

Basic Orthopedic Immunobiologics

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“Bone marrow signaling cell concentrates and molecular treatment modalities in the setting of orthopedic surgical manifestations of musculoskeletal disease: Arthritic knee pain”.

Abstract

Musculoskeletal biologic therapeutic technologies have emerged as safe, viable, disease modifying options for primary (RA) and secondary (OA) inflammatory arthritis patients who often have had no option other than a potentially complicated surgery with uncertain outcomes. Understanding the basic science of immunologic cell signaling pathways and tissue response will continue to lead to more specific, targeted biologic treatments. We present an easy to follow, infographic that we believe serves as a reasonable baseline to help patients and surgeons understand the principles of biologic treatment in orthopedic surgery and neurosurgery.

Keywords: *Knee Arthritis; Orthopedic Surgery; Osteoarthritis; Stem Cells; Signaling Cells; Regenerative Medicine; Arthritis; Knee Pain; Biologics; Neurosurgery; Cartigram; Diffusion Weighted MRI*

Introduction

Knee arthritis is increasing by projected prevalence extrapolations [1]. By 2030, the number of US adults with arthritis and its associated activity limitation is expected to increase substantially, resulting in a large impact on individuals, the health care system, and society [2]. The growing epidemic of obesity may also significantly contribute to the future burden of arthritis. Improving access and availability of current clinical and public health interventions aimed at improving quality of life among persons with arthritis through lifestyle changes and disease self-management as well as the use of modern, non-operative orthopedic biologic techniques may help lessen the long-term impact [3].

Twenty years later, it is clear that biologics have earned a place in the armamentarium of the orthopedic surgeon and any other physician treating arthritis. An immunomodulatory approach to treating rheumatoid, or primary inflammatory arthritis has been successful [4]. Admittedly, there is no data on the potential efficacy of this approach to secondary, or classical arthritis that is often referred to as osteoarthritis (OA).

An immunomodulatory approach to rheumatoid or inflammatory arthritis has been clinically successful. Biologics were a mega game-changer when Embrel® (etanercept, Immunex® Corporation, Thousand Oaks, CA) [5] was first introduced in 1998. Third party payers historically resistant to coverage for biologics now routinely reimburse these drugs because clinical use is supported by protocol and evidence-based outcomes analysis. The menu of biologics available from big pharma continues to grow. Multiple biologic medications like tumor necrosis factor alpha (TNF- α) antagonists, interleukin one (IL-1) receptor antagonists. The role of other biologics like alpha-2-macroglobulin and tumor necrosis factor-stimulated gene 6 protein has been elucidated over the last decade. The definition of identical final common pathways in primary (RA) and secondary (OA) suggests a potential role for DNA recombinant technology in the setting of OA, as well as RA. The costs of pharmacologic biologics eclipse the costs of autologous biologic harvest, concentration and clinical administration. One study examines the cost of biologics available from big pharma demonstrated the cost difference between DNA recombinant versus autologous biologics. Autologous biologics cost approximately \$200 - \$250/month for a minimum of two years in our hands. Where pharmaceutical recombinant products are concerned, total costs per treated patient average \$3880 per month per drug across

indications. Specifically, costs were as follows: adalimumab, \$23,427 to \$26,304; infliximab, \$22,824 to \$28,907; and etanercept, \$21,468 to \$27,748, whereas abatacept, certolizumab, golimumab, rituximab and ustekinumab were associated with a larger range: \$17,017 to \$41,888 indicating the need for further study and a closer look at autologous biologic solutions [6].

This review article discusses autologous bone marrow signaling cell based clinical therapeutics used in combination with an activated, proprietary fibrin scaffolding application in orthopedic surgery that we have used successfully since first introducing the application in 2006, reflecting over a decade of experience with signaling cell therapeutics. This article is unique in that it describes the molecular medicine involved in the immunomodulatory signaling sequences thought to be responsible for the clinical anti-inflammatory and pain-relieving effects that have been widely reported and duplicated. An easy to follow infographic presents the basic molecular mechanism as they are currently understood.

