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Growth Factors and Articular Cartilage Rejuvenation: Where are we up to with reversing OA?

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Abstract

Osteoarthritis has eluded a curative/disease modifying treatment despite extensive research over the last century. This is largely due to the extremely slow metabolic turnover of articular cartilage in an essentially avascular environment, along with a pro-catabolic inflammatory cascade that is induced by damage to the healthy cartilage structure. There has been promising data emerging whereby this poor chondrocyte healing process can be improved by applying autologous stem cell populations (harvested from marrow/adipose tissue) that have been programmed to undergo rapid and sustained chondrogenesis with the assistance of numerous chondrogenic growth factors. Here we aim to provide a comprehensive review article about the growth factors employed for the purpose of articular cartilage rejuvenation. Disease modifying agents incorporating chondrogenic growth factors have been extensively researched in the last 2 decades, and it has been identified that the likely chondrogenic growth factor families of most therapeutic value are the Transforming Growth Factor beta (TGF-B superfamily), Fibroblastic Growth Factor (FGF - specifically FGF-18) and Insulin Growth Factor (IGF) in combination with many of the aforementioned factors. There is still a need for consensus on appropriate dosing and long-term studies should be performed to assess the durability of current therapies over many years. The application of growth factor enriched stem cell populations to osteoarthritic cartilage appears to be very near to effective therapeutic use.

Introduction

Arthritis in Australia currently affects 3.6 million people, or 15% of the total population. When looking at specific age groups; 57% of females and 40% of males over the age of 65

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are suffering with this disease [1]. Osteoarthritis (OA) makes up the majority (66%) of these arthroses, and has been recognized as a National Health Priority Area in Australia since 2002 [2]. It is described as a degenerative disorder not only of the articular (hyaline) cartilage but the entire joint organ, including the subchondral bone, periarticular ligaments and synovium. It arises from the progressive biochemical breakdown of articular cartilage, often preceded by some form of inappropriate biomechanical precipitant (e.g. excessive or abnormal load bearing, postural or orthopaedic abnormalities, or traumatic injuries) [3], then compounded by inflammatory and metabolic processes [4]. In summary, it is the unbalanced see-saw, favoring catabolic breakdown over anabolic synthesis.

Hyaline cartilage is an extremely compliant tissue found on the articulating surfaces of long bones, providing a lubricated, low friction surface to assist in the transmission of load across joints [5]. It is comprised of a sparse distribution of specialized cells called chondrocytes, surrounded by a dense extracellular matrix (ECM) made up of mostly of water, collagen and proteoglycans (with small amounts of other proteins) [6]. Throughout a human life, cartilage is continually remodeled as chondrocytes replace the degraded matrix macromolecules with newly synthesized components. This is an exceptionally slow process in adults; taking up to 2 decades [7]. Although the structure of articular cartilage allows it to tolerate a large amount of rigorous and repetitive physical stress, it demonstrates a poor capacity to heal even a trivial injury due to its poor vascularity and glacial metabolic activity [7]. Once damage has been established, a positive feedback cascade of inflammation develops which if left unchecked, will eventually lead to a pathological change in chondrocyte gene expression patterns, causing a decreased capacity for ECM production and increased release of matrix degrading enzymes, eventually destroying the joint involved [8-10].Our current accepted approach to managing OA is only focused on stalling this destruction, with no publicly funded means of reversing the destructive disease process. The focus of this review is to summarize the research which will hopefully lead to non-surgical methods of rejuvenating osteoarthritic joints.

Current OA Management: What are we doing now?

The current 'gold standard care' for treatment of OA in Australia, as suggested by Therapeutic Guidelines Ltd is outlined in (Table 1) below. It promotes a wholistic approach with individualized treatment targeted at patients' needs, goals and level of health literacy.

Table 1: Summary of OA management recommendations from Therapeutic Guidelines
*TENS = transcutaneous electrical nerve stimulation.

