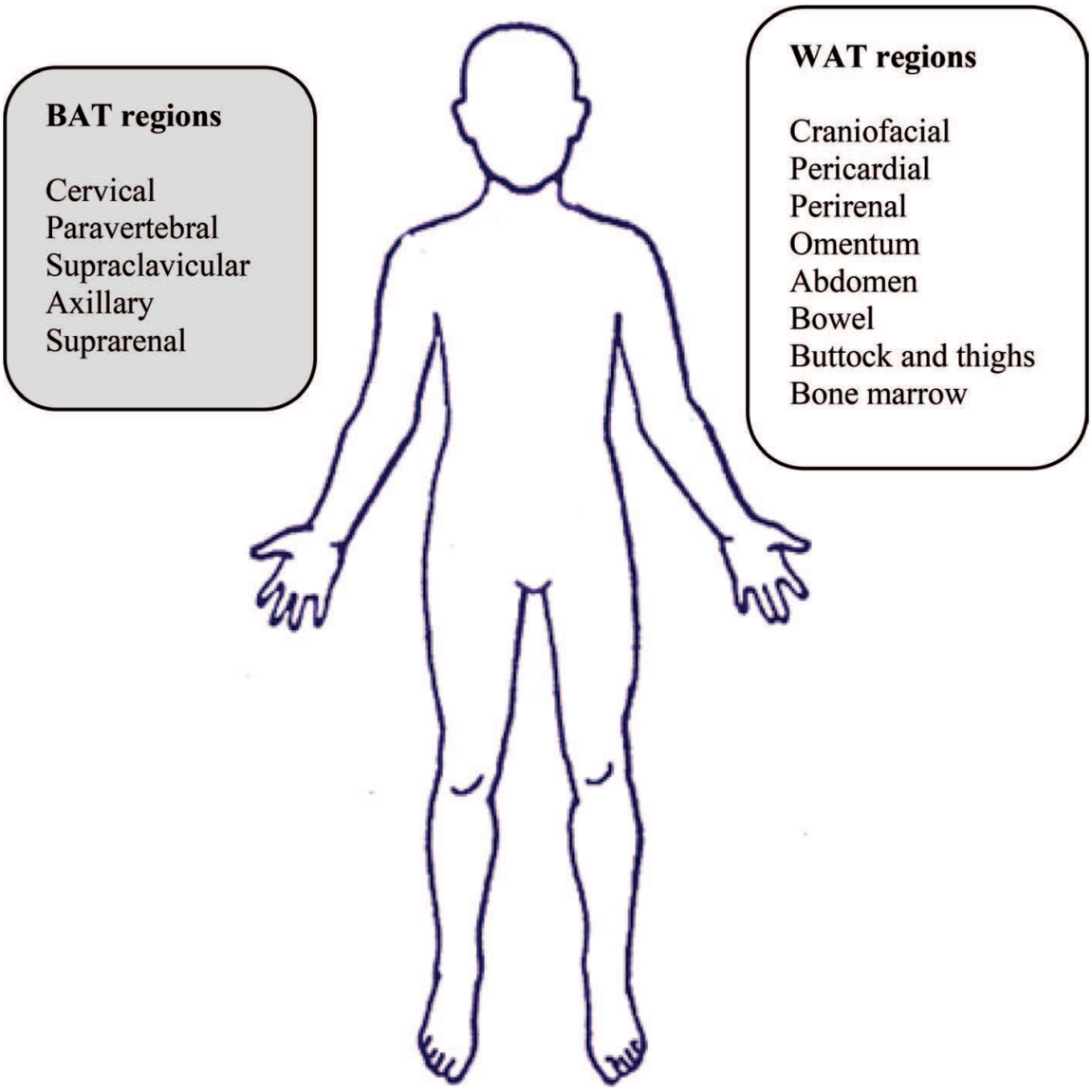

Figure 5. Distribution of brown and white adipose tissue within the human body (courtesy of Kocan et al. [29]).

paracrine mechanisms enable numerous growth factors to be secreted including basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), keratinocytes growth factor (KGF), transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF), which in turn promotes angiogenesis and therefore wound healing [29, 33]. These growth factors are thought to have anti-inflammatory actions, enhancing wound healing by dampening down inflammation at the wound site [29]. Macrophage recruitment is increased. Macrophages are classified as classically activated (M1) and alternatively activated (M2). M2 macrophages have an important role in the progression of wound healing and it is thought that MSCs increase macrophage polarisation in wounds and therefore enhance wound healing [36]. Endothelial cell recruitment is also increased [36]. MSCs have the ability to differentiate into the resident site-specific cells, including, fibroblasts, myofibroblasts, keratinocytes and pericytes [36].