An algorithm-based approach that uses an arthroplasty protocol favoring the patient rather than payers is the most appealing, but least sustainable. Even when performed by appropriately trained and educated orthopedic surgeons, third party payers have a good reason to deny orthopedic biologic procedures. Payer board of trustees have obligations to shareholders and as such, must consider the downstream consequences of regeneration versus replacement. Decisions are made by payers based on what's most affordable not what's best for patients. While that may be appropriate in the business world, that algorithm has never and will never satisfy the demands of honest medical practice. Biologic procedures per se are not more expensive than joint replacement procedures and average costs to the patient are approximately equal with an average third-party payer deductible of \$4,000 to 6,000. However, restoration of athletic function, particularly with advancing patient maturity, may represent the threat of a future sports-related procedure that will require additional third-party reimbursement before the patients is most appropriate for joint replacement. Patients suffering from arthritic knee pain who undergo joint arthroplasty are instantly dequalified from the most aggressive, impact activities they love, although some benign activities like simply kneeling in church threaten the knee construct where failure leads to more surgery that is typically complicated some benign. For patients who qualify for joint preserving procedures rather than joint sacrificing procedures, who elect to undergo orthobiologic Injection protocols, like our proprietary signaling cells, iSC[®] rather than joint replacement are more likely to engage in activities they may not have been able to enjoy for years. That means that a patient who is able to return to playing softball doubles tennis, or pickleball for instance is, in the eyes of the third party payer, more likely to suffer another sports-related injury that will also require treatment (and payment by the payer). Neither Medicare nor any other third-party payer can afford either of these major paradigm shifts in treatment that clearly represent disruptive technology. One and done is the ideal business model in the setting of orthopedic joint disease management for payers.

Any beneficial clinical anti-inflammatory or analgesic clinical properties of corticosteroid are tempered by important catastrophic metabolic consequences. The catabolic effects of corticosteroid preparations on connective tissue have been thoroughly elaborated and well understood for decades. As a result, many insurers have refused reimbursement claims for corticosteroid injections into the shoulder and the knee. Blue Cross Blue Shield of North Carolina (BCBSNC) announced in August 2016 that it would no longer reimburse corticosteroid injections of the knee or shoulder on the basis of limited efficacy and known harmful effect on connective tissues per their report [7]. Repeated corticosteroid assaults lead to chondral fissuring and promote dose-independent structural changes (occurs during the first exposure) that serves as a segue to progressive joint degeneration and the potential need for expensive joint arthroplasty as well. In addition, there are numerous clinical reports of spontaneous tendon ruptures following the use of local corticosteroid injections or systemic steroids.

Biologics make sense. A basic knowledge of immunology and stem cell biology reveals the basis for treatment concepts and management techniques. The following infographic may serve as a helpful teaching aid for surgeons, musculoskeletal physicians, patients and the general public. We hope it will serve as a foundation for establishing a fundamental treatment algorithm in regenerative medicine that can be built upon as scientific translation from bench to clinical application progress.

In 2006, we began focusing on signaling cell and molecular treatment modalities for orthopedic surgical manifestations of musculoskeletal disease. We adhered to gold standard treatment recommendations and exhausted multi-modality conservative interventions before we considered cell treatments as part of our treatment algorithm. More recently, we have begun to question the terminal utility of that approach in favor of earlier diagnosis with GE® MR Cartigram® (General Electric Corporation, Boston, MA) technology [8]. Earlier diagnosis leads to more thorough patient education and enables the physician to offer inexpensive, effective early conservative management techniques that would primarily focus on joint loading characteristics. Similar diffusion weighted imaging (DWI) technology with MRI EDC images offer similar promise for axial disease, now that emerging biologic therapies have emerged to treat these disease decades before they appear clinically.