Education and Self-Management	• Education: Likely progression, Fluctuating nature of symptoms, Modifiable factors, realistic goals/expectations ○ Individualised, health literacy appropriate

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	• Self-management: Coping with chronic pain, pacing activities, lifestyle changes, physical aids, symptoms minimisation, medication education.
Lifestyle management	• Exercise: aerobic and strengthening • Weight loss: obesity is major risk for lower limb OA

Non-pharmacological Therapy	• Physical Therapy: Taping, Thermotherapy, Acupuncture, TENS*, orthotics/braces, magnets
	  ○ Low levels of evidence, minimal side effects, likely placebo, potential financial risk
	• Psychological Therapy: Cognitive Behavioural Therapy
	  ○ To manage living with long term pain, functional decline, decreased quality of life

Pharmacological Therapy	• Topical NSAIDs: small benefit identified in literature • Systemic Analgesia: Paracetamol +/- NSAIDs • Intra-articular injections (Corticosteroids): varying evidence from joint to joint, 4-12 weeks effectiveness • Intra-articular injections (Hyaluronan): inconsistent evidence • Duloxetine: mildly effective adjunct to oral NSAIDs • Opioids: very limited role, fraught with issues
Complementary Therapy	• Fish oil: poor evidence • Glucosamine + Chondroitin: poor evidence • Krill oil: No evidence in favour • Turmeric: inadequate evidence to comment

Surgical Management	• Osteotomy
	• Joint replacement
	  ○ Both of the above are reserved for end-stage disease that can no longer be managed conservatively.
	  ○ Patient age is also a factor due to ‘life span’ of replacements

Despite a better understanding of OA pathophysiology, current mainstream treatment modalities have not yet been able to safely incorporate the use of disease modifying agents, due to a lack of high-power evidence for their use [11]. Research has been focusedon mediating the inflammatory component of the disease, at the same time as promoting the function of intrinsic chondrocytes to repair any damage to the articular cartilage structure.

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This is a comprehensive review article about the growth factors employed for the purpose of articular cartilage rejuvenation.

The emerging role of Chondrogenic growth factors

It is now well established that there is a significant inflammatory component to osteoarthritis [12-18].The inflammatory mediators, mechanical and oxidative stress conspire to compromise the function and viability of chondrocytes, reprogramming them to undergo hypertrophic differentiation and early "senescence", making them even more sensitive to the effects of pro-inflammatory and pro-catabolic mediators [4] (Figure 1).

It can be surmised then that there needs to be a 2-pronged attack to managing OA. The first element needs to address the positive feedback of chronic inflammation throughout the joint organ which promotes ongoing cartilage destruction. The second element then is to re-establish the articular surface as it was prior to breakdown.

For decades now, the secret to cartilage regrowth has been suspected within human growth factors. In a 1975 presidential address to the association of bone and joint surgeons, Chrisman demonstrated the first use of growth hormone to heal damaged cartilage [20]. The inspiration for the study came from finding that acromegalics demonstrate continuous cartilage regeneration to the point that they suffer from the negative effects of articular cartilage hypertrophy. Since then, many growth factors have been identified to contribute to cartilage regrowth/remodeling.

Figure 1: Diagram representing the complex signaling pathways leading to chronic inflammation and disease progression seen in OA. ADAMTS=a disintegrin and metalloproteinase with thrombospondin-like motifs. IL=interleukin. MMP=matrix metalloproteinase. TNF=tumor necrosis factor. IFN=interferon. IGF=insulin-like growth factor. TGF=transforming growth factor. VEGF=vascular endothelial growth factor.Image reproduced from Glyn-Jones et al. [19].

