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The regeneration of damaged connective tissue: wishful thinking or reality?

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Abstract

This review examines the current status of various cellular and non-cellular regeneration technologies used for the repair and regeneration of damaged connective tissue. The article explores the clinical use of bone marrow-derived mesenchymal stem cells, adipose tissue-derived mesenchymal stem cells, growth factors, cytokines, platelet-rich plasma and GOLDIC® method. To compare the regenerative capacity of these technologies, a systematic analysis of the regeneration quality is necessary, and a high-resolution magnetic resonance imaging (MRI) using a quality scoring system is needed. It is likely that in future clinical practice a combination of such technologies will offer the optimal treatment to patients with different connective tissue disorders, which must always be our ultimate goal.

Introduction

Connective tissues such as ligaments, tendons, intervertebral discs, and articular cartilage have a limited capacity to heal following structural damage[1]. Nevertheless, bone can heal when injured thanks to the high degree of vascularization and the appropriate cellular environment to promote tissue repair[2]. It is known that urodele amphibians such as the newt can regenerate their tails, limbs, lens, retina, jaw, and even a large portion of the heart[3,4], but the capacity for regeneration of whole tissues and organs has been lost in mammals[5]. The inadequacy of true connective tissue regeneration in mammals has been attributed to the absence of blastema formation (a reverse developmental process occurring partly via cell de-differentiation in tissues local to the amputation plane and partly via a contribution of muscle stem cells) and to the rapid fibroproliferative response after wounding[6].

The physiological healing process of the connective tissue can be broadly separated into the processes of regeneration and repair[7]. Regeneration results in the complete restitution of lost or damaged tissue, whereas repair may restore some original structures but involves collagen deposition and scar formation[8]. Chronic inflammation stimulates scar formation through local production of growth factors and cytokines that promote fibroblast proliferation and collagen synthesis[9].

Tissue repair and regeneration depend not only on the activity of humoral factors, but also on interactions between cells and the components of the extracellular matrix (ECM)[10]. The ECM regulates the growth[11], proliferation[12], migration[13], and differentiation[14] of the cells residing within it. It is proposed that the ECM constantly undergoes remodelling in both physiological and pathological processes. The synthesis and degradation of ECM is associated with morphogenesis[15], wound healing[16], chronic fibrosis[17], regeneration[18], and metastatic processes[19]. The ECM components can regulate cell proliferation by signaling through cellular receptors belonging to the inte-

grin family[20]. The type of ECM proteins can affect the degree of cell differentiation[21], and the maintenance of normal tissue structure requires a basement membrane or stromal scaffold[22]. The integrity of basement membrane and parenchymal cells is critical for the organized regeneration of tissues[23]. It is worth noting that tissue injury results in restitution of the normal structure only if the ECM is not damaged, although labile and stable cells are capable of regeneration. Disruption of the ECM ultimately leads to collagen deposition and scar formation[24].

The regenerative capacity of any tissue depends on fibroblast growth factors[25] and cell signaling mechanisms[26]. Therefore, it is not surprising that regenerative therapeutic approaches are focused on the use of cells (including stem cells) and growth factors. Of note, the use of growth factors, platelet-rich plasma (PRP), autologous differentiated cells and mesenchymal stem cells (MSCs) has shown the most promise for the treatment of musculoskeletal diseases[27-30]. The efficacy of these treatments is based on their potential to regenerate tissues which cannot be regenerated under physiological conditions. However, the proof of concept of the efficacy of such new therapies has not been fully achieved yet[31]. Indeed, true tissue regeneration has to be proven by histology or high-resolution magnetic resonance imaging (MRI). Some technologies have demonstrated promise, but none of them has proven to induce true connective tissue regeneration, which consists of complete restitution of damaged tissue on a histological level)[32].