Our original treatment concepts were based on well-described biologic signaling pathways [9]. Our theory largely focuses on modulation of immune surveillance plus direct and indirect anti-inflammatory effects from both the cellular component and the protein components of treatment that effect clinical relief of symptoms.

Initially, there was great excitement over the ability of signaling cell procedures to form regenerate rather than repair cartilage [10]. While never duplicated, one author claimed to document new cartilage growth on postoperative imaging, while in-flight airline journals ran ads showing the full restoration of joint space after ‘miraculous’ stem cell injection [11]. The general public was globally misled and frequently exploited based on media hype. This led to a setback in the field as far as orthopedic surgery was concerned. As the result, the treatments were only taken seriously by a handful of clinician scientists practicing orthopedic surgery [12], one of whom was Dr. Dan Eglinton, the true pioneer in the field who unfortunately passed away unexpectedly in 2015.

Most orthopedic surgeons recognized this as false advertising by doctors in other fields attempting to capitalize on the media frenzy that was created over the magical claims being made over what were dubbed “stem cell injections”. Until the recent announcement by FDA chairman Scott Gottlieb, the FDA has not addressed the major problems plaguing the field. Physicians with no musculoskeletal training at all are able to feign expertise in what was prematurely referred to as ‘regenerative medicine’. There has been no oversight over the past decade and the already at-risk elderly patient subset may have been exploited. It may be that the governing bodies of the American Board of Orthopedic Surgery and the American Academy of Orthopedic Surgeons will recognize a potential public responsibility and launch a massive patient and surgeon education campaign on behalf of patients. After over a decade, the release of a position statement on biologics December 28, 2017 (N0. 1187) is a step in the right direction [13].

To the dismay of the orthopedic more than the scientific community, actual cartilage tissue growth was soon determined not to be the primary mode of clinical pain relief in humans as it had been assumed to be in the pre-clinical animal model treated with MSCs. However, this false start seemed to slip by either unrecognized or unnoticed because over the past decade, there has been a massive proliferation of clinics offering what are advertised widely as ‘stem-cell’ procedures. Often, these procedures or products are mislabelled, mis-marketed or plain fraudulent. In the past, these clinics have not been subject to any FDA or other oversight as to what is offered, how therapy is provided or who it is providing the skilled injections required for treatment. Some clinics even offer purified fat products, amniotic tissue products and unfiltered platelet rich plasma products that they claim are ‘stem cells’ or stem cell products.

Since we first introduced our techniques in 2006, there has been virtually no regulation in the field of what has become known as regenerative medicine. When we first introduced the concepts and techniques, these were considered advanced orthopedic surgical techniques.

Since the time we first started marrow cell concentrating procedures, hundreds of clinics have popped up all over the United States and globally. Only a handful of these clinics offer treatment by an orthopedic surgeon or musculoskeletal expert (often a retired orthopedic surgeon) who is familiar with all aspects of joint disease and management. With very rare exception, although there are some, there

should be no adequate substitute when considering these high-priced procedures. Typically, it is recommended that patients seek at least one opinion from an experienced orthopedic surgeon practicing these methods. This is an important time in the history of regenerative medicine. Orthopedic surgeons must establish a firm knowledge base and become familiar with these techniques before the science become even further distorted and the field slides backwards in the wrong direction. Our treatments are protocol based on our patient database of validated outcomes analyses. Our current algorithms are the most advanced and proprietary. Before we even offer the procedure, patients must meet rigorous standards to ensure avoidance of expectation/result mismatch, which we have not found to be an issue in any case.

Patients have now become very well aware of the availability of these treatments, although awareness and understanding of the immunologic signaling concepts by both physicians and patients remains extremely poor. The inconsistent treatment experience between patients likely reflects the lack of a uniform knowledge base of physicians who are performing the procedures and the lack of protocol-driven algorithms. Clinics offering protocol-driven algorithms based on their own patient outcomes analysed with serial, validated outcome instruments offer patients the best chance at a successful biologic procedure. Orthopedic surgeons can be trusted to perform the procedure only when indicated because they are able to complete the full suite of treatment options. Perhaps the most important component of cell-based therapies (CBT) is that the mechanically induced faulty mechanotransduction must be reversed to restore Young’s Modulus to the subchondral bone. This can be accomplished through many surgical and non-surgical means described elsewhere.