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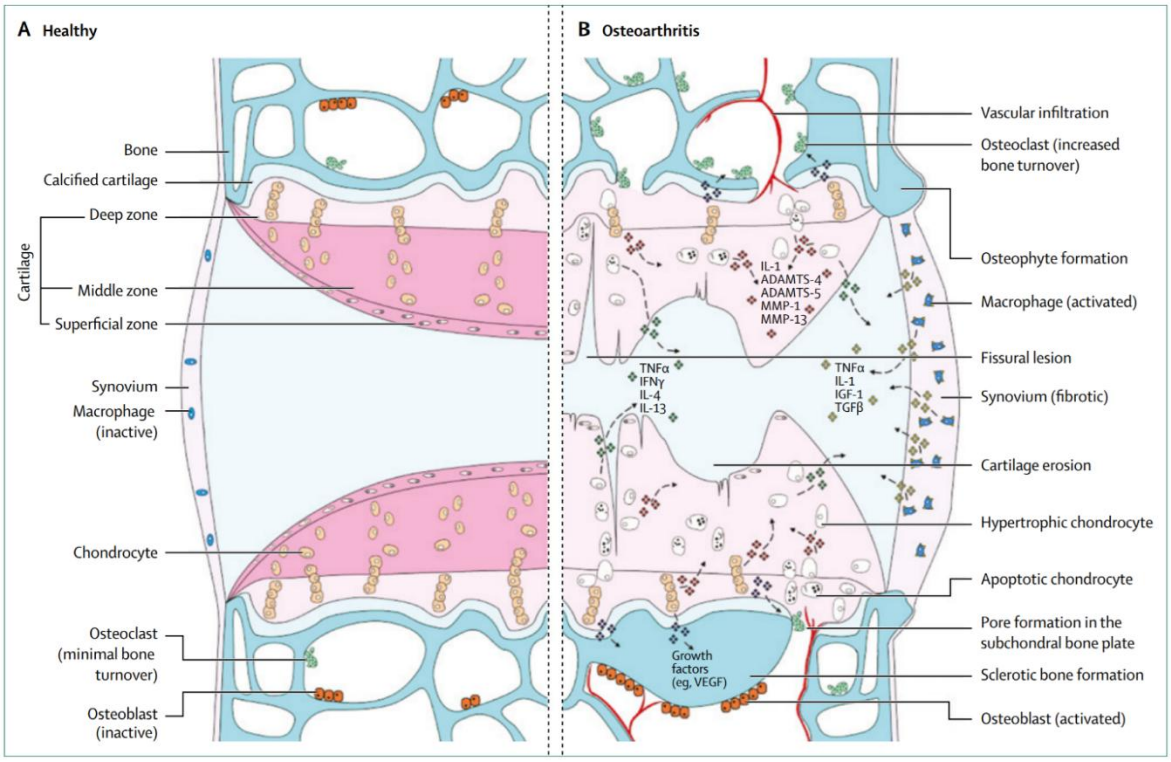

The task for researchers now is to find safe, cheap and effective methods to re-establish in vivo human cartilage that is phenotypically appropriate to serve its joint support function long term. Below is a table 2 outlining some of the current growth factor families being trialed for this purpose, as well as an image demonstrating where in the cell differentiation process, they are each relevant (Table 2).

Table 2: Summary of some growth factor families and their function. Some of these families have over 40 subtypes within them, many of whom have roles yet to be identified.

Growth Factor Family	Functions	Ref
Transforming Growth Factor beta's (TGF B)	Stimulates the proliferation of undifferentiated MSC, stimulates chemotaxis of endothelial cells and angiogenesis	[21]
Basic Fibroblast growth factors (bFGF)	Promotes the growth and differentiation of chondrocytes and osteoblasts stimulates mitogenesis of mesenchymal cells, chondrocytes and osteoblasts.	[22]
Platelet Derived Growth Factors (PDGF)	Regulates the secretion and synthesis of collagen	[23]
Insulin-like growth factor (IGF)	Cartilage homeostasis, balancing proteoglycan synthesis and breakdown	[23]
Epidermal Growth Factor	Causes cellular proliferation, endothelial chemotaxis and	[24]

