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Review article

Autologous liquid platelet rich fibrin: A novel drug delivery system

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ABSTRACT

There is currently widespread interest within the biomaterial field to locally deliver biomolecules for bone and cartilage regeneration. Substantial work to date has focused on the potential role of these biomolecules during the healing process, and the carrier system utilized is a key factor in their effectiveness. Platelet rich fibrin (PRF) is a naturally derived fibrin scaffold that is easily obtained from peripheral blood following centrifugation. Slower centrifugation speeds have led to the commercialization of a liquid formulation (liquid-PRF) resulting in an upper plasma layer composed of liquid fibrinogen/thrombin prior to clot formation that remains in its liquid phase for approximately 15 min until injected into bodily tissues. Herein, we introduce the use of liquid PRF as an advanced local delivery system for small and large biomolecules. Potential target molecules including large (growth factors/cytokines and morphogenetic/angiogenic factors), as well as small (antibiotics, peptides, gene therapy and anti-osteoporotic) molecules are considered potential candidates for enhanced bone/cartilage tissue regeneration. Furthermore, liquid-PRF is introduced as a potential carrier system for various cell types and nano-sized particles that are capable of limiting/by-passing the immune system and minimizing potential foreign body reactions within host tissues following injection.

Statement of Significance

There is currently widespread interest within the biomaterial field to locally deliver biomolecules for bone and cartilage regeneration. This review article focuses on the use of a liquid version of platelet rich fibrin (PRF) composed of liquid fibrinogen/thrombin as a drug delivery system. Herein, we introduce the use of liquid PRF as an advanced local delivery system for small and large biomolecules including growth factors, cytokines and morphogenetic/angiogenic factors, as well as antibiotics, peptides, gene therapy and anti-osteoporotic molecules as potential candidates for enhanced bone/cartilage tissue regeneration.
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1. Introduction

Modern tissue engineering strategies aim to predictably restore lost or defective tissues following injury, age, congenital deformity or infection [1,2]. While various attempts have been proposed to regenerate host tissues, affected patients remain prone to various setbacks including functional ailments, social concerns and economic/financial burdens [2]. Therefore, patients and clinicians seek cost-effective regenerative modalities to fulfill the esthetic and functional requirements to restore defective/missing tissues.

These issues are particularly important in the fields of bone and cartilage regeneration [2,3]. Both fields have seen a steady increase in affected patients worldwide with a dramatic impact on the patient's quality of life. More than 250 million people are now estimated to be affected by osteoarthritis (OA) and another 200 million by osteoporosis worldwide [4]. Understanding knee degeneration has become a pivotal area of research to design better regenerative materials to predictably restore these defective tissues [5]. Similarly, our key understanding of bone biology resulted in the development of various osteoinductive growth factors, such as bone morphogenetic protein-2 (BMP-2), which has since been approved by the FDA as a local delivery recombinant growth factor for bone regeneration [6]. Nevertheless, great interest remains in further optimizing novel regenerative strategies to predictably restore missing cartilage and bone.

Research to date has focused on biological agents that may be utilized to either delay the advancement of many degenerative disorders or promote their regeneration [1]. One of the difficulties faced in knee degeneration is in regard to the associated tissue, which is lowly vascularized and often requires joint arthroplasty and various other surgical interventions. Nevertheless, widespread research is ongoing to repair articular cartilage defects with improved short- and long-term clinical outcomes [1]. This research includes acellular (hyaluronic-acid, collagen) modalities as well as cellular (stem cells, chondrocytes) constructs. Central to the success rate of such procedures is the immune system's response

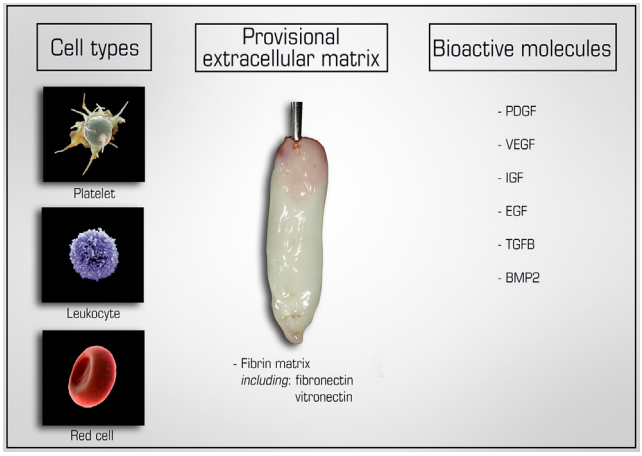

Fig. 1. Representative diagram of the cell types, extracellular matrix components and bioactive molecules found in platelet-rich fibrin. Reprinted with permission from Miron et al. [8].

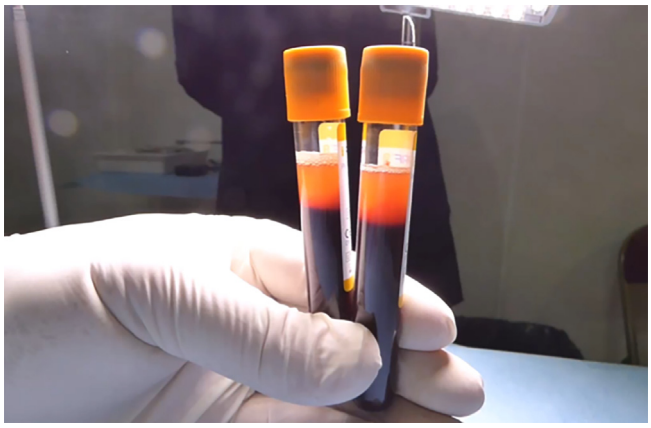

Fig. 2. Liquid PRF fabricated after whole blood without anticoagulants is centrifuged for 3 min at 700 rpm. The upper layer contains a plasma-rich layer concentrated with growth factors and leukocytes that remains liquid for approximately 15 min prior to injection.

towards these foreign injected/surgically implanted biomaterials [1].

Interestingly, more than 15 years has now passed since platelet-rich fibrin (PRF) was developed as a regenerative scaffold for tissue engineering applications [7]. PRF fulfills the 3 main criteria by simultaneously 1) acting as a scaffold containing 2) living cells and 3) growth factors (Fig. 1) [8]. The advantages of PRF over the previously utilized platelet-rich plasma (PRP) is that PRF does not contain anti-coagulants and therefore wound healing events take place more naturally without interruption [8]. However, pioneering research utilizing lower centrifugation protocols has recently led to the development of a novel liquid formulation of PRF (Fig. 2). In circulating blood, liquid fibrinogen is cleaved by thrombin once exposed to oxygen to produce non-soluble fibrin (Fig. 2). This newer formulation of PRF remains liquid for approximately 15 min where it can be utilized as an injectable biomaterial. Liquid PRF has since been utilized for a variety of regenerative procedures including the repair of articular joints, osteoarthritis management, treatment for temporal-mandibular joint disorders and in combination with various biomaterials for bone regeneration including bone grafting materials and collagen membranes [9]. Shortly following injection into host tissues, the liquid fibrinogen rapidly converts to fibrin where it forms a clot that is highly concentrated with blood-derived growth factors, leukocytes and platelets [9].