We believe that the infographic, while by no means the complete story, introduces a ‘mathematically-proven’ cellular and molecular baseline that all specialties, including orthopedic surgery can agree on as a starting point. It is hoped that by publishing the infographic both patients and physicians will be encouraged to dig deeper and contribute to the knowledge base going forward, as so many have in the past. By ‘showing our work’ to our patients like we did to our middle school teachers, we’re likely to be far more convincing that we understand the concepts and the equations. “If you can’t show your work, it doesn’t count”.

A lengthy and detailed description of all of the molecular pathways involved in orthopedic biomolecular homeostasis and mechano-biology and is beyond the scope of this article. Many excellent resources can be easily found online and in text format.

Infographic

Physical component of arthritis

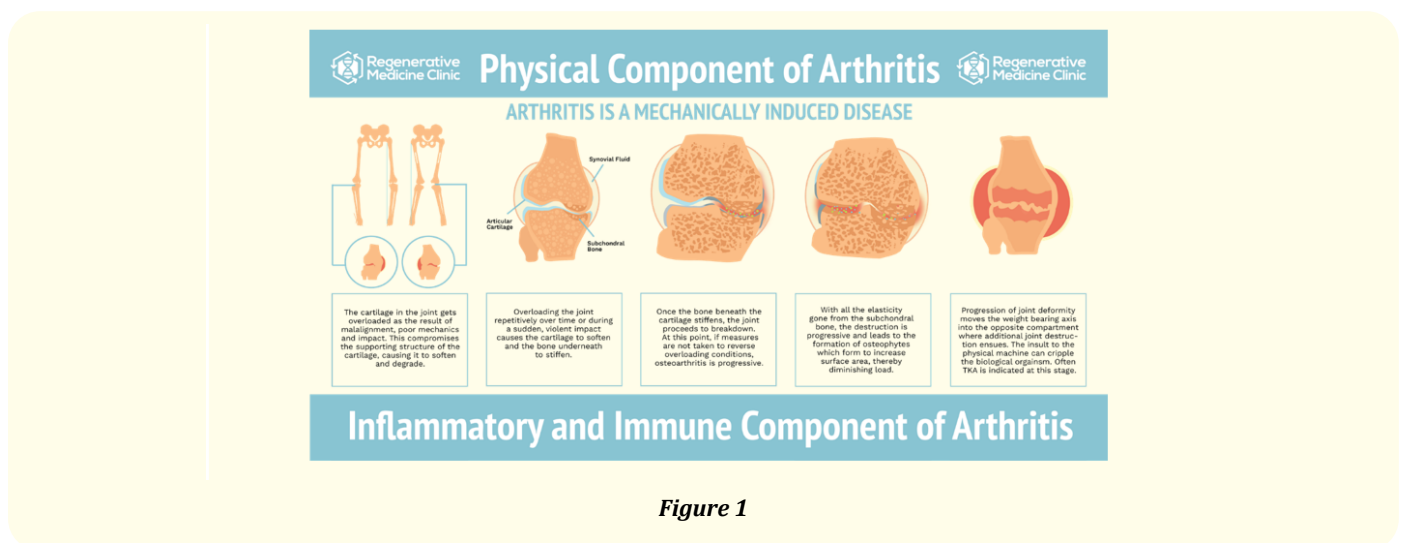


Figure 1

Arthritis is a mechanically induced disease. The number of cyclic loads against gravitational forces is finite before the material mismatch between cartilage and bone is exceeded. Relative to matrix loading, chondrocytes and chondroblasts migrate into clusters aligned to gravitational load. Mechanotransduction prompts ECM remodeling that follows with less and lower quality proteoglycan (PG) and stiffer collagen production from the cellular DNA. This leads to increased articular fluid concentrations of PG, meaning poor load distribution and transfer of load now to the subchondral bone. Typically, the proteoglycan is very hydrophilic and able to absorb physiologic loads much like a wet sponge. Once the PG holding the water is out of the sponge, the load transfer leads to synovial inflammatory monocyte activation when removal of both extracellular matrix and cellular breakdown products accumulate. Once the subchondral bone load exceeds physiologic loading capacity, mechanotransduction is initiated