Cells known as pericytes, with similar features to mesenchymal cells, have been discovered within the blood vessels in multiple organs. Crisan et al. described that certain perivascular cells isolated from various organs, including the skin, showed differentiation into multiple lineages

both *in vitro* and *in vivo* [37]. This research surmised that it is likely that blood vessel walls may hold a reserve of mesenchymal-like stem cells that are involved in the repair and neovascularisation of wounds. However, the exact mechanisms and significance remains unknown.

Patient selection for harvesting is an important factor because biologic properties can be affected by systemic disease. Adipose tissue that is extracted from patients with diabetes is inferior to adipose tissue that has not been subjected to systemic disease. In tissue exposed to systemic illness, there is loss of cell differentiation ability, increased levels of failed division and apoptosis and an overall reduction in the levels of growth factors secreted [38].

There are few human clinical trials involving the applications of MSCs and even fewer evaluating the utilisation of adipose cells. The current use of ASCs in clinical practice remains limited to trials. A number of animal model studies have demonstrated the promising possibilities of adipose-derived stem cells and there are a number of small pilot clinical trials, which have been published in the literature recently with many new studies emerging frequently. This exciting data gives promise to the potential clinical applications of ASCs and with new information continuing to evolve, the routine use of stem cells in clinical practice remains a tangible prospect in the near future. This section of the chapter provides up to date evidence and a summary of recent studies involving ASCs.

Nie et al. investigated the mechanisms of action of ASCs in wound healing [39]. ASCs were incorporated into full thickness excisional wounds in both diabetic and non-diabetic rats. The study showed that wound healing was accelerated and time taken to close wounds in both groups was shortened. There was increased re-epithelisation and advanced development of granulation tissue within the wound. Enhanced neovascularisation was also shown due to the increased secretion of angiogenic growth factors.

Park et al. recently investigated the role of allogenic ASCs in the treatment of complex perianal fistulas secondary to Crohn's disease [40]. In this small pilot multicentre, clinical trial participants had complex non-healing perianal fistulas, which had not healed by conventional techniques (surgery or infliximab treatment). The initial group of participants received a smaller dose of ASCs than the second group. At 6-month follow-up, 50% of participants had achieved complete closure of the fistula, which was maintained at the final follow-up at 8 months.

A phase one clinical trial demonstrated the effect of autologous-derived adipose stem cells in patients with severe peripheral arterial disease with chronic non-healing ulcer disease. All participants had non-vascularisable critical limb ischaemia with lower limb rest pain or ulcers and a low ankle systolic oxygen pressure. ASCs were injected intramuscularly into the ischaemic limb with no complications recorded. Most participants showed an increase in trans-cutaneous oxygen pressure and improved ulcer healing [41].

Kim et al. studied the effectiveness of stem cell treatment in patients with chronic non-healing wounds following complications of soft tissue nasal fillers [42]. ASCs were harvested from the patient's subcutaneous adipose tissue. Following preparation in the laboratory, the adipose cell containing solution was injected into the dermis and subcutaneous layer around the wound. All participants experienced enhanced wound healing and at 6 months post treatment all wound sizes were reduced. These results lead the authors to propose that stem cells could be considered in the future for routine use as a treatment of complications of filler injections.

In addition to skin wound healing, there have been advances within the role of stem cells in orthopaedics. A recent study focused on the role ASCs in the repair of meniscal injuries. Toratani et al. created meniscal defects in rabbits and injected autologous stem cells from adipose tissue into half of the subjects [43]. ASCs were found to promote meniscus healing in the rabbit model. This paper offers promise for future clinical uses as a potential new treatment for meniscal injuries subject to further studies.

Stem cells could potentially revolutionise the treatment of chronic heart disease. Atherosclerosis is the leading cause of morbidity and mortality in the developed world with risk factors including diabetes, hypertension, smoking and obesity. Researchers have endeavoured to develop a stem cell-based therapy for the treatments of ischaemic heart disease and cardiac failure. Numerous preclinical studies have demonstrated promising therapeutic benefits using ASCs with the improvement in left ventricular function and reduction in infarct size [44]. However, these successful results have yet to be seen in human trials. The difference in results is thought to be due to the source of stem cells. In animal trials, MSCs were harvested from healthy donors; however, in comparison in the clinical trials, the stem cells were collected from the patient with known atherosclerotic disease and potentially other serious co-morbidities [45]. Further research in this field continues to evolve to in order to create a successful therapy.