This review article provides an introduction to this low-cost and completely autologous biomaterial as a potential carrier system for the delivery of both large (recombinant growth factors/cytokines, morphogenetic/angiogenic factors) and small (silencing RNA, antibiotics, peptides, anti-osteoporotic, and anti-microbial factors) biomolecules for bone and cartilage tissue regeneration. Furthermore, liquid-PRF is introduced as a potential carrier system for various cell types and nano-sized particles that are capable of limiting/by-passing the immune system and minimizing potential foreign body reactions within host tissues following injection.

2. From PRP to PRF to liquid-PRF – Biological understanding of platelet concentrates

Platelet concentrates have been utilized in regenerative medicine for over 2 decades [10]. They were initially developed with anticoagulants to prevent the rapid coagulation of blood prior to centrifugation. Original protocols were designed utilizing a two-step centrifugation procedure, which produced what was later termed platelet-rich plasma (PRP), and many fields of medicine and dentistry have benefitted from the ability of these protocols to induce a 6- to 8-fold increase in blood-derived growth factors [11–17]. Despite the widespread use of PRP in many fields of medicine, including for cartilage (primarily knee) and bone regeneration, concerns were raised regarding the use of anti-coagulants that were later shown to negatively impact wound healing by preventing clot formation [18], which is an essential step during the natural wound healing process.

For these reasons, in 2001 Choukroun et al. pioneered new research aimed at utilizing platelet concentrates without incorporating anti-coagulants within their preparations [7]. This novel formulation, later termed platelet-rich fibrin (PRF), was the first strategy utilizing platelet concentrates without anti-coagulants [19–23]. Two main advantages reported were the fact that the wound healing cascade was not inhibited by the anti-coagulants and that natural clot formation occurred. Furthermore, PRF contains a high concentration of host immune cells (namely leukocytes), which act to promote local wound healing and fight infection [24]. In the absence of anti-coagulants, PRF forms a 3-dimensional scaffold following 10–12 min of centrifugation at 200–700*g* force (Fig. 1).

More recently, lower centrifugation speeds and time have been proposed to further optimize the number of leukocytes and subsequent release of growth factors from PRF formulations [25]. When centrifuged at extremely low g-forces (~60*g* for 3 min as opposed to 700*g* for 12 min to produce standard PRF), the blood separates into a plasma-rich upper liquid layer without the use of anti-coagulants (Fig. 2). This liquid upper layer is primarily composed of fibrinogen and thrombin that has not yet converted to fibrin. Therefore, prior to fibrin formation, injectable PRF remains in its liquid consistency for approximately 10–15 min following centrifugation.

During this time, additional growth factors, cytokines, antibiotics and other regenerative biomolecules have been proposed as combination strategies with liquid-PRF for delivery into host tissues. Liquid PRF is currently being utilized for the local delivery of angiogenic and regenerative growth factors following injections in a similar manner to PRP for the management of various conditions including osteoarthritic knees and rotator cuff tears [19,26,27]. Unlike PRP, liquid PRF rapidly converts into fibrin following local injection. This review provides a discussion of the potential advantages of liquid PRF as an autologous carrier system for large and small biomolecules, as well as various cell types and biomaterials.

3. Fabricating platelet rich fibrin from peripheral blood

Prior to initiating any blood collection, it is important that all centrifuges be prepared, opened and ready for use at the appropriate settings. Since no anti-coagulants are being utilized, blood collection must occur rapidly and then centrifuged to maximize the regenerative potential of the PRF scaffolds. After blood collection, blood tubes are added to the centrifuge and centrifugation occurs. To fabricate a liquid, typical centrifugation cycles are between 60 and 200*g*-force for 3–4 min. The tubes are then removed and a syringe may be utilized to draw the liquid upper PRF later and later utilized accordingly or mixed with growth factors/biomolecules/-cells as discussed later in this article.

4. Advantages of liquid-PRF as a drug delivery vehicle

One of the primary requirements for a drug delivery system is that the delivered biomolecules/growth factors are released in a controlled manner [28]. Additionally, the biological activity of growth factors and their conformational stability are key to their success during the active regenerative phase [29]. Natural fibrin is formed when fibrinogen, a soluble protein present in the blood stream, is cleaved by thrombin [30]. The polymerized fibrin, unlike fibrinogen, is insoluble and forms a fibrin network that is responsible for forming a blood clot. When peripheral blood is collected and rapidly centrifuged, this fibrin clot will instead form in the plasma-rich layer, thereby forming PRF. Interestingly, fibrin has been previously utilized as a biomaterial for surgical scenarios, where it serves as a 'glue'-like biomaterial; it has also shown regenerative properties for the repair of hard-to-heal defects such as the articular cartilage (AC) of the knee [31,32]. The only reported disadvantage for utilizing fibrin matrices alone is their poor mechanical stability, although they may positively be combined with various other materials such as polymers for AC regeneration [1]. Therefore, fibrin in general has been described as acting as 'glue' for cells, growth factors and various other biomaterials following implantation [33,34]. Furthermore, the incorporation of collagen type I within fibrin has been shown to dramatically improve AC regeneration, and cells resuspended within fibrin have also demonstrated substantially better survival rates compared to other delivery methods including culture medium [35].

In light of these previous reported advantages utilizing fibrin for AC/bone regeneration, the present article highlights the potential use of a naturally derived autologous fibrin matrix (liquid PRF) collected from peripheral blood. Liquid PRF may be utilized in a manner similar to bovine-derived fibrin but carries the advantages of being derived at lower costs, being entirely autologous (no foreign body reaction) and additionally contains a number of blood-derived growth factors that are capable of further promoting angiogenesis and regeneration in defective tissues. Liquid PRF contains a variety of autologous growth factors found in blood, including platelet-derived growth factors (PDGF), transforming growth factor-beta (TGF-β1) and vascular endothelial growth factor (VEGF) as well as cells (platelets and leukocytes), which concurrently assist in the wound healing process. Therefore, although previous research has successfully incorporated cells and/or growth factors/biomolecules with non-autologous fibrin alone, the development of liquid-PRF offers many additional advantages as a carrier system for cells and growth factors. Below, we discuss possible biomolecules and cell-based tissue engineering strategies that are capable of further enhancing the activity of liquid-PRF for local delivery.

5. Understanding knee and bone degeneration

To locally deliver growth factors and other biomolecules for bone/cartilage regenerative strategies, it is crucial to understand their pathogenesis and breakdown. While the aim of this article is not to describe these events in detail, readers may reference other excellent review articles on this topic [5,36,37].

Osteoarthritis is an inflammatory condition that affects several joints including the knees, ankles, lower back and hands and is characterized by inharmonious functioning of the tissue components [38,39]. While considered hereditary, numerous elements, including age, body mass index and gender, are known risk factors of the disease. Excessive mechanical load during physical activity, inadequate nutritional supply and a lack of rest are also known contributors to the disease [40].