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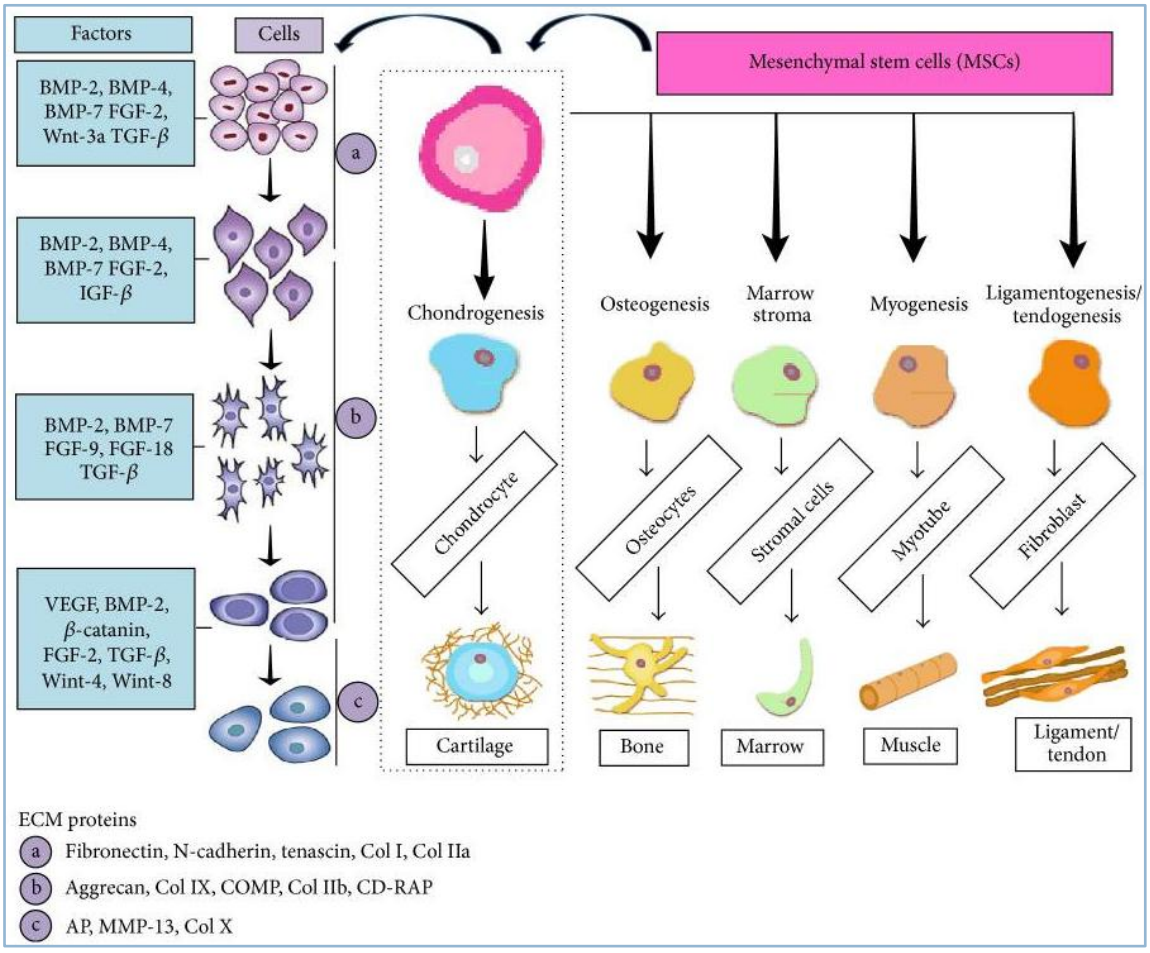
receptor (EGFR)	angiogenesis	
Vascular Endothelial Growth Factor (VEGF)	Increases angiogenesis and vascular permeability	[25]

Since the identification of the relevant growth factors to cartilage homeostasis and regrowth, the next major step was how to successfully employ them to create what could be considered phenotypically appropriate or 'normal' articular cartilage (Figure 2).

Figure 2: Mesenchymal stem cells (MSCs) differentiations towards chondrocytes and other cell types. Differentiation and growth factors profile are schematically represented in sequence. Characteristic extracellular matrix (ECM) proteins at different stages are presented. Col, collagen; COMP, cartilage oligomeric protein; CD-RAP, cartilage-derived retinoic acid-sensitive protein; AP, alkaline phosphatase; MMP, matrix metalloprotease; BMPs, bone morphogenetic proteins; FGF, fibroblast growth factor; Wnt, Wingless Factors; TGF, transforming growth factor; IGF, insulin-like growth factor; VEGF, vascular endothelial growth factor. Image reproduced from Phull A, et al. [26].



