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Orthobiologics: The Drug Within Us

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Abstract

The musculoskeletal system involves a diverse organisation of tissues exposed to the complex series of biological and mechanical stimuli.(1)

Musculoskeletal problems continue to represent a growing source of death and disability world-wide, particularly with the growing burden of disease associated with an ageing population and increase in the rates of road traffic accidents.(2)

Normal bone healing is a complex process that eventually restores original structure and functions to the site of trauma.(3)

The use of "Ortho-biologics" or regenerative therapies in the orthopaedic surgeries has grown in the recent years.(2) Particular interest has been raised with regard to platelet-rich plasma, bone marrow aspirate, adipose-derived cells, amniotic cells, platelet-derived growth factor are currently in use.(4)

But in the end, the analysis has shown that no study has got an complete coverage about how the novel technique as a whole has evolved.(5)

KEYWORDS: Ortho-biologics, musculoskeletal, platelet-derived, bone-implant

Introduction

Unlike some musculoskeletal tissues, bones have the ability to regenerate after injury. Under ideal biomechanical conditions, which include proper alignment and stability of the fracture site, bone will heal and remodel into its original form.(4) Typical fracture healing is commonly described in three phases: inflammation, repair & remodelling.

Whether, it happens following a fracture or a bone graft, involves a well organised set of events that leads to re-constitution of the biological and mechanical integrity of bone.(5) The regenerative process is initiated by an inflammatory response, which plays an important role in stimulating repair.(6) Inflammatory cytokines & growth factors-β(TGF-β), platelet-derived growth factor(PDGF) & bone morphogenetic proteins (BMPs), coordinating inflammatory cell and stem cell migration.(7)

However, circumstance exist in the field of orthopaedic surgery in which this normal healing process is inadequate.(8) Fracture non-union is defined as a lack of complete healing after 6 months. Depending on the site & type of fracture, rates can vary between 4.8 and 10%

Injury of tendons and/or ligament independent of bone can lead to complications and extended periods of recovery which can also have debilitating effects similar to bone therapy.(9)

The regeneration of cartilage is a hot topic. Cartilages can be damaged by injury, inflammation, infection and degeneration. Destruction of articular cartilage in rheumatoid arthritis and osteoarthritis involves inflammatory cytokines such as TNF06, IL-1 or IL-6, which have been the target for current therapies.(8)

After injury, articular cartilages has a poor capacity to repair itself and tends to heal through the formation

of fibrocartilage, which has inferior biomechanical characteristics to resist compression stress compared to normal articular hyaline cartilage.(10)

For decades, scientists and surgeons have been exploring treatments that facilitate cartilage repair, including micro fractures and more recently cell-based tissue engineering using autologous chondrocytes and mesenchymal stem cells combined with scaffolds. Now here, biologics play some crucial role in developing the treatments of orthopaedic based issues.(9)

Many techniques & materials have been developed as a way of improving bony regeneration and healing.(2) Of the particular interest & relevance to this review is about the orthopaedic surgeries, biologic adjuvants to augment this process & the recent researches on the Ortho-biologics.(10)

Ortho-biologics:

Regenerative medicine in orthopaedic surgery is an evolving and rapidly expanding field. Numerous blood-based (Platelet-rich plasma [PRP], autologous protein solution, α2 macro globulin concentrate), cell-based (e.g.:- Cells derived from bone marrow, adipose tissue,(or) amnion, placenta, or umbilical cord blood); and various other (e.g.- cortical & cancellous bone grafts, 3-D printed biomaterials, viscosupplementation, growth factor isolates such as bone morphogenetic proteins) approaches have been developed and marketed and/or are actively being investigated as therapeutics, for variety of musculoskeletal conditions across orthopaedic subspecialties. (11)

These biologic therapeutics, often colloquially referred to a " Ortho biologics ", includes a widely heterogeneous group of substances that may be harvested from or involve autologous, allogenic, xenogenic (or) bioengineered. Synthetic sources and hold tremendous potential to enhance tissue healing and restores tissue architecture and function after injury (or) disease.(12)

Particularly, we an see some adjuvants were been discussed and reviewed all along these period, especially regarding the use of PRP and mesenchymal stem cells for the treatment of musculoskeletal conditions.(13)

Platelet-rich Plasma (PRP) was the first clinical biologics to be described in the literature (in 1970) and was first used in vivo (in 1987) in cardiac surgery. It is been mostly focused on soft tissues rather the bone. PRP involves concentrating platelets in a small volume of plasma by centrifuging autologous blood.(14) Activated platelets release a milieu of growth factors and mediators that augment natural healing. While there is still debate as to whether the white blood cells (WBCs) included in the PRP preparations are beneficial (or) harmful to the healing response. PRP contains very high concentrations of PDGP, VEGF, and FGF. Because of this, it is thought that PRP may be able to assist in many situations that require tissue healing.(15)

Currently, more than 40 commercial PRP concentrations systems are available, and there is high variability in the concentrations of growth factors present, even within a given technique. (14)

The recent (or) latest updated PRP shown to decrease pain after patellar tendon auto graft ACL reconstruction and rotator cuff repair, but neither shows significant change on clinical outcome & no studies has analysed how the ortho-biologics literature as a whole has evolved.(15)

Mesenchymal-stem cells(MSCs) are the adult stem cells derived from bone marrow but also derived from other body tissues like blood, adipose tissue, skin, trabecular bone, liver and lungs & also derived from amniotic tissues.(14) MSCs have the ability to promote cellular regeneration and tissue repair through differentiation into multiple specialized cell types (multipotent) within the mesenchymal-derived cell linkage as well as through the release of growth factors and modulation of the inflammatory response.(15) Many of the current MSC trials involve the use of isolated and cultured allogenic cells.

Allogenic MSCs have been shown to avoid immune detection by lacking major histocompatibility complex type II(MHC II) and co-stimulatory molecules as well as modulating the surrounding inflammatory environment.(14)

De-mineralized bone matrix is the biological adjuvant created by demineralizing ground cadaver bone and it contains BMPs, collagen, and other growth factors that are then combined with a carrier.(14) Much like PRP, each process of DBM creation from the harvesting to the final product is unique from company to company, with no standardization across the industry.(15) Overall, most of the research has been done in spinal fusions, utilizing it as a bone graft extender to be combined with existing bone. It has not been shown to produce efficient (or) durable fusion when used alone. More recently, the use has been expanding, with good results seen in the ankle fusion when compared with ICBG and some success with femoral non-unions or segmental defects.(16)

Parathyroid hormone is another interesting trend identified in the trial search is the use of teraperatide, which is recombinant parathyroid hormone. (PTH). Physiologically, PTH acts on osteoblasts and osteoclasts to resorb bone, increasing serum calcium.(14) However, when given in the pulsative fashion during treatment of osteoporosis, it increases bone mineral density(BMD) and improves bone architecture. This likely occurs due to preferential osteoclast bone resorption.(15) Limited clinical studies of off-label use have shown positive effects on bone repair. Therefore, the results of these clinical trials involving bone repair and fusion have the potential to add another treatment option in these difficult cases.(16)

Nel-like molecule-1 is a growth factor originally identified in the patients with craniosyntosis as Protein kinase C-binding protein. Since its discovery, animal studies involving overexpression as well as deficiency have confirmed its importance in bone formation.(14) Investigators have attempted to utilize the osteoinductive effects of NELL-1 to enhance bone repair in experimental animal models. Rat and mouse explant studies demonstrated its ability to induce and accelerate bone growth.
(15)

NELL-1 has also been investigated in many in-vivo models, including a rat, critical-sized femoral defect model and rat and sheep spine models, showing positive effects on bone growth and repair.(16) The exact actions of NELL-1 in the signalling cascade are still being defined, but it is thought to act through RUMX 2 and interact with BMPs and the sonic hedgehog (SHH) signalling pathway. This protein has demonstrated enormous potential in pre-clinical studies and further progress towards a clinical use is anticipated.(15)

Orthopaedic biomechanics is a specific sub-field of orthopaedic research that involves the application of engineering principles to examine the mechanical behaviour of human musculoskeletal system.(17) Topics of interest within orthopaedic biomechanics include mechanical testing of orthopaedic tissues and structures, medical implant design and testing, kinesiology (the study of human motion), and tissue engineering.(18) A select list of currently popular research topics in orthopaedic Biomechanics for particular subspecialties is presented in table(19)

There is a large body of research focused on characterising differences between normal vs diseased orthopaedic tissues at the tissue-level, such as elastic compressive behaviour of the annulus fibrosis as a function of intervertebral disc degeneration.(20) The potential applications of tissue-engineering implants, quantifying the effects of different drug therapies on tissue-level mechanism behaviour, and providing accurate material property information for computational models.(21)

ORTHOPAEDIC SUB-SPECIALITY	
Spine	* Quantifying spinal-kinematics in normal versus diseased cases. * Understanding biomechanical contributions to adjacent segment disease * Comparison of motion preserving versus fusion technologies.
Trauma & Sports medicine Arthroplasty	* Comparison of traditional versus less-invasive implants for bone fracture and soft tissue repair. * Investigating the use of cements and adhesives to create more rigid fracture repair constructs that can support immediate weight bearing. * Optimization of bearing surfaces for total hip and knee prosthetics * Geometric and bearing surface optimization for total disc and total ankle replacement.
BROAD-BASED ENGINEERING TOPICS	
Computational modelling Wearable and implantable sensor	* Translating established continuum-based constitutive models for orthopaedic tissues into finite-element based algorithms. * Element modelling like High-resolutionfinite, Iterative finite element technique to study the bone-implant systems. * Application of MEMS technology to traditional implant designs to measure loading in-vivo

These studies frequently involves head-to-head comparisons of the ex-situ or in-situ mechanical performances of currently used orthopaedic implants or surgical techniques.(20) These types of studies determine which procedure is most mechanically competent, and the data can be interpreted in the context of any existing clinical information regarding relative rates of patient morbidity and mortality, the amount of surgical skill needed to perform the procedure, and the cost and availability of any technology necessary to perform the procedure.(21)

DEVELOPMENT OF AN ORTHOPAEDIC RESEARCH PROGRAM.

The Initiation of research programs requires complex decision making as directional, logistical, financial, and other consideration must be evaluated.(22) The greatest barriers to the development of new basic research facilities include available technical expertise, space and finances.(23) This section reviews the basic infrastructure and equipment needs for the development of orthopaedic molecular biology and

biomechanical research laboratories, as well as some of the financial considerations required to develop these facilities.(24)

INFRASTRUCTURE & EQUIPMENT FOR ORTHOPAEDIC BIOMECHANICS LABORATORY.

Research programs of the Orthopaedic biomechanics generally have either experimental or computational focus, with a select group of more established laboratories undertaking both investigative approaches.(25) The computational approach is generally preferred by new research group in the US and Europe with limited financial resources.(24) It can be established with minimal investment in infrastructure and may be staffed effectively by 3-D software and finite element techniques.(26) As projects are fundamentally computerised, collaborations may be established internationally with communication largely through video conferencing, secure file transfer protocols and other forms of electronic communication.(23)
More specialized equipment can be used as the necessity of the laboratories dictates. e.x., Quantitative reverse transcriptase PCR (qPCR) can be used to assess gene expression pattern is cells and tissues.(26)
Experimentally-focused orthopaedic biomechanics research programs are substantially more challenging to develop, as they involve substantial up-front investment in laboratory infrastructure, have high-operational costs, and require close clinical collaboration and experienced technical staffs.(28)

CONCLUSION

The field of orthopaedic research will continue to grow in order to address the increasing global burden of musculoskeletal injury and disease.(29) The complex nature of the musculoskeletal system requires multi-disciplinary collaboration between investigators who possess a wide diversity in expertise.(30)
The field of orthopaedic surgery currently uses several biologic adjuvants in the treatment of a vast assay of bone pathologies. Research is actively seeking ways to refine and optimize currently used treatments while simultaneously investigating promising new molecules.(31) Although, the development of research laboratories and opportunities require extensive planning and resource development, ultimately basic discoveries have the potential to develop into translational projects that can impact patient care. Guidelines from journals & professional societies may help to encourage the medical professionals & common people to adapt towards these kind of therapeutic measures.(32)

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