Articular cartilage (AC) is greatly affected by OA pathology, and at the center of this is a group of affected macromolecules including collagen type II, aggrecans and glycosaminoglycans [41,42]. While the matrix is synthesized entirely by chondrocytes, adult cells are normally quiescent and have extremely low blood perfusion and therefore have an extremely low turnover rate compared to other tissues. During OA onset, chondrocytes typically undergo a metabolic reactivation manifested by their increased proliferative ability and biosynthetic activity [39,43]. Unfortunately, this imbalance in homeostasis has been shown to cause cellular hypertrophy of chondrocytes initiating AC calcification and breakdown [44]. Moreover, the biosynthetic activity of the recently activated chondrocytes consequently release proteases including matrix metalloproteinases (MMPs), aggrecanases and cathepsins, therefore favoring catabolism, whereas the synthesis of important regenerative macromolecules is suppressed [45,46]. AC destruction is therefore in part due to the lack of ECM production as well as the catabolic effect of excessive proteolytic activity. Therefore, regenerative strategies aimed at either 1) increasing ECM production or 2) blocking proteolytic activity are regenerative solutions discussed later in this article.

As osteochondral debris and calcium crystals accumulate in the synovial fluid, inflammation begins within the joint, especially in response to abnormal stress [47]. During synovitis, pro-inflammatory mediators produced by macrophages, lymphocytes and synoviocytes stimulate an upregulation of proteases and cytokines from chondrocytes [48–50]. These include tumor necrosis factor alpha (TNFα), interleukin-1β (IL-1β), leukemia inhibitory factor, cyclooxygenases (COX-1 and COX-2) and prostaglandins (PGE2) [51–57]. Blocking such molecules is another strategy discussed later.

Furthermore, reactive oxygen species, including nitric oxide and superoxide anion (O_2^-), are also expressed in higher quantities, causing chondrocyte apoptosis and early senescence [58–60]. In response, chondrocytes secrete a variety of growth factors, including TGF-β1, BMP-2 and insulin-like growth factor 1 (IGF-1), among others [61–63]. The reparative process includes the secretion of pro-angiogenic factors, such as VEGF and nerve growth factor,

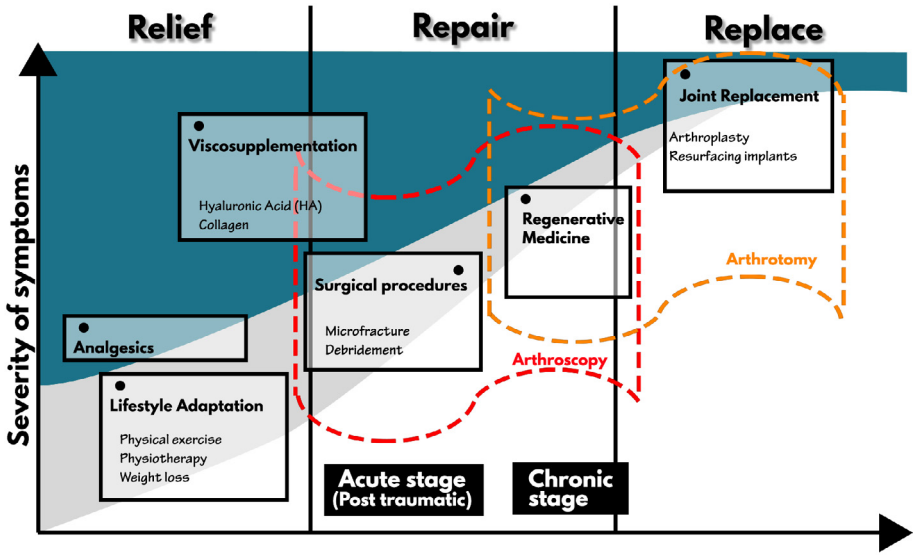

Fig. 3. Schematic representation of the current approaches for osteoarthritis management, depending on the severity of symptoms. Analgesics and lifestyle adaptation are the first options to postpone osteoarthritis development and provide pain relief. Visco-supplementation represents a more invasive approach and is usually applied when there is an increasing pain experience caused by damage to the cartilage. Visco-supplementation is applied to restore the rheological properties of the synovial fluid and to ease pain. Surgical procedures, such as microfracture and debridement, are applied to slow cartilage erosion, while autologous chondrocyte implantation (ACI) aims to regenerate the degenerated cartilage surfaces. In cases where the above applications are insufficient, the only remaining solution is joint replacement. Arthroplasty and surface replacements are the most invasive approaches at present and are only applied in established osteoarthritis. Figure modified from Ondresik et al. [37].

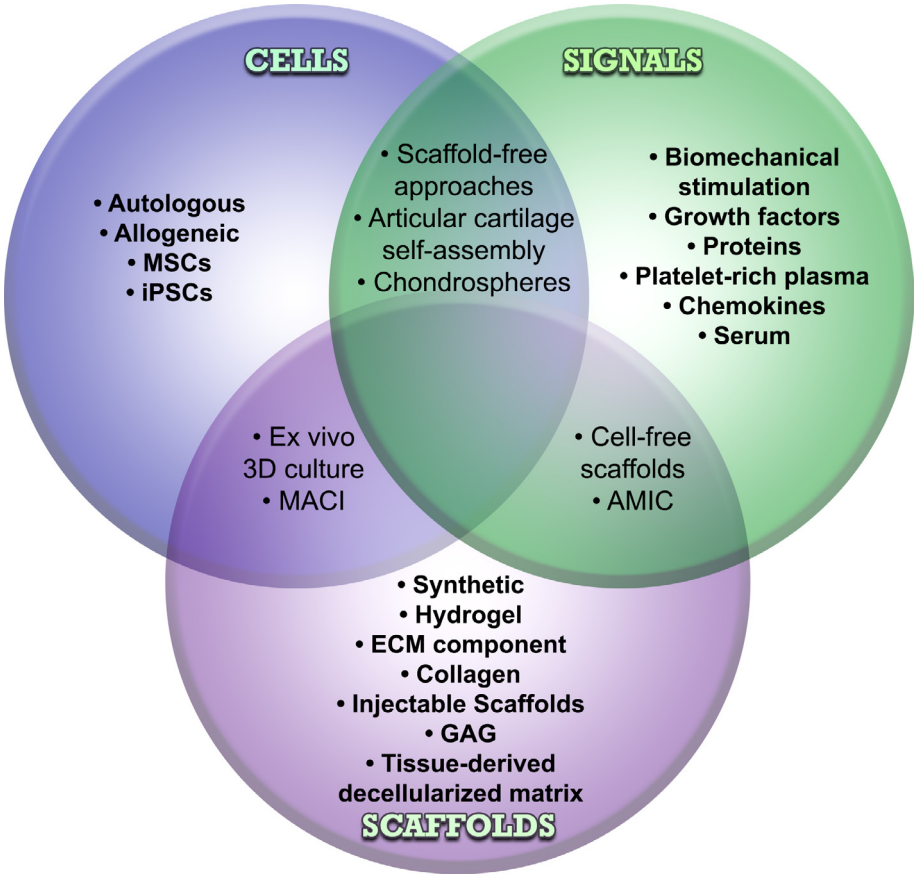

Fig. 4. Tissue engineering tripod including cells, signals and scaffolds. Various regenerative strategies have combined these properties to further promote tissue regeneration.