4. Gene regulation

Other novel tissue regeneration methods have been trialled in both animal and human studies. For example, genetics is an ever-evolving field when it comes to finding ways and methods of aiding tissue regeneration. Animal studies provide a starting point for future discoveries—for example, Kang et al. investigated tissue regeneration enhancer elements (TREEs), providing evidence that these elements trigger gene expression in injury sites [46]. The authors of this particular study felt that these findings could further be extrapolate in the future to assess their regenerative potential in vertebrate organs [46]. Gene regulation to aid tissue regeneration has been investigated in human studies, too. Recent studies by Finkel et al. and Mendell et al. showed promise in motor neurone diseases, specifically spinal muscular atrophy [47, 48]. Finkel et al. modified promoted increased production of the survival motor neurone (SMN) protein with an antisense oligonucleotide drug and showed that infants with spinal muscular atrophy receiving this drug were more likely to be alive and have improved motor function that the control group [47]. Patients in the Mendell et al. study received adeno-associated viral vector infusion containing DNA coding for SMN; these patients again, survived longer, achieved motor milestones better and had improved motor function than historical cohorts [48]. Musculoskeletal tissue regeneration is a great challenge for scientists and lots of studies have looked into potential options, in addition to the two mentioned already. Padilla et al. discuss a variety of techniques, including blood derived biological drug delivery therapies, which have significant potential for tissue regeneration [49]. For example, platelets release hepatocyte growth factor and stromal cell-derived growth factor 1, both known to be involved in wound healing and proliferation [49]. There is a significant need for further randomised trials and systematic reviews to assess if these therapies could be used routinely for the treatment of musculoskeletal

conditions. These are just examples of how gene regulation can lead to significant changes in tissue regeneration and improved clinical outcomes; and future research will be needed to assess safety of such gene therapies for widespread use.

5. 3D printing

In addition to novel gene regulation techniques, there have also been advancements made in the promising area of three-dimensional (3D) printing for medical needs. 3D printing has revolutionised many aspects of our lives, with its uses and benefits still being tested in medicine. 3D printing has the potential to revolutionise the way we practice medicine and tissue regeneration and transplantation are two fields where opportunities are endless. It is a well-known fact that the need and demand for organ and tissue replacement largely outweighs the supply, even with recently increasing numbers of deceased donors [50]. What if we could eliminate the need for donors and, at the same time, resolve a major issue associated with