Bone marrow-derived mesenchymal stem cells (BM-MSCs)

Stem cells are characterized by self-renewal properties and by their capacity to differentiate into different cell lineages[33]. MSCs are multipotent cells, which means that they have potentially important therapeutic applications since they can generate chondrocytes, osteoblasts, adipocytes, myoblasts, and endothelial cell precursors depending on the tissue to which they migrate[34]. MSCs migrate to injured tissues and generate stromal cells or other cell lineages, but they do not seem to participate in normal tissue homeostasis. More recently, some authors have proposed that MSCs play an important role in normal tissue homeostasis[35], which may reflect the true role of MSCs in tissue homeostasis. At the time of writing, MSCs have been isolated from bone marrow[36], periosteum[37], trabecular bone[38], adipose tissue[39], synovium[40], skeletal muscle[41], deciduous and adult teeth[42], umbilical cord blood[43], umbilical cord tissue[44-46], placenta[47], and several other sources such as menstrual blood[48] and milk[49], which are in the early stages of research and development.

BM-MSCs can differentiate into cells belonging to the connective tissue lineage, including bone[50], fat[51], cartilage[52], intervertebral disc cells[53], ligaments[54], and cardiomyocytes[55]. BM-MSCs generate rapidly dividing cells known as transit-amplifying cells (TACs) which lose their capacity of self-renewal and give rise to cells with restricted developmental potential known as progenitor cells[56]. BM-MSCs can be isolated and expanded *in vitro* ideally using an automated bioreactor to optimize the quality and safety of the expanded cell product[57].

BM-MSCs clearly have a great potential in the treatment of damaged connective tissue, particularly in osteoarthritis[58]. However, there are some problems that still need to be resolved. These problems include clinical challanges[59] and a careful consideration of regulatory issues arising from the use of expanded human stem cells for clinical applications[60] (Table 1).

Adipose-derived mesenchymal stem cells (AD-MSCs)

In general, adipose-derived mesenchymal stem cells (AD-MSCs) are characterized by a reduced expression of bone morphogenetic protein (BMP)-2, BMP-4 and BMP-6, and by the lack of expression of transforming growth factor (TGF)-β type 1 receptor when compared to BM-MSCs[61]. Therefore, supplementation of these factors is needed if osteogenic or chondrogenic differentiation is desired from AD-MSCs. Currently, adipose-derived cells and tissues can be prepared with increasing regenerative therapeutic potency through different strategies, including:

1. Fat grafting, which is usually associated with cosmetic and plastic/reconstructive surgery applications[62].
2. Micronized or emulsified fat, which is commonly used in plastic and reconstructive surgery[63].
3. Mechanically and enzymatically processed stromal vascular fraction (SVF), which contains free AD-MSCs[64].

Table 1. Description of the different regenerative techniques for connective tissue repair and regeneration based on their regenerative capacity, regulation, side effects, risks, costs, and availability.

	BM-MSCs	AD-MSCs	Adipose SVF	Adipose Tissue	Cytokines and growth factors	PRP	GOLDIC®
Regenerative capacity	+	+	+	+	+/-	+/-	++
Regulatory requirements	ATMP	ATMP	ATMP	Medical Product	Pharmaceutical	Medical Product	Medical Product
Collection procedure	Bone marrow aspiration	Adipose tissue harvesting	Adipose tissue harvesting	Adipose tissue harvesting	None	Venepuncture	Venepuncture
Preparation	*In vitro* culture and differentiation of cells with various protocols	*In vitro* culture and differentiation of cells with various protocols	Single step aspiration and preparation (mechanical or enzymatic processing)	Single step aspiration and preparation, washing or emulsification without enzymes	Ready to use	Centrifugation of whole blood	In vitro culture of whole blood with defined gold particles for 24 hours
Risks	Moderate	Moderate	Moderate	Minimal	Minimal	None	None
Costs	High	High	Moderate	Moderate	Moderate	Low	Low
Availability	Veterinary market; few in human market	Veterinary market; few in human market	Worldwide (although regulatory constraints exist)	Worldwide	Worldwide	Worldwide	Veterinary market worldwide; human market in Europe

Abbreviations: AD-MSCs: adipose-derived mesenchymal stem cells; ATMP: advanced therapy medicinal products; BM-MSCs: bone marrow-derived mesenchymal stem cells; GOLDIC®: gold-induced cytokines; PRP: platelet-rich plasma; SVF: stromal vascular fraction.

4. Mechanically digested SVF mixed with the ECM concentrate, which is also referred to as "stromal vascular matrix" (SVM) and combines both free AD-MSCs and associated ECM[65].
5. *In vitro* expanded AD-MSCs containing much higher numbers of AD-MSCs[66].