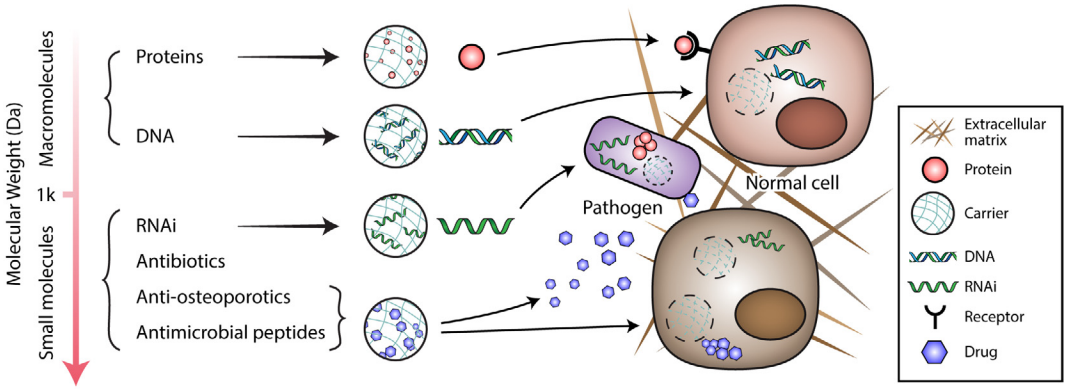

Fig. 5. Classification and controlled release of biomolecules involved in therapeutic applications in CMF bone regeneration. Macromolecules, primarily including proteins and DNA, can be loaded by carrier devices and released extracellularly or intracellularly to guide cell behaviors and regulate the bone healing process, whereas small molecules, herein defined as biomolecules with a molecular weight lower than 5 kDa, primarily target bone regeneration under compromised conditions such as infection, skeletal malignancies and metastases in CMF bone and osteoporosis. (Small molecule sizes). Figure modified from Ji et al. [28].

which are known to induce the penetration of blood vessels from the underlying bone and facilitate bone formation at the osteochondral junction [64,65]. Therefore, in summary, chondrocytes feature a phenotypic switch from pro-resolution to pro-inflammation and vice versa in response to stress.

Regenerative strategies for OA encompass both non-pharmacological and pharmacological therapies aimed at relieving pain and improving patient quality of life (Fig. 3). Therapy may also include a variety of analgesics and non-steroidal inflammatory drugs, such as aspirin, ibuprofen, naproxen, celecoxib and diclofenac [66].

6. Potential target genes for bone and chondrogenesis

Both bone and cartilage regeneration involve a complex balance between anabolic and catabolic processes. Important for the regenerative process is that progenitor cells migrate to damaged sites and begin differentiating into host tissues [28]. As such, a number of candidate genes have been proposed to fulfill this task including hormones, cytokines and growth factors involved in their regenerative process [28]. Based on a number of preclinical studies investing the individual role of various biomolecules, it is not surprising that even an exogenous dose of a single gene (such as BMP2) can

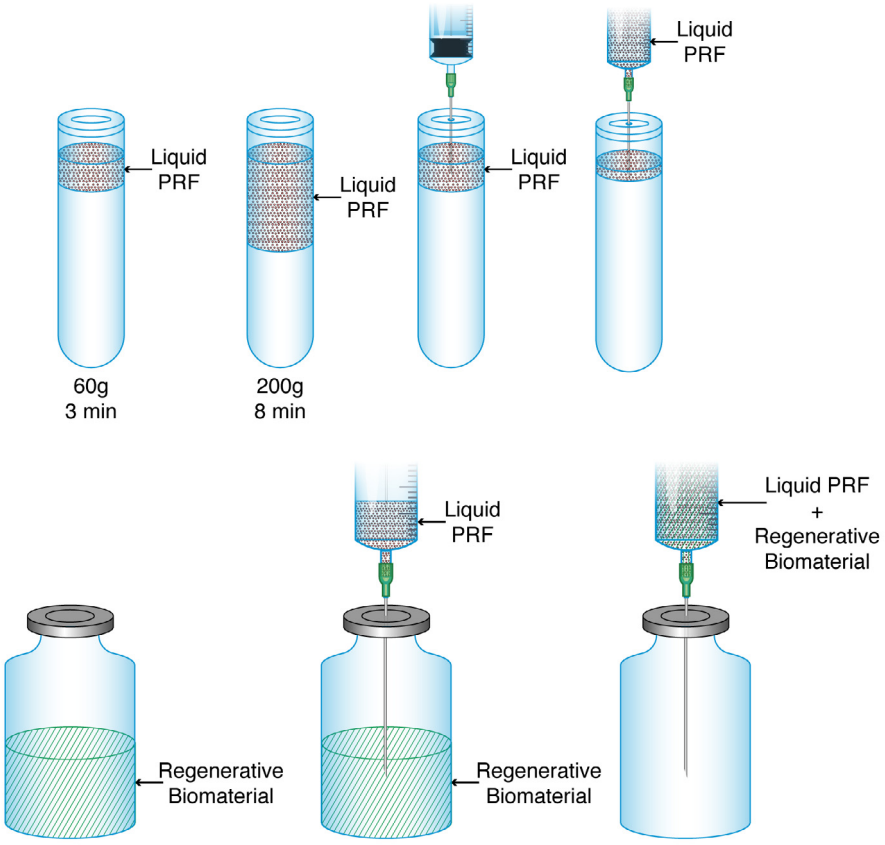

Fig. 6. Modifications to centrifugation speed and time can alter the volume of liquid PRF. Shorter and slower centrifugation speeds produce more highly concentrated PRF with higher concentrations of growth factors and cells, whereas longer centrifugation times produce more volume. Thereafter, liquid PRF can be mixed with various regenerative biomolecules or biomaterials and injected within the human body to regenerate various tissues.

drastically and rapidly promote wound healing in defective tissues [67].

The larger macromolecules comprise growth factors, cytokines and their corresponding encoding nucleic acids, which are responsible for the regulation of morphogenesis. Smaller molecules typically comprise drugs, peptides and oligonucleotides. While a number of these biomolecules are routinely administered systemically, major advantages for their local delivery are favored because a lower dose can be utilized with less associated secondary side effects due to their tissue specificity and potential dose-dependent carcinogenicity [68,69]. Below we highlight the use of candidate biomolecules for delivery via liquid PRF for either bone or cartilage regeneration.

7. Strategy 1: Candidate biomolecules for cartilage and bone regeneration

Tissue engineering strategies for bone and cartilage regeneration include cells, signals and scaffolds (Fig. 4). Candidate biomolecules for therapeutic applications include large and small molecules that promote bone or cartilage regeneration. These biomolecules can be categorized as follows. 1) Large molecules include a family of i) inflammatory cytokines and chemokines, which orchestrate inflammatory responses and chemotaxis of regenerative cells; (ii) morphogenetic factors, which regulate skeleton formation and morphogenesis; (iii) angiogenic factors, which directly affect vascularization and allow the transport of oxygen, nutrients and waste products during tissue regeneration. Small molecules include (iv) short peptides derived from therapeutic proteins, (v) anti-infection molecules and (vi) anti-osteoporotic molecules (Fig. 5). The regenerative strategy proposed in this article aims to collect liquid PRF from peripheral blood and thereafter to mix this regenerative modality with various specific biomolecules and biomaterials to further promote tissue regeneration by utilizing liquid PRF as an advanced delivery system (Fig. 6).