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Initial trials in the 1970's tested systemic administration of human Growth Hormone (hGH), but this application was limited by the systemic consequences of essentially inducing acromegaly, without significant improvement in their clinical OA features.

The process has evolved significantly to become more precise and complex, starting from intra-articular application of growth factors straight into the synovial fluid, to utilizing agents/scaffolds that promote extended release of the factors once injected. Surgeons have drilled through sub-chondral bone to expose the joint space to the underlying marrow and all its innate stem cells and growth factors, leading to the formation of fibrocartilage plugs to fill deficits. From osteochondral autologous transplants (moving cartilage from non-weight bearing sections of joints to fill cartilage defects) to more advanced techniques including autologous chondrocyte implantation (ACI) and now matrix-associated autologous chondrocyte implantation (MACI), as well as autologous matrix-induced chondrogenesis (AMIC) [27] we are close to seeing an answer to the problems caused by OA.The newest and most promising area of study is developing in the field of tissue bioengineering, utilizing stem cell therapy to grow and then implant cartilage into OA affected joints.

There are numerous studies into the use of growth factors to regrow phenotypically appropriate articular cartilage, and the table below captures a sample of these with a summary of their findings (Table 3).

Table 3: Outline of growth factors being investigated for cartilage regeneration therapy
GH = Growth Hormone, PRP = Platelet Rich Plasma, IGF = insulin-like growth factor, PDGF = Platelet derived growth factor, VEGF = Vascular endothelial growth factor, TGF-B = Transforming growth factor Beta, BMP = Bone morphogenic protein, FGF = Fibroblast Growth factor.

Growth Factor family	Study	Model	Summary of Results	Ref
GH	Dunn A et al, 2012	Human in vivo	13 of 14 patients with severe ankle OA had clinically significant improvement in function and symptoms over 1 year after injection with hGH (Omnitrope) and avoided surgery for which they were all candidates	[28]
PRP	Liu X el al, 2017	Animal in vivo	PRP photocrosslinked into hydrogel scaffold demonstrated significant macroscopic/histologic and clinical improvements to damaged cartilage.	[29]
	Multiple, see references	Human in vivo	Autologous mesenchymal stem cells injected along with PRP into human knees with OA lead to clinical improvement in pain and function, and developed hyaline like cartilage	[30,31]
	Multiple, see references	Human in vivo	Multiple studies comparing PRP to placebo and physical therapies and hyaluronic acid for early OA. All studies	[32-36]

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			demonstrate short term improvements in function and symptoms, statistically significant to comparisons.	
IGF	Sundararaj SKC et al, 2012	Animal in vivo	IGF-1 on PLGA scaffolds led to formation disorganised cartilage within damaged areas. Scaffolds without IGF-1 only produced bone. Not a phenotypically desirable result	[37]
	Florine EM et al, 2014	In vitro	IGF-1 bound to EGF-like growth factor resulted in increased proteoglycan synthesis compared to IGF-1 alone	[38]
	Fukumoto T et al, 2003	Human In vitro	Combination of IGF-1 and TGF-B1 give off a strong proliferative stimulus to MSC's undergoing chondrogenesis.	[39]
	Goodrich L et al, 2007	Animal in vivo	Genetic modification of chondrocytes in horses to produce more IGF-1. Filling defects improved in damaged cartilage at 4 weeks, almost normal hyaline cartilage seen at 8 months	[40]
PDGF	Schmidt M et al, 2006	In vitro	PDGF promoted cell proliferation and proteoglycan synthesis in vitro.	[23]
VEGF	Marsano A et al, 2016	In vitro	VEGF blockade is a robust strategy to enhance cartilage repair by endogenous or grafted mesenchymal progenitors, forming phenotypically appropriate articular cartilage in vitro	[25,41]
TGF-beta (family includes BMPs)	Ying J et al, 2018	Animal in vivo	TGF-B1 applied to MSCs significantly enhanced healing at 4 and 8 weeks compared to controls with no treatment or MCSs alone. Cartilage was phenotypically appropriate histologically/macroscopically	[42]
	Singh N et al, 2012	Animal in vivo	TGF-B1 within collagen scaffolds leads to phenotypic appropriate cartilage formation in rabbit OA knees	[43]
	Lee B et al, 2018	Human In vivo	Cellular/gene therapy to implant allogenic chondrocytes infected by programmed retrovirus to overexpress TGF-B1 x3 more than normal (INVOSSA). Statistical improvement in pain/function for knee OA, mild structural improvement.	[44]
	Lew S et al, 2019	Human In vivo	Long term (4-8 years) efficacy and safety of INVOSSA. Safety confirmed, efficacy confirmed out to 2 years	[45]
	Schneider MC et al, 2019	Animal in vivo	Matrix metalloproteinase (MMP)-sensitive poly (ethylene glycol) (PEG) hydrogel containing TGF-β3. Fantastic results in vivo (Porcine) compared to in vitro. Phenotypically appropriate	[46]