across the tidemark and subchondral remodeling ensues. To avoid patient and physician dissatisfaction with treatment, uni-compartmental overload that is at the core of knee osteoarthritis must be addressed. Otherwise, results following iSC® will be shorter lived and suboptimal. We may recommend surgical or non-surgical re-alignment modalities depending on individual patient characteristics and expectations. In our experience with hundreds of injections, concentrating and injecting bone marrow cells and plasma products as standalone do not provide relieve that lasts much past two years, unless patients are very carefully selected.

Patients who have cartilage preservation in only one of the weights bearing compartments of the knee are the best candidates for treatment. It has been our experience that varus gonarthrosis is easier to manage and results are better for varus as opposed to valgus conditions. During treatment, the more normal joint compartment bears the load it was typically spared by virtue of the patient’s native alignment. Restoration of subchondral bone elasticity is a function of the length of time the joint compartment remains unloaded relative to gravity. Biomechanics with a focus on posture, gait mechanics and locomotion, joint range of motion, strength and general conditioning are addressed by a physical therapist in the pre-habilitation phase and post iSC® phase starting at three weeks. Once both the medial and lateral weight bearing compartments have been severely compromised, the success of the procedure suffers significantly. The importance of identifying and meeting patient expectations cannot be overemphasized.

Signaling cell treatments include a cell component and a protein component. The protein component can be further subdivided into a soluble fraction and a sequestered fraction. The soluble fraction includes the acellular portion of the plasma. The sequestered fraction includes the contents of the alpha and dense platelet granules.