7.1. Strategy 1.1: Inflammatory cytokines and chemokines

Cytokines and chemokines are some of the most widely used inflammatory mediators within the human body [70]. During the initial stages of bone healing, a number of cytokines are secreted by macrophages and other inflammatory cells [71], including important pro-inflammatory mediates such as interleukin 1 (IL-1) and TNF-α, as well as anti-inflammatory interleukins including IL-4 and IL-13 [72,73]. Various antibodies against pro-inflammatory molecules, such as anti-IL1 or anti-TNF-α, have been proposed as molecules to reduce/eliminate inflammatory diseases such as OA. Furthermore, chemotactic cytokines, such as stromal cell derived factor-1 alpha (SDF-1α), have been studied as powerful modulators involved in cell recruitment [74]. SDF-1α is critical for the migration of hematopoietic stem cells and has been utilized in various regenerative strategies to target stem cells to a desired site [75]. Furthermore, the combination of SDF-1α with BMP2 improves the number of osteoprogenitor cells that are mobilized from the bone marrow towards defective tissues [76].

7.2. Strategy 1.2: Morphogenetic factors

Morphogenetic factors represent the majority of FDA-approved regenerative growth factors that are commercially available. Dur-

ing this process, soluble factors, including TGF-beta superfamily members (BMPs), fibroblast growth factors (FGFs), sonic hedgehog (SHH) and wingless- and Int-related proteins (Wnts), have been shown to participate in mesenchymal cell differentiation [77–80].

Naturally, the TFG-beta superfamily (including the 5 isoforms TGF-β1-5) as well as related BMPs and their inhibins/activins are extensively studied [81]. While each BMP has a specific role and function during morphogenesis in various tissues [77], BMP-2 has been the most widely utilized due to its ability to assist in either intramembranous or endochondral ossification [82]. Other molecules, such as FGF2, have more recently been assessed in large clinical studies to facilitate the regeneration of various tissues due to its ability to stimulate cell proliferation [83,84]. However, there are 22 members of the FGF family, each with various biological roles, many of which are yet to be fully explored [83]. Other growth factors known to stimulate tissue regeneration, including PDGF, IGFs, growth hormone, parathyroid hormone and vitamin D, have been shown to play a role in bone formation [85]. Lastly, though not fully explored clinically, Wnts and SHH have gained increasing interest in recent years due to their potent ability to affect craniofacial development [86,87].

7.3. Strategy 1.3: Angiogenic factors

Without question, optimal healing of bone and cartilage requires adequate blood supply [88]. This is one of the primary factors indicating that PRP and liquid-PRF promote regeneration in various tissues even when utilized alone. Nevertheless, many attempts to utilize recombinant human VEGF or angiopoietin into various biomaterials and improve tissue angiogenesis have been made [89]. Various BMPs are known to act more favorably when VEGF is simultaneously supplied locally [90–92]. Furthermore, a previous study demonstrated that Ang-2 and its receptor Tie-1 were significantly increased during cartilage regeneration [93]. While perhaps not a primary target for liquid PRF, it is important to note that angiogenic factors are highly desired biomolecules to improve tissue regeneration.

7.4. Strategy 1.4: Peptides derived from therapeutic proteins

Interestingly, small fragments of peptides derived from large active proteins have been shown to exert biological functions that are similar to their full recombinant sources but are either more easily producible or favor protein structure/folding. The most widely used peptides are those derived from BMP2. For example, a short peptide from residues 68–87 from BMP2 (NSVNSKIPKACCVPTELSAI) has been shown to positively increase osteoblast osteocalcin expression and induce ectopic calcification [94]. Another synthetic peptide, KIPKASSVPTELSAISTLYL (residues 73–92) also induces osteoblast differentiation and improves bone formation in vivo [95]. Synthetic peptides for BMP-7, including SNVILKKYRN, (residues 121–130), KPSSAPTQLN (residues 101–110) and KAISVLYFDDS (residues 110–120), have also been reported to affect bone formation in vitro or in vivo [96]. While the clinical use of peptides has not yet been fully utilized in mainstream clinical practice, they represent easily producible methods with great regenerative potential.

7.5. Strategy 1.5: Anti-infective molecules

Infection caused by osteomyelitis, periodontitis or other diseases is a prominent reason for tissue loss [97–99]. An estimated 40% of the North American population is affected by some form of periodontitis caused by the more than 600 micro-organisms living in the oral cavity [100]. Burn victims and diabetic ulcers also represent infection risks. Therefore, combination approaches utilizing regenerative agents with effective anti-microbial agents are indispensable to regrow tissues during disease. Antibiotics, including tetracyclines, penicillins (amoxicillin), metronidazole and cephalosporins, are a few known agents utilized over the last several decades [98,101]. However, their increasing microbial resistance has become a prominent challenge, and alternatives or combination approaches are necessary [102]. While most studies to date have focused on local delivery of antibiotics [103–106], new strategies and combination approaches are needed to reduce the amount of tissue lost due to infectious disease.

7.6. Strategy 1.6: Anti-osteoporotic molecules

One final area of small molecules that has gained momentum in recent years is the incorporation of anti-osteoporotic molecules into regenerative scaffolds. To date, strategies have incorporated bisphosphonates, calcitonin, estrogen or an estrogen agonist/antagonist into biomaterials. In addition, other molecules, such as 1) genistein and zinc and 2) vitamin D, have been shown to improve bone mineral density [107–117]. In addition to this, parathyroid hormone (PTH) and several PTH analogs have been investigated for regenerative solutions; however, research is necessary to further implement their use into regenerative strategies [118,119].

8. Strategy 2: Gene therapy with non-viral and viral vectors

Gene therapy represents an avenue of research with tremendous potential [120]. Its use in repairing articular cartilage was introduced by Evans et al. in 1996, utilizing anti-cytokine therapy in joints affected by rheumatoid arthritis. Many forms of gene therapy currently exist. Much like the first and second strategies, Ondresik et al. recently proposed that gene therapy targets (i) inhibit inflammatory and catabolic pathways, (ii) stimulate anabolic pathways or (iii) prevent cell senescence and apoptosis [5]. While similar genes can be targeted, as presented in strategies 1 and 2, gene therapy can be achieved by a variety of methods including both non-viral and viral gene carriers, such as adenoviral, retroviral, lentiviral and recombinant adeno-associated viral vectors (rAAVs).

9. Strategy 3: Cells

Naturally, the incorporation of various cell types into biomaterials has seen widespread use in various fields of regenerative medicine. Below, we highlight many such strategies that are highly applicable to the bone and cartilage fields.

9.1. Strategy 3.1: Bone marrow stromal cells and stem cells derived from various tissues

BMSCs were some of the first stem cells utilized in regenerative medicine, and several attempts have been made to incorporate this cell type into various bone and cartilage regenerative procedures [121–124]. BMSCs are easier to isolate and proliferate from donors more favorably than chondrocytes. Extensive research using BMSCs has also shown that they may differentiate into cartilage [125–128] or bone [129], meriting their use for regenerative purposes in either field [130–132].