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	Multiple, see references	In vitro	Scaffolds encapsulating BMP-7 and TGF-β3 can efficiently deliver a cooperative growth factor combination that drives efficient cartilage formation in human mesenchymal stem cell cultures.	[47,48]
	Das R et al, 2015	In vitro	Increased TGF-β2 signalling through ALK5 plays a role in hypoxia-induced redifferentiation of chondrocytes.	[49]
	Knippenberg M et al, 2006	In vitro	BMP-7 triggers adipose tissue derived stem cells to take on a chondrogenic phenotype, feasible tool for tissue engineering	[50]
	Hayashi M et al, 2008	Animal in vivo	Weekly injection of BMP-7 inhibited OA progression in rabbits	[51]
FGF	Lohmander LS et al, 2014	Human in vivo	Intra-articular recombinant human fibroblast growth factor 18 didn't lead to statistical change in cartilage thickness. There were some improvements in secondary end points.	[52]
	Ellman, M et al, 2013	Review	FGF-2/FGFR1 antagonists, FGF-18/FGFR3 agonists, and FGF-8 antagonists as potential therapies to prevent cartilage degeneration and/or promote cartilage regeneration and repair	[22]
	Zhou S et al, 2016	Animal in vivo	Intra-articular injection of exogenous FGF9 delays articular cartilage degradation in post-traumatic OA, while aggravates osteophyte formation	[53]
	Cucchiarini M et al, 2009	In vitro	OA affected chondrocytes triggered to create FGF-2/SOX9 overexpression revert back to normal phenotypic articular cartilage in this in vitro study	[54]
	Maehara H et al, 2010	Animal in vivo	FGF-2 in hydroxyapatite/collagen scaffold in rabbit model demonstrates reliable phenotypic production of articular cartilage and obtains an optimal dose of FGF-2 to achieve it	[55]
	Howard D et al, 2015	Animal in vivo	FGF-18 application to Surgical microfracture of OA sheep knees led to significant improvement in weight bearing and histological findings consistent with regeneration of normal articular cartilage.	[56]
	Miyakoshi N et al, 2005	Animal in vivo	Intra-articular FGF in hyaluronic acid is superior to FGF alone for osteochondral repair in rabbit OA. No comment on phenotype of cartilage	[57]
	Im H et al, 2008	Human In Vitro	FGF-2 has a pro-catabolic effect on cartilage homeostasis	[58]

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Discussion

In general terms, the methods presently identified for reversing OA involve incorporating either individual or combinations of growth factors into artificial micro-scaffolds that deliver bioengineered stem cell populations to articular injuries. These stem cells are ideally autologous (bone marrow or fat derived) and with proper growth signaling, will proliferate and differentiate into phenotypically appropriate populations of anabolic ally active chondrocytes. This has ultimately been shown in animal and human studies to result in the creation of histologically, macroscopically and functionally rejuvenated articular surfaces with practically complete reversion to pre-morbid structure. Of the specific growth factors looked at so far, those from the families of IGF, TGF and FGF seem to have the most utility for this chondrogenic function. The aim of these factors is to stimulate populations of Mesenchymal Stem Cells (MCS's) to undergo chondrogenesis (see Figure 2).