Inflammatory and immune components of arthritis

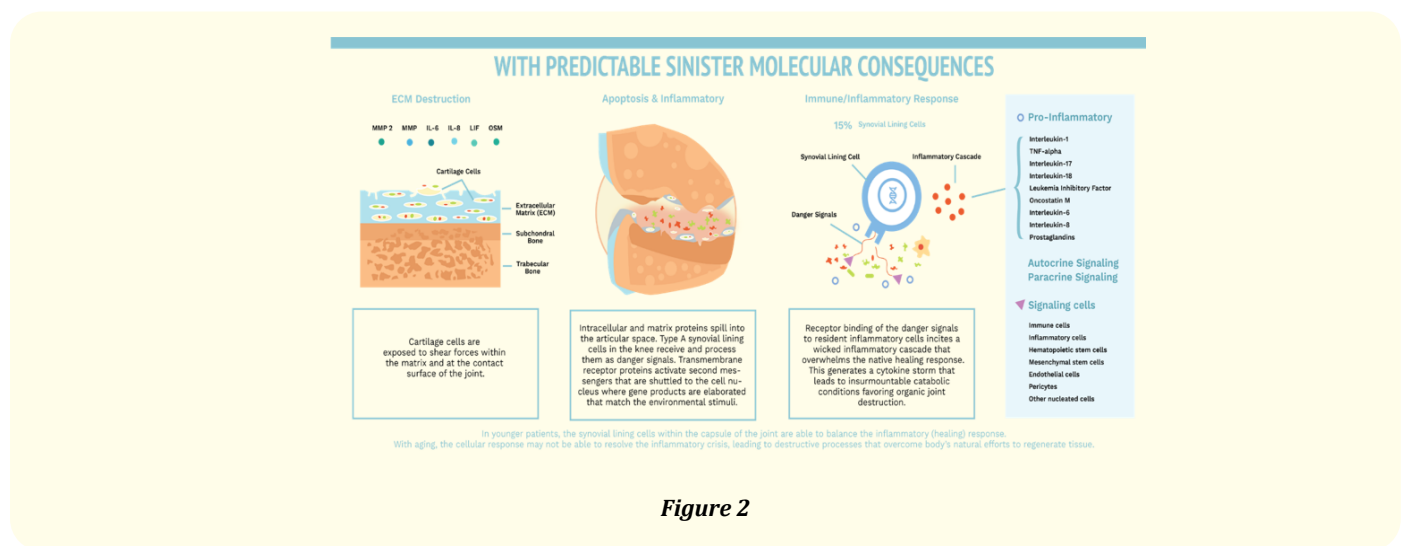


Figure 2

Summarizing, with repeated cyclic overload, the extracellular matrix of articular cartilage is compromised. Proteoglycan and collagen content of the matrix is diminished, while these matrix protein concentrations rise in the articular fluid increase. In much the same way as tissue collagen exposure during acute injury prompts inflammation, collagen fragments in articular fluid play a similar role. When exposed to breakdown products of the ECM, synovial monocytes/macrophages launch the inflammatory cascade. Depending on many factors relative to the overall health of the biological organism (age, sex, biological and mechanical factors, metabolic disease, etc.), the process may be subclinical, acute and limited or chronic and unlimited. Although controversial, serial measurements of serum IL-6 may provide a baseline assessment of general health and guide treatment.

The inflammatory process is incited further as the ECM is physically worn down and chondrocytes become exposed at the joint surface, much like a cobblestone street. The chondrocytes are weak in shear and cellular lysis causes release of typically intracellular proteins into the articular fluid. This pathophysiological condition further ignites the inflammatory cells of the synovial lining. Cells are under paracrine and autocrine control by secreted and soluble factors in a complex, spatiotemporally controlled signaling system dominated by immune influence.

The major chemokines involved in the destructive, degenerative inflammatory process involve matrix metalloproteinases 1, 2, 8 and 13, Interleukin 6 and 8, leukemia inhibitory factor (LIF) and oncostatin M (OSM). Many excellent descriptions of the important molecules and signaling pathways can be found in the literature but are outside of the scope of this article. Each bioactive amine is counterbalanced by one or more biological counterparts that can have spatiotemporal and concentration dependent effects that directly oppose one another in the complex biological systems that can be best, but oversimply, described as multivariate. In the healthy organism this counterbalancing provides tissue homeostasis that preserves the life of the organism. After the third decade, as the pituitary secretion of growth hormone fades and causes tissue insulin like growth factor one (IGF-1) concentrations to diminish, the biological organism begins to accumulate age related changes that begin to favor a catabolic, rather than an anabolic state.

Pro-inflammatory mediators include interleukin-1 (IL-1), Tumor necrosis factor alpha (TNF-a), IL6, IL8, IL17, IL18, LIF, OSM and the prostaglandins with the exception of PGE2 among many others. The ability of the immune system of offset the negative effects of inflammation that cause terminal degeneration typically matches the lifespan of the human organism. Nevertheless, 78 million US adults are projected to have arthritis by 2040 indicating the need for more advanced, efficacious treatment options.

Orthopedic biologic treatments: signaling cell and molecular management strategies