In a cartilage repair setting, bone marrow MSCs may enable a targeted repair system that promotes trophic effects through the release of synthetic, proliferative and regenerative factors directly into chondral lesions [133]. By releasing chemotactic factors [134], bone marrow MSCs may also drive surrounding host stem cells to enter cartilage and bone defects, further aiding in damaged tissue

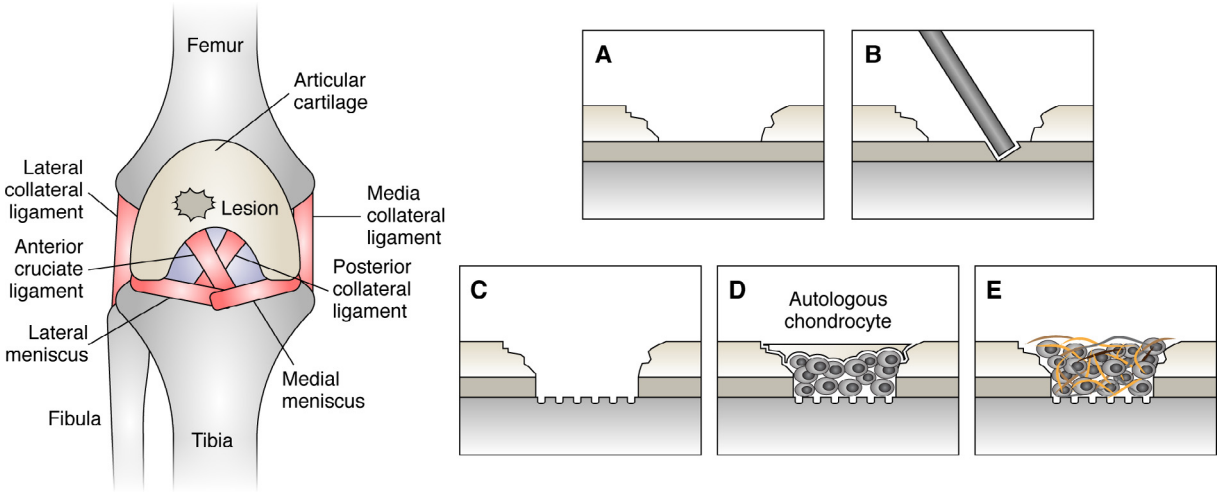

Fig. 7. Defect knee cartilage remains one of the most difficult areas in the body to regenerate due to the low vascularity to these tissues. Regenerative strategies have utilized cell-based matrices delivered by injectable means to further promote knee regeneration.

regeneration. BMSCs have been clinically injected for the treatment of osteoarthritis where patients report less pain and improved joint mobility without any adverse effects at either 6 or 12 months follow up [135–138]. Based on these pioneering studies, other isolations of stem cells derived from aspirates can also be collected from adipose tissue, muscle, bone, synovium, periosteum and the umbilical cord [139]. Furthermore, autologous peripheral blood stem cells have also been investigated as a potential stem cell source for knee regeneration [140–142].

9.2. Strategy 3.2: Autologous differentiated osteoblasts and chondrocytes

Due to a limited supply of effective surgical options for the management of osteoarthritis and other degenerative diseases, injection with various quantities of differentiated osteoblasts and chondrocytes has been the focus of many research groups [143–145]. In this technique, biopsies harvested from a first arthroscopic operation are necessary to provide a pool of chondrocytes that may be expanded to reach 12–48 million cells for local injection (Fig. 7). During a second procedure, chondrocytes may either be implanted or injected with/without a carrier system [146,147].

Interestingly, autologous chondrocytes have been utilized in regenerative medicine for over a decade with positive outcomes [148–150]. Long-term follow up studies greater than 10 years convincingly showed that autologous cells could be transferred into knee cartilage defects >4 cm^2 with successful long term follow up [148,149]. Other reports have found similar findings [151,152] highlighting the benefits of combining chondrocytes with a corrective osteotomy [153]. Nevertheless, the major drawback is that this regenerative modality has a long recovery time of 6–12 months. Furthermore, a secondary complication has been reported with the periosteal flap to seal the implanted cells resulting in flap hypertrophy [154]. For these reasons, alternative artificial matrices have further been combined with porcine membranes derived of collagen types I and III or hyaluronic acid [155–157]. One of the main limitations reported to date is the likelihood of creating an immune reaction following injection of allogeneic scaffolds, which further supports the use of liquid PRF (liquid fibrin) as a scaffold that possesses complete immune biocompatibility.

9.3. Strategy 3.3: Induced pluripotent stem cells

Induced pluripotent stem cells (iPSCs) represent an area of high research interest [158–160]. The strategy involves harvesting cells from various parts of the body and de-differentiating/re-differentiating them towards either cartilage [126,161] or bone [162,163]. An in vitro study showed that iPSCs derived from reprogrammed human synovial cells could be used to generate mesenchymal lineage cells [163]. Despite these positive results, potential limiting factors include the risk of teratogenesis or other in vivo tissue malformations. Future research is ongoing and is urgently needed.

10. Strategy 4: Synthetic biomaterials

Another area of the potential combination of biomaterials with liquid PRF is in regard to small injectable biomaterials. While the aim of this review is not to provide extensive details over all biomaterial options, any scaffold capable of mimicking the extracellular matrix of bone or cartilage and aid in its repair with sufficient mechanical strength would greatly benefit the regenerative properties of liquid PRF for either bone or cartilage generation. Naturally, all biological materials must have good biocompatibility and biodegradability, an ideal porous surface structures and sufficient mechanical properties [164–167]. Below, we highlight some of these materials as they relate to their potential combination with liquid PRF.

10.1. Strategy 4.1: Hydrogels

Hydrogels have recently been a highly investigated biomaterial for the controlled delivery of biomolecules in the field of tissue engineering [168–170]. They are water-swollen, soft materials composed of crosslinked hydrophilic polymers. They offer many advantages in that they have a favorable biological performance, hydrophilic properties, mild preparation conditions, versatility for biomolecule encapsulation and tunable release characteristics but maintain their injectability/moldability phenotype [171,172]. They offer a hydrophilic network of hydrogels that enables the incorporation of large volumes of aqueous solutions into their polymer network that protects the biomolecules from detrimental conditions [173,174]. For these reasons, hydrogels have increasingly been advocated as storage devices for the delivery of both biomolecules and stem cells, which can be obtained and prepared via minimally invasive methods to fill shape-specific defects [175]. Furthermore, when delivered in situ, chemical crosslinking may be applied via polymerization upon thermo-response or short UV radiation [176]. Therefore, hydrogels offer an ideal injectable gel

that can be administered with liquid PRF in a non-invasive manner that is capable of filling irregularly shaped defects for either bone or cartilage regeneration.

10.2. Strategy 4.2: Porous scaffolds

A variety of porous scaffolds have also been proposed in recent years with precise architecture tailored according to their application [177]. These have been fabricated via various methods including (i) conventional techniques, such as solvent casting, freeze-drying, gas foaming and salt leaching; or by (ii) more advanced approaches, such as rapid prototyping and electrospinning [178,179]. The size dimensions of the scaffold architecture that may improve liquid PRF remain virtually unknown; however, modifying the interconnected pores to facilitate cell migration, nutrition supply and transition of chemical and mechanical stimuli can lead to various properties depending on the desired final results. Porous scaffolds also favor the attachment of various cell types including MSCs, osteoblasts and chondrocytes [178,180].