The TGF family (TGF beta1-3 and BMP2, 4-10) act via signaling cascades across the MSC cell membranes, transducing signals through signaling mediators known as receptor-regulated Smad proteins (R-Smads) [59] which lead to increased expression of Sox9, the transcription factor which is currently known to act earliest in the pro-chondrogenic program (60). This has been shown in numerous trials (Table 3) to successfully differentiate MSC's into phenotypically appropriate populations for articular cartilage formation, and incorporate well (with the help of various micro-scaffolds) into OA affected cartilage. Some data has demonstrated effective viability and durability out to 3+ years, but due to the relative youth of this therapy, there are yet to be long term studies assessing its feasibility for long lasting cartilage repair. The FGF family was also a notable family for cartilage repair and maintenance. FGF-18 has a well-established anabolic effect on chondrocyte populations, activating Fibroblast Growth Factor Receptor-3 (FGFR3) which triggers an increase in the formation of matrix as well as stabilizing chondrogenic differentiation into the ideal mature chondrocyte, without triggering hypertrophy or apoptosis [61]. However, FGF2 was found to be both pro-anabolic and pro-catabolic, depending on numerous factors occurring simultaneously within the affected cartilage. As a result of this, FGF2 needs to be better understood before its application can become prevalent. IGF-1 has been identified for a long time to have numerous roles within chondrocyte anabolic activity. It modulates MCS's to undergo chondrogenesis by stimulating proliferation and increased expression of chondrocyte markers, as well as controlling their phenotype/morphology. It upregulates the gene expression of type-2 collagen (hyaline/articular) and enhances synthesis of essential ECM components. It has the added benefits of reducing ECM degradation by decreasing the production of metallopeptidase13 (MMP-13) [62]. Its successful use has been reported as a solo agent as well as in combination with other factors from all growth factor families (eg. TGF-B1, BMP-7, EGF-like GF etc.).

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For the most part this promising data is supported by meta-analyses and systematic reviews [63-65]. It has also been identified that this treatment comes with very few risks, mainly just transient fever in some patients when stem cells are involved [66,67]. However, some meta-analyses have identified that much of the evidence at present is lacking statistical power due to low sample sizes, dosing consistency and recognized high risk for bias [27].

There is still no published consensus on which individual or combination of growth factors is ideal for the best treatment outcome. It is also still to become clear on how to best dose these factors with regards to individual concentrations and frequency of application. It is these aspects that have, in the past, held back large population studies and is slowing the progression to approved development of OA disease modifying therapy. There is however good news in that many large-scale clinical trials have been developed and recently approved. Some are currently in progress and are aiming to address these very issues [68].

Looking at the current climate of health care in Australia, now more than ever we need to move away from symptom management and salvage procedures in osteoarthritis, and towards restorative and preventative measures. The cost to the economy can be felt in both health care expenses and productivity losses, specifically reduced workforce capacity, lost tax revenue, social, psychological and quality of life costs(69, 70). In 2012, healthcare costs for OA exceeded $3.75 billion, an increase of almost 200% since 2007 [71]. The same report found the productivity costs associated with musculoskeletal conditions (including OA) were around $36.9 billion. OA is the second ranked chronic health condition (after back pain) contributing to lost workforce productivity in people aged 45-64 in 2010 [72]. Furthermore, evolving data suggest that the use of opioid medications is high for musculoskeletal conditions, including osteoarthritis, and continues to increase in developed nations such as Australia [73-75]. We need now more than ever to find an effective disease modifying agent for the management of osteoarthritis. Given the demonstrated safety, it is time to perform more and bigger clinical trials in the use of these chondrogenic growth factors.

Disclosures

Dr Matthew Elliott is an RMO, currently not affiliated with any companies or specific health services. Dr. Gordon Slater is an Orthopaedic Surgeon and is lead designer at Integrant Pty Ltd. No funds were received for the publication of this paper. There are no conflicts to disclose.

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