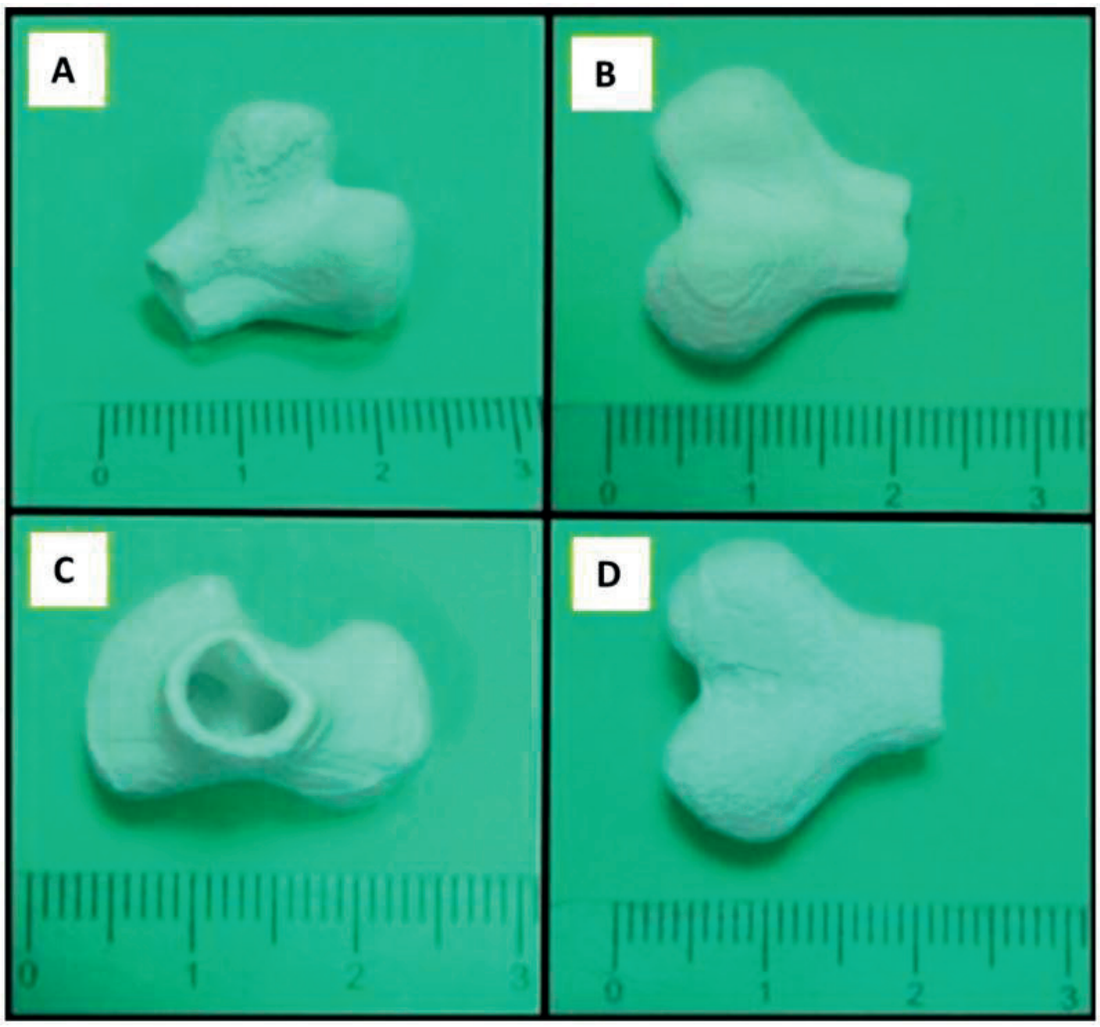

Figure 6. Bone scaffolds generated by selective laser sintering, (A) image of the scaffold, (B) front view, (C) top view and (D) back view of bone scaffold parts, courtesy of Do et al. [50].

organ transplantation – the risk of immune rejection? Do et al. speaks about this in an article about 3D printed scaffolds and their potential applications [51]. The aim would be to create scaffolds that have properties of the native recipient microenvironment and the ability to promote angiogenesis and osteogenesis, and various tissue engineering techniques could be used in order to facilitate this process and this is still a work in progress, albeit an ever-expanding and promising field (see **Figure 6**). Other studies have suggested that 3D scaffolds could also exhibit bactericidal properties, and aid not only tissue regeneration, but also prevent the high risk of infection that comes with any foreign body or implant. Correiaa et al. have shown that silver nanoparticles could be a suitable way to achieve this [52]. The idea of 3D printing has attracted neuroscientists, too, and Zhu et al. hypothesised that the combination of 3D printed scaffolding and low-level light therapy could aid neural regeneration, and favourable results have been achieved in this in vitro neural stem cell study [53]. Further studies will be needed to assess how effective and useful the proposed 3D printing methods for tissue regeneration in humans will actually be.

6. Conclusion

This comprehensive chapter summarised the subject of tissue regeneration in a variety of different fields of surgery. We explored the use of acellular dermal matrices in plastic and reconstructive surgery (e.g., for treatment of burns), breast surgery (e.g., for immediate breast reconstruction after mastectomy) and general surgery (e.g., abdominal wall repair). Stem cell-based therapies were also discussed to reflect the promise they hold in aiding tissue regeneration in the coming years. Particular focus was placed on adipose tissue-derived stem cells and adult mesenchymal stem cells, both of which are a potentially revolutionary therapy in regenerative medicine. Finally, we discussed potential future benefits of using three-dimensional printed scaffolds and gene regulation—both of these fields are currently being investigated by scientists across the world to discover how best to adapt these techniques in day-to-day clinical practice.

Author details

Emma Iddles[1], Gabija Lazaraviciute[1], Shuchi Chaturvedi[2] and Shailesh Chaturvedi[1]*

*Address all correspondence to: s.chaturvedi@nhs.net

1 Department of Surgery, Aberdeen Royal Infirmary, Aberdeen, United Kingdom

2 Kings College, University of London, United Kingdom

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