Editorial

Biological approach to support surgery achievment

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Management of orthopedic cases cannot stand alone. For example, when talking about fracture cases, it must be understood that the problem is not only mechanical, but there are also other problems ranging from physical, chemical, biological to psychotherapy. Likewise, in the case of bones that infected by Mycobacterium tuberculosis (TB spondylitis) with a spinal defect of more than one corpus, then the problem that occurs cannot be overcome only by giving anti-tuberculosis (OAT) or antibiotic drugs, because the patient will experience spinal instability, that if not overcome by mechanical approach with fixation installation, will cause problem such as pain that reduces the quality of life of these patients.

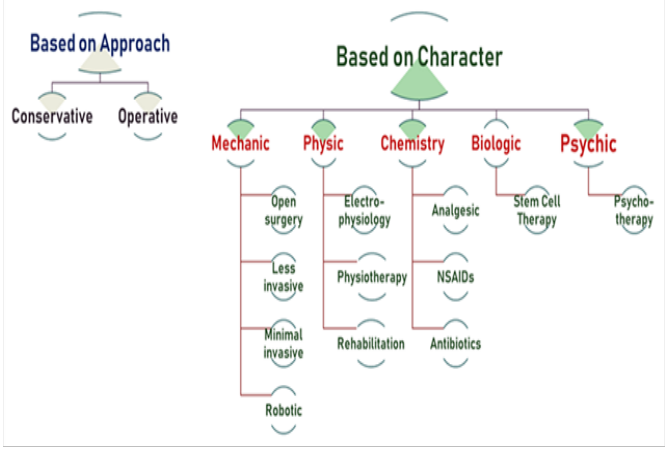

Figure 1. Management modalities for musculoskeletal problems

Mechanical problems in fracture cases can be satisfactorily overcome by attaching fixation to the bone, both externally and internally. Fixation used can be made from metals such as stainless steel, cobalt chrome to titanium, or non-metals such as plaster and plastic polymers. But in cases where there is a large defect in the bone or a non-union condition occurs, then the problem must be overcome by other approaches, one of which is a biological approach.

Diamond Concept and Bone Fracture Healing

Non-union defects are bone defects with tissue loss > 2.5 cm which have impaired bone healing after nine months, or for three consecutive months have not shown the growth of callus bridges (callous bridging). An orthopedic surgeon, when faced with a fracture with a non-union needs to consider and prepare early on to take a biological approach other than a mechanical approach. The term 'diamond concept' has been known in fracture healing, where there are four important components for fracture healing including osteogenics (osteogenesis/ osteoprogenitor cells), osteoconductive matrix (scaffold), osteoinductive signaling (growth factor) and vascularization and mechanical stability.

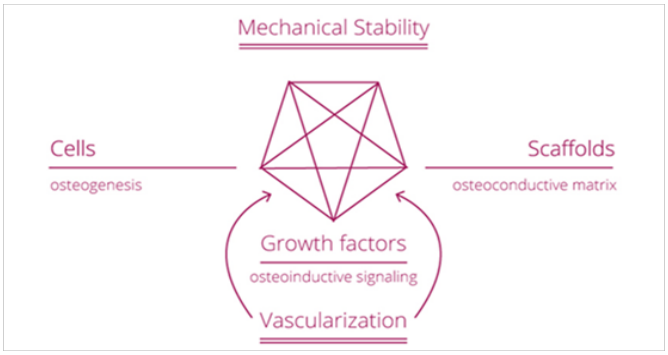

Figure 2. Diamond concept of healing bone fractures

Osteogenic: Cell Therapy

Any form of tissue healing is driven by certain cells which, when triggered by signaling factors, will produce optimal microenvironment for the tissue to recover and eventually continue its mechanical function. But what

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needs to be remembered before an orthopedic surgeon takes a biological approach to deal with musculoskeletal problems, the orthopedic surgeon must take into account several aspects, including; from where the cell originates, what type of cell will be given and how many, through what route it is given during implantation and what mechanism may occur biomolecularly, will the cell stimulate the formation of collagen or synthesize other molecules to produce an extracellular matrix?

At present, there are more than 800 complete or ongoing clinical trials to evaluate the use of mesenchymal stem cells (SPM) to address various cases (see clinicaltrials.gov). This is done to prove that this biological therapy can truly be scientifically useful and can be accountable for the results to support its use and understanding of the principles of its use.

Micro Environment

Biological approaches must always begin with an understanding of the underlying microenvironmental injury. From the perspective of injury, specific cell deficiencies, cytokines, or mechanical environments that contribute to pathology must be identified. Whereas from a regeneration perspective, the opportunity to increase certain components of the healing response can then be exploited. After a biological target for a particular scenario is identified, the ideal biological formulation must then be adjusted to the clinical setting. The effects of biological strategies depend on the complex interactions between the damaged microenvironment and the biological preparations given. Other factors that also have important contributions are the type of tissue that is injured and the mechanism and chronicity of the injury that occurs. This is based on "needs" a biological approach that is carried out for each different and individual injury.

Growth Factors and Cytokines

Growth factors are part of the normal response to injuries that act to promote tissue regeneration and healing injuries. Most growth factors are pleiotropic, causing various biological effects on various types of cells. The term cytokine is often used interchangeably with growth factors. In fact, cytokines are just one of the growth factors that have unique and important properties in cell signaling. The release of cytokines will affect the behavior of cells around them because they can be involved in autocrine signaling, paracrine signaling, and endocrine signaling as immunomodulating agents. Whereas growth factors are specifically bound to receptor molecules and target cell surfaces and the existence of these receptors determines the capacity of cells to respond to signals. A large number of growth factors has a relevant effect on musculoskeletal regeneration and hence represents potential and specific therapeutic targets.

Currently there are three growth factors that have been registered in the Food and Drug Administration (FDA) and have been proven to support the musculoskeletal regeneration process, namely platelet-derived growth factor (PDGF), bone-morphogenetic-protein (BMP)-2 and fibroblast growth factor (FGF).

Scaffold

Cells are often planted/seeded in an artificial structure that is able to support three-dimensional tissue form - usually called as scaffold. Scaffold's nature is sensitive, both ex vivo or in vivo, and mostly used for:

1. Attaching and migration of cells
2. Protecting cells from biochemical factors
3. Activating nutritional diffusion of vital cells and producing products
4. Enabling certain mechanical and biological effects to modify cells' phase behavior.

As the support used for tissue reconstruction