Fat graft has minimal to no potency as the MSCs are not liberated from their perivascular niche and are difficult to activate. Micronized or emulsified fat has improved biochemical activity as stem cells are found in smaller micro-niches. Mechanical washing and removal of fibrous tissue enable cells to survive longer in their implanted microenvironment. SVF and SVM require mechanical or enzymatic digestion of whole adipose tissue and separation from other cell types by centrifugation. In most countries, enzymatic adipose tissue processing results in an "advanced therapy medicinal products" (ATMP), whereas mechanical processing does not result in an ATMP making it relatively easier to use. The use of expanded AD-MSCs is considered a higher regulatory risk because of the increased manipulation of these cells, which are therefore more strictly regulated. In general, AD-MSCs exhibit immunomodulatory[67] and trophic properties[68], and originate from local pericytes liberated from the broken blood vessels during processing. *In situ* activated AD-MSCs secrete a range of bioactive agents that locally inhibit the overactive immune system, resulting in an important line of defence against the development of autoimmune responses due to the antigen exposure following tissue injury. On the other hand, the trophic effects of AD-MSCs help to establish an optimal regenerative microenvironment at the site of injury by: i) inhibiting ischemia-related apoptosis[69], ii) downregulating scar formation[70], iii) stimulating angiogenesis via secretion of vascular endothelial growth factor (VEGF)[71], iv) promoting capillary stabilization through AD-MSC-derived pericytes[72], v) secreting tissue progenitor-specific mitogens that enhance tissue regeneration[73].

AD-MSCs are considerably promising for the regeneration of damaged connective tissue. However, as with BM-MSCs, there are technical, regulatory and translational issues that need to be

resolved before AD-MSCs can be brought into routine clinical use. Limitations and regulatory issues of AD-MSCs are shown in Table 1.

Role of growth factors in the regeneration of damaged connective tissue

Growth factors have many roles in normal cellular homeostasis, including promotion of cell survival[74], induction of cell proliferation[75], and stimulation of cell contractility[76], cell locomotion[77], cell differentiation[78], and angiogenesis[79]. Growth factors act as ligands by binding to specific cell surface receptors, which in turn deliver signals to the target cells. These signalling pathways stimulate gene transcription[80] that may be silent in resting cells and may involve genes that control the entry into the cell cycle[81].

Platelet-derived growth factor (PDGF)

Platelet-derived growth factor (PDGF) constitutes a family of several closely related polypeptides, consisting of chains linked by disulphide bridges and resulting in five dimeric isoforms[82]. PDGF is stored in platelet granules and is released upon platelet activation[83]. PDGF is also produced by a variety of cells other than platelets, and it has been shown to play an important role in bone regeneration[84].

Vascular endothelial growth factor (VEGF)

Vascular endothelial growth factor (VEGF) induces blood vessel formation in early development through a process known as vasculogenesis[85], and it has a central role in the growth of new blood vessels (angiogenesis) in adults[86]. Specifically, vasculogenesis is defined as the differentiation of precursor cells (angioblasts) into endothelial cells and the *de novo* formation of a primitive vascular network, whereas angiogenesis is defined as the growth of new capillaries from pre-existing blood vessels[87].

VEGF promotes angiogenesis in chronic inflammation[88], wound healing[89], and tumorigenesis[90]. VEGF acts via three tyrosine kinase receptors (Vascular endothelial growth factor receptors, a.k.a. VEGFRs): VEGFR-1, VEGFR-2 and VEGFR-3. VEGFR-2 is expressed in endothelial cells and many other cell types. These are the main receptors associated with the vasculogenic and angiogenic effects of VEGF[91]. The role of VEGFR-1 is less well understood, although it is thought to facilitate the mobilization of endothelial stem cells and to have a role in inflammation[92]. VEGF-C and VEGF-D bind to VEGFR-3 and act on lymphatic endothelial cells to induce lymphangiogenesis[93]. The pivotal role of VEGF in vasculogenesis, angiogenesis and lymphangiogenesis indicates that VEGF is an important component of the regenerative mechanisms for damaged connective tissue.