10.3. Strategy 4.3: Nano- and micro-spheres

Another prominent area of research has been via the development of nano- and micro-spheres, which serve as delivery systems for cells, drugs, genes and other agents, allowing their controlled release into cartilage and bone [181–186]. They can be designed in the nano (1–10 nm) or micro (1–1000 μm) ranges, and these hollow materials are ideal mediators for the incorporation of small molecules that can be delivered via injection with or without other scaffold requirements. Furthermore, they may be fabricated from either natural or synthetic polymers and can thereafter rapidly degrade with the subsequent release of biomaterials or cells contained within them [187–189].

10.4. Strategy 4.4: Ceramics

Especially in the bone field, various ceramics formed from either calcium phosphate, tricalcium phosphate or biphasic calcium phosphates have seen more widespread use because they can also be utilized to deliver biomolecules in various sized micro-granules or as injectable cements [190–193]. They offer the ability to adsorb various biomolecules found in liquid PRF directly to the biomaterial surface yet also improve the mechanical properties of PRF, especially in the bone field.

10.5. Strategy 4.5: Synthetic polymers

While potentially not as biocompatible as natural polymers, synthetic polymers offer easier fabrication and better mechanical properties [194]. Most commonly used synthetic polymers for bone and cartilage repair are poly(ethylene glycol) and their derivatives including poly(lactide-co-glycolide) (PLGA) [195,196] and poly(l-lactic acid) (PLLA) [197–201]. They are often combined with each other or with other derivatives and natural polymers [202–209].

11. Strategy 5: Natural matrices

Following much research investigating the individual roles of various natural matrices, a distinct set of naturally occurring materials including collagen, fibrin, silk, as well as carbohydrate-based materials including alginate, agarose and chitosan have also been proposed.

11.1. Strategy 5.1: Collagen

Without question, collagen is the most widely used natural material incorporated into all types of biomaterials due to its ability to promote cell adhesion and proliferation or the differentiation of various cell types [210–212]. Collagen also offers an advantage in that it is more resistant to proteolytic breakdown yet is also highly biocompatible [213]. It is most commonly derived from the enzymatic digestion of various animal tissues and tendons [210,214–216]. Its use alone has been shown to improve cartilage regeneration [217–219], and its incorporation into bone grafts strongly favors better protein adsorption and bone formation.

11.2. Strategy 5.2: Hyaluronic acid

Hyaluronic acid (hyaluronan) has also been widely used as a natural constituent of connective tissues for the repair of either AC or bone. Hyaluronic acid is able to promote cell attachment, proliferation and differentiation including matrix deposition in various cell types [220–226]. Crosslinking strategies have been employed to improve material properties, including biodegradability and mechanical properties [176,227]. The beneficial addition of chitosan [228] or PLLA [204] scaffolds to HA significantly enhanced the final regenerative outcomes.

11.3. Strategy 5.3: Silk

Silk is also a favored biopolymer utilized for AC repair [229–231]. It is a natural biopolymer extracted from the cocoon of *Bombyx mori* silkworms or spun by spiders composed of amino acids, alanine, glycine and serine [232]. Advantages of silk include its high biodegradability with low immune reactivity and robust mechanical properties [233]. Silk has been utilized for the development of various other biomaterials including hydrogels, membranes, sponges and fibers [229,234–237] and can be used for the delivery of bioactive molecules [235,238–240].

11.4. Strategy 5.4: Alginate and agarose

Alginate is a naturally occurring linear polysaccharide isolated from brown seaweed [241]. Agarose is a polysaccharide extracted from Chinese algae [227]. Both have been utilized in various strategies for bone and cartilage tissue engineering [33,227,241–247]. Furthermore, both materials can be blended with other biomaterials or utilized in various combination approaches by maintaining an injectable method for delivery via minimally invasive administration [248]. Furthermore, agarose has already been positively supplemented with PRP [249] and other growth factors [250], demonstrating more favorable results.

11.5. Strategy 5.5: Chitosan

Chitosan is a popular cationic polymer that is derived from chitin, which is the natural component of the arthropod cuticle with good biocompatibility and excellent degradation properties. Its degradation products, including chondroitin sulphate, dermatan sulphate and keratin sulphatase, are building blocks of the AC [251]. Chitosan is known to support both cartilage and bone regeneration when utilized alone or in a combination approach with other biomaterials [223,252–257].

12. Strategy 6: Combination approaches

Lastly and potentially the most widely utilized, combination approaches utilizing scaffolds, cells and growth factors have under-

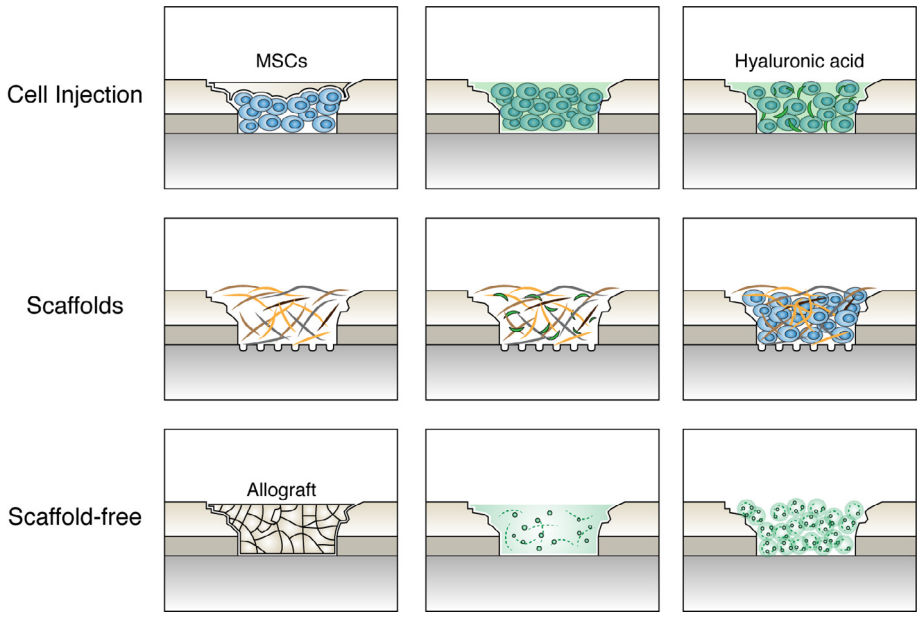

Fig. 8. Various strategies are now employed to regenerate defective tissues. These include cell injections, scaffolds and non-scaffold-based regenerative strategies, as well as combinations thereof.

gone widespread research with substantial translational potential in future clinical use. These include a combination of scaffolds with and cells with growth factors and scaffolds [258–262] (Fig. 8). The ideal regenerative strategy aims to develop novel approaches to introduce autologous cells into 3-dimensional matrices that may facilitate the growth of tissues and the release of potent growth factors. With these concepts in mind, the additional use of liquid fibrinogen is thought to improve the biological activity of various tissue engineering strategies due to its incorporation of fibrin, cells and growth factors. Therefore, its combination with various additional regenerative growth factors and/or injectable biomaterials is currently being investigated to assist with complicated defect wound healing. This strategy would incorporate all of the angiogenic properties of platelet concentrates; however, these concentrates lack the specific differentiation parameters or mechanical properties to further facilitate chondrocyte or bone regeneration.