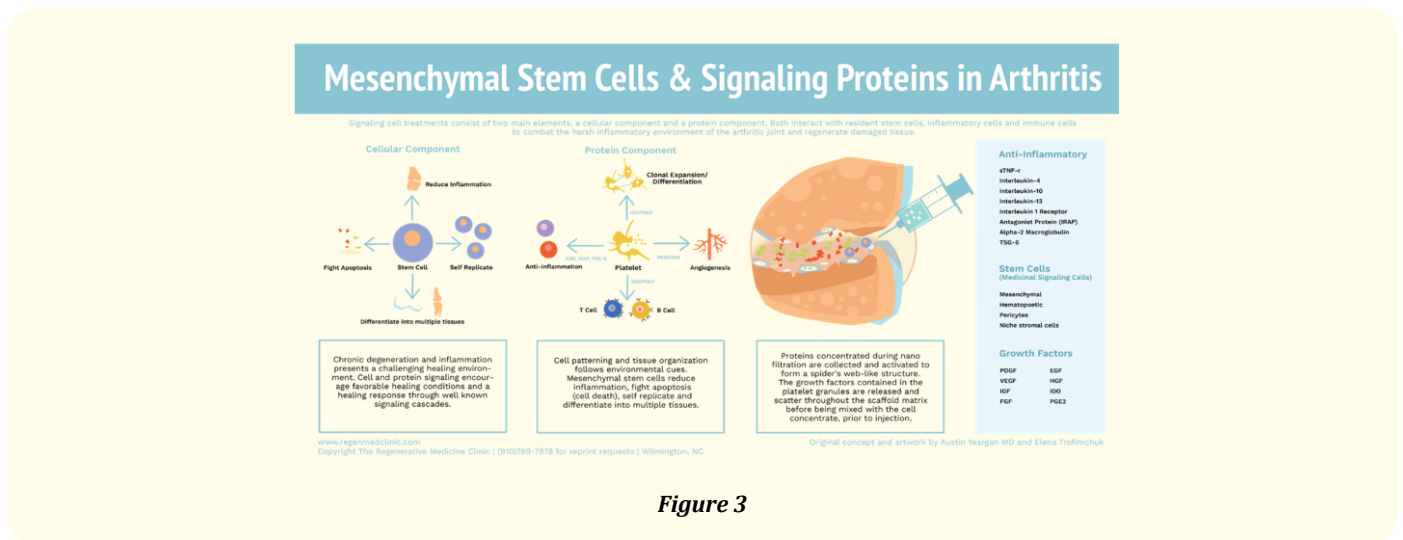


Figure 3

Signaling cells

Signaling cells harvested and concentrated during bone marrow aspiration include but are not limited to immune cells, inflammatory cells, hematopoietic stem cells, mesenchymal stem cells, endothelial cells, pericytes, dendritic cells and other nucleated cells. A lengthy discussion of the biology and biochemistry of these cells is beyond the scope of this article, but many excellent online sources can be easily sought out.

Mesenchymal Stem Cells deserve special mention because of their ability to function as drugs. These cells are responsive and bioactive based on the environmental milieu they are subjected to. The degree of inflammation determines whether MSCs respond with a pro- or anti-inflammatory phenotype, which is incredibly important when considering the use of orthobiologics in the setting of disk disease.

Difficulty to control radiculitis and diskitis have been reported particularly following injection of PRP (versus BMC) into the disk space and the problem is likely more than is reported. Caution is particularly advised for PRP with higher levels of leukocytes in particular because, in general, platelets increase anabolic signaling and, in contrast, leukocytes increased catabolic signaling molecules. Outside of the acute setting, the role for PRP with high leukocyte levels is negligible in our opinion. We also believe for a pain indication, plasma nanofiltration likely to lead to a superior product again based on the elimination of pro-inflammatory mediators and concentration of anti-inflammatory mediators.

MSCs have direct and indirect effects on inflammation. They are capable of self-replication and specialization into cartilage, bone, tendon, muscle and fat (tissues of mesodermal origin). MSCs direct tissue responses to injury, stimulate resident stem cells, fight apoptosis and cell lysis and prompt a healing response in tissues.

Signaling proteins

Soluble proteins in the plasma include both pro-inflammatory and anti-inflammatory molecules that can be separated by polyether-sulfone (PES) nanofiltration on the basis of their molecular weight. One commercially available system (ART[®] 2 Plus, Celling Biosciences[®], Austin, Texas) provides this routine option on the cell processor, limiting sterile breaks and enhancing the iSC[®] product. In our experience, the ability to filter out proteins smaller than 65 kD with the PES filter has resulted in a much faster patient response rate immediately after iSC[®] and the clinical longevity of our procedures is unmatched, although we are very selective in defining patient candidacy to treatment.