Fibroblast growth factor (FGF)

Fibroblast growth factor (FGF) exists in more than 20 isoforms[94]. Acidic FGF (aFGF, or FGF-1)[95] and basic FGF (bFGF, or FGF-2)[96] are the best characterized FGF isoforms in terms of structure and function. Most FGF molecules transduce signals via four tyrosine kinase receptors: fibroblast growth factor receptor (FGFR)-1, FGFR-2, FGFR-3 and FGFR-4[97,98]. FGF-1 is capable of binding to all these receptors[98]. FGF-7 is also known as keratinocyte growth factor (KGF)[99]. FGF signaling contributes to wound healing[100], angiogenesis[101], hematopoiesis[102], skeletal development[103], and many other biological processes. The wide range of biological activities exerted by FGFs suggests that these growth factors play an important role in the regeneration and repair of damaged connective tissue.

Transforming growth factor-β (TGF-β) and related growth factors

There are approximately 30 different types of transforming growth factors (TGFs) which include three TGF-β isoforms, namely: TGF-β1, TGF-β2 and TGF-β3[104,105]. TGF-β is a homodimeric protein produced by many different cell types such as platelets[106], lymphocytes[107], macrophages[108], and endothelial cells[109]. TGF-β has multiple and often opposing effects depending on the tissue and the type of injury[110]; for instance, TGF-β has growth inhibition properties in most epithelial cells[111]. In this regard, loss of TGF-β receptors may occur during tumorigenesis, providing a proliferative advantage to cancer cells[112]. Overall, TGF-β seems to participate in most cellular processes and is therefore an excellent candidate molecule potentially involved in the repair of damaged connective tissue.

Cytokines

Cytokines have important functions as mediators of inflammation and immune responses[113]. Cytokines contribute to the homeostasis of bone and

connective tissue[114] and play an important role in the regeneration of bone and connective tissue[115]. It is highly likely that cytokines play a critical role in the regeneration of damaged connective tissue and it is therefore important to consider their use in parallel with both cell- and non-cell-based therapies[116]. The potential clinical applications and limitations of the use of growth factors and cytokines for the regeneration of connective tissue are shown in Table 1.

Platelet-rich plasma (PRP)

Platelets are small non-nucleated cells found in the peripheral blood that are involved in hemostasis[117]. Platelets are important in wound healing regulation through the release of a number of different cytokines, proteins and other biologically active molecules[118]. Platelet-rich plasma (PRP) is a blood product defined as a portion of the plasma fraction of autologous blood with an increased platelet concentration and an associated increase in growth factor concentration. PRP is obtained from autologous blood and prepared by simple centrifugation[119]. PRP has been shown to have a role in skin repair and healing[120] and it is becoming increasingly used in many regenerative medicine protocols[121,122].

The platelet alpha granules contain many growth factors including TGF- β, PDGF, insulin-like growth factors (IGF-1 and IGF-2), FGF, VEGF and epidermal growth factor (EGF)[123]. The aforementioned growth factors have important regulatory effects on tissue homeostasis and MSC function which, as described earlier, have an important role in regenerative medicine and may even be an immunomodulatory route to treatment of coronavirus disease 2019 (COVID-19)[124]. The immunomodulatory and anti-inflammatory properties of PRP are becoming increasingly important for the use of PRP in the treatment of musculoskeletal conditions and connective tissue diseases[125-126].

The use of Gold-induced cytokines (GOLDIC®) in the repair of damaged connective tissue

The development of GOLDIC® technology has enabled the production of autologous conditioned serum which is rich in anti-inflammatory cytokines (autologous gold-induced cytokines). GOLDIC® is an *in vitro* gold treatment of autologous whole blood. The resultant gold-treated plasma is readministered to the patient without the presence of any residual gold compounds. Gold compounds have been used historically in the treatment of different inflammatory disorders, especially in musculoskeletal and rheumatic diseases, although these compounds are associated with many side effects[127-129]. *In vitro* studies have shown that incubation with gold particles inhibits catabolic factors, increases anti-catabolic and anabolic factors, and increases the level of gelsolin (GSN), which is a protein exerting an important role in cellular metabolism[130]. The mechanism of action of GOLDIC® procedure has yet to be fully defined, but *in vitro* studies have shown a significant increase in plasma GSN levels in the autologous serum, as well as increased GSN levels in synovial fluid after intra-articular GOLDIC® injection therapy[131]. GSN is a cytoplasmic regulator of actin organization, which is responsible for the viscoelasticity of the cell cytoskeleton and regulates important cell functions including cell motility, phagocytosis, apoptosis[130]. Plasma gelsolin (pGSN) can modulate pro-inflammatory pathways in rheumatoid arthritis, but local GSN levels in the affected joints are reduced even more than in plasma[132]. This considerably reduces the efficacy of endogenous GSN in rheumatoid arthritis and increases the importance of exogenous GSN (e.g., via GOLDIC® method) to treat inflammatory rheumatic diseases. It is clear that pGSN has a fundamental role in the modulation of pro-inflammatory responses, and, consistent with these functions, decreased pGSN levels have been detected in clinical conditions such as acute respiratory distress syndrome, sepsis, major trauma, prolonged neonatal hyperoxia, malaria, and liver injury[133,134]. Moreover, the potential clinical utility of pGSN as a diagnostic tool has emerged in the aforementioned diseases, where circulating pGSN concentrations are below the normal values[134].

The first trial investigating the use of GOLDIC® method to treat lameness in horses showed a significant improvement in lameness-associated equine diseases following treatment[135]. The first human clinical study using GOLDIC® method investigated the use of this technology in Achilles tendinopathy and found significant clinical and radiological (MRI) improvements[136]. In another clinical study conducted in patients with osteoarthritis of the knee, intra-articular GOLDIC® injections

produced a rapid and sustained improvement in all symptoms, suggesting that GOLDIC® method represents a promising option for the conservative management of moderate to severe osteoarthritis of the knee[137]. Most recently, an open-label, non-randomized, non-controlled study involving a heterogeneous patient population showed that GOLDIC® was safe and effective in the treatment of various systemic diseases such as allergies, fibromyalgia, psoriasis, rheumatoid arthritis, ulcerative colitis, polymyalgia rheumatica and osteoporosis[138].

Conclusions

In the regenerative technologies described in this review, a combination of connective tissue repair and regeneration processes occur following different interventions. The relative contributions of repair and regeneration are influenced by the proliferative capacity of the cells residing within a given tissue, by the ECM integrity and by the resolution or the chronic nature of injury and/or inflammation. Nevertheless, the most tissue-destructive diseases are caused by infections, autoimmune responses, trauma and other types of tissue injury, which may persist as chronic disease resulting in organ dysfunction and (often) organ failure. The persistence of disease leads to chronic inflammation, which is associated with the proliferation and activation of macrophages and lymphocytes, along with the production of a plethora of pro-inflammatory and pro-fibrotic growth factors and cytokines. Therefore, the intrinsic regulation of inflammation is critical for a proper tissue healing, repair and regeneration. In order to characterize the potency of the technologies described in this review, it is necessary to redefine such technologies according to the quality of the tissue regeneration that they produce:

- grade 1: complete restitution of damaged tissue without scar tissue or inflammation.
- grade 2: restitution of damaged tissue with low scar tissue content or inflammation.
- grade 3: restitution of damaged tissue with moderate scar tissue content or inflammation.
- grade 4: restitution of damaged tissue with high scar tissue content or inflammation.

In clinical settings, this grading can be defined by using histology and/or high-resolution MRI (3 Tesla MRI or higher). In order to avoid the ethical issues posed by invasive tissue biopsy, MRI image analysis seems to be the most appropriate procedure for the assessment of repair and regeneration of damaged connective tissue. According to these criteria, GOLDIC® method may have the highest regenerative capacity and the lowest risk of side effects among all the regenerative procedures described in this review. In conclusion, it is likely that in future clinical practice a combination of technologies aimed to promote connective tissue repair and regeneration will offer the optimal treatment to patients suffering from various inflammatory diseases, which must always be our ultimate goal.

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Ulrich Schneider is the inventor of GOLDIC® and CEO of Arthrogen GmbH (Manufacturer of GOLDIC-Sets). William Murrell and Peter Hollands declare that they have no conflicts of interest to disclose.

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