12.1. Strategy 6.1: Scaffolds + Cells

Matrix-induced autologous chondrocyte implantation has been described as the most common scaffold-plus-cell-based cartilage repair technique currently utilized in clinical practice. During this procedure, 2 surgeries are required, first to collect autologous tissues to expand the cells on a porcine-derived mixed collagen scaffold followed by a second surgery to implant the scaffold [263,264]. A fibrin glue is currently utilized for such procedures. In addition, several reports have shown that hyaluronic acid-based scaffolds with autologous chondrocytes lead to marked improvements 1 year post-op [157,265] and better quality of life for patients 3 years following surgery [157]. In the bone field, a variety of strategies have been proposed utilizing various scaffolds with cells [266].

12.2. Strategy 6.2: Scaffolds + Growth factors

Autologous matrix-induced chondrogenesis (AMIC) represents a developing cell-free technique that can be performed in a single surgery. The technique involves using a mini-arthrotomy to expose and clean the defect site; microfracture then releases both blood and bone marrow containing MSCs. Thereafter, a mixture of collagen type I and III are sutured or glued into the cartilage defect [267]. The role of the implanted collagen matrix is thought to involve clot stabilization, which helps promote early mechanical stability for cartilage regeneration [268–271]. Similar to the strategy proposed by AMIC, which does not contain host cells, other researchers have proposed utilizing growth factors to actively recruit and stimulate MSCs towards cell-free scaffolds. While implanted polymer-based materials have been combined with PRP and/or hyaluronic acid [272–274], once again the advantages of liquid PRF, which contains a high percentage of regenerative cells including stem cells within its formulation, is thought to greatly improve outcomes compared to PRP. Similarly, in the bone field, bone morphogenetic proteins, whole blood serum, chemokines and platelet-rich plasma have also been proposed as growth factors for either pure bone or osteochondral bone regeneration [275,276]. One remaining feature is to better tailor regenerative strategies according to the anatomical location. Fig. 8 presents many potential uses of liquid PRF with scaffolds, cells or growth factors for the regeneration of various tissues in the body. Further ideal growth factor-/cell-/scaffold-based strategies that tailor the release of growth factors and cells in a controlled manner are needed to advance the field of bone and cartilage regeneration [277].

13. Future research

After fully reviewing the various options for loading liquid PRF with either small or large biomolecules, cells and various biomaterials, it remains interesting to note that there are many options to further tailor the regeneration of either cartilage or bone. Regardless of the combination approaches utilized, it is important to note that small biomolecules necessitate the controlled long-term delivery of growth factors, which is essential for therapeutic applications [278].

Furthermore, biomolecules require the preservation of their biological activity. In this regard, small biomolecules and peptides are easier to utilize compared to large biomolecules, which are more prone to degradation and a loss of activity in situ. The conformational stability of proteins is prone to variation (i) during carrier/protein construct fabrication, (ii) during carrier/protein storage, (iii) during surgery or when loading onto biomaterials and (iv) following implantation [29]. A variety of events, such as noncovalent degradation (i.e., hydrogen bonds, van der Waals interactions, salt bridges, and hydrophobic interaction), must be minimized and are often caused by a loss of the natural protein structure following elevated temperature, pH extremes, denaturants, and adsorption to hydrophobic surfaces [279]. Secondly, chemical inactivation is also possible and can be caused by hydrolysis of the peptide bonds, deamidation, oxidation, β-elimination, isomerization, and disulfide bond breakage and formation [279]. It is therefore urgently necessary to better understand how each biomolecule adsorbs to each biomaterial surface and similarly to what extent a fibrin network within liquid PRF may serve to better preserve the bioactivity of various biomolecules.

Another advantage of utilizing liquid PRF is that a general slow and gradual release of growth factors occurs over a 10–14 day period following coagulation into a platelet-rich fibrin clot [9]. The release kinetics is of great importance in the future regenerative potential of various biomolecules in tissue engineering, and PRF offers an easy method for a slow and constant release of growth factors entrapped within its fibrin clot. In contrast, previous clinical reports utilizing PRP have demonstrated that the bioavailability of platelet injections and platelet-derived biomaterials was poor due to denaturation and several acute problems. Furthermore, it remains relatively unknown at which specific time points growth factors should be delivered following liquid PRF injections. For instance, some growth factors should optimally be delivered at initial timepoints whereas others may benefit from either a late growth factor release or even a slow and gradual release over time. Naturally the delivery of growth factors 'should' be optimally delivered at appropriate time-points for each specific regenerative strategy however, clinically very few FDA approved growth factors available on the market have been designed with specifically timed delivery. For instance, both rhPDGF and rhBMP2 (both FDA approved recombinant growth factors) are delivered with either a bone grafting material or collagen sponges [280]. The growth factors are typically released as the biomaterial scaffold is degraded over time. While this review article focused on optimal target genes/cells/nanoparticles that could further be utilized with liquid PRF, much further research must address the timing and release kinetics of such biomacromolecules. Future research investigating the release kinetics of proteins from liquid PRF is therefore necessary.

The targeted delivery of biomolecules is also of great importance. Because liquid PRF can be delivered locally to defective tissues in a minimally invasive manner, it presents regenerative potential to act as a local delivery system for various biomolecules. Drugs can be extremely harmful when administered to non-specific tissues. Because liquid PRF forms a stable fibrin clot, it is possible to 'glue' all biomolecules within the fibrin scaffold with little release to the surrounding media until resorption of fibrin has occurred. This would ensure the direct and local administration of biomaterials to the intended environment. Because fibrin itself derived from various animal sources has already been utilized for this function, many additional advantages are hypothesized by simply replacing the use of animal fibrin with autologous liquid PRF.

While the combination of liquid PRF with the above-mentioned strategies offers new strategies and possibilities to the field of tissue engineering, some limitations may also exist. For example, it remains relatively unknown how various growth factors, cytokines and biomolecules will behave when combined with liquid PRF. Since PRF has previously been shown to contain degradation proteins such as MMPs, it may be that certain regenerative growth factors added to liquid PRF may undergo more rapid degradation than expected from within the PRF scaffold. Future research is therefore needed to better characterize the combination of liquid PRF with each individually added biomolecule. Furthermore, gene therapy functions primarily by transfecting cells and inducing their release of transcribed viral genes. Since liquid PRF contains many different cell types within its formulation, it may be that gene therapy targets a mixture of cells contained within liquid PRF as opposed to regenerative cells in the implanted tissues. Thirdly, cell-cell cross-talk has become imminently important in regenerate therapy [88,281,282]. The additional combination of stem cells has been found to greatly co-talk with immune cells and therefore much research remains to further optimize this behavior is necessary [283–285]. Lastly, the additional use of various synthetic and natural biomaterials has been a proposed therapeutic option as a combination approach with liquid PRF. However, much further research is necessary to determine how the injectable properties of PRF may be affected when pre-mixed with various biomaterials as proposed throughout this article.

While this review article highlights many novel future tissue engineering strategies for the regeneration of either bone or cartilage, it is important to note that all combinations must be adequately investigated prior to clinical use. Nevertheless, the combination of an autologous pro-angiogenic liquid PRF with various tissue-specific growth and differentiation biomolecules and scaffolds is thought to represent a new wave of research possibilities to improve patient care worldwide. Future research is therefore urgently needed to determine which combinations with liquid PRF are necessary under which clinical conditions for the repair of both cartilage and bone.

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