Sequestered proteins of interest in the platelets include the growth factors, whose functions are self-explanatory: Platelet derived growth factor (PDGF), transforming growth factor (TGF), vascular endothelial growth factor (VEFG), epidermal growth factor (EGF), insulin like growth factor (IGF) and prostaglandin E2, which ironically causes fever, but plays a role in T cell receptor signaling that limits inflammation. Growth factors may have an anti-inflammatory role in the setting of iSC[®] injection arthritic knee pain.

Human or bovine thrombin is typically added to the concentrated platelet poor plasma causes fibrinogen dimers to form strands and clot. Platelets are activated with either calcium chloride or calcium gluconate to form a lysate. Combining this globular autologous fibrin scaffold with dispersed growth factors encourages cell adhesion and cohesion through integrins and cadherin interaction. The injectate is relatively hypoxic, which also favors cell survival once delivery is complete.

Conclusion

Initially, the excitement over the discovery of adult “stem cells” that was present in “niches” of every tissue led to a media and marketing frenzy over regenerative medicine that has led to a great deal of confusion amongst physicians and patients unfamiliar with the science and/or technology behind the currently available but seemingly futuristic treatments. Over the last decade, we have carefully

attempted to advance the field by dissecting out the cellular and molecular pathways that underlie the now undeniable clinical success of the interventions with a focus on restoring (regenerating) native tissue in favor of repair (scar) tissue based on numerous proof-of-concept studies in orthopedic animal models.

Subchondral puncture techniques have conclusively been shown to produce (temporarily) stable scar cartilage tissue containing primarily type 1 collagen. Good clinical results have been reported in comparison to other more advanced a costly procedures. The partial clinical success in these cases led us to consider a process where we could expand the marrow cells and hopefully regenerate native cartilage (type 2 collagen) that would be a regenerative tissue rather than a repair tissue. Our initial hypothesis in 2006 was that if just a few stem cells (MSCs are 0.001% of the bone marrow cell population) leaking into the joint through subchondral puncture could form scar cartilage, then perhaps increasing the cell population would lead to better tissue formation and therefore better clinical results for patients. Based on early animal studies and scientific theory, we believed that injection of concentrated MSCs accomplish the goal of cartilage regrowth. Using advanced imaging, it became clear that was certainly not the case. However, not unlike the history of the willow bark, clinical relief was undeniable in many if not most patients, regardless of the Kellgren-Lawrence grade on radiographs. Working backwards from the molecular landscape of arthritis, we have now determined conclusively that the clinical effects are due to the immunomodulatory and anti-inflammatory properties of the concentrated cellular and molecular injections.

Although some early authors rushed to prove tissue growth on MRIs, those reports have not been duplicated and must be discounted at present. The inability across orthopedic surgical clinics nationwide and globally to consistently demonstrate any tissue regeneration with these methods led scientists to focus on the potential anti-inflammatory and immunomodulatory components of cell therapy. It was clear that a mechanism other than tissue regrowth was responsible for the clinical effects noted in the human model.

Direct changes to the microstructure of the biophysical machine were absolutely determined not to be the primary mode of pain relief in patients suffering with arthritic pain. However, even today, the vast majority of physicians offering this therapy are unaware of the potential mechanisms behind the clinical relief that follows these universally expensive treatments because we believe that until now, no theoretical mathematic type of 'proof' involving the cells and molecules involved in the clinical mechanism has been suggested.

We believe that the infographic, while far from perfect and perhaps frankly wrong in the eyes of some of the most advanced researchers (who introduced us to the basic concepts in the first place) will stimulate discussion and serve as a baseline for all specialties to discuss the future direction of biologics in orthopedic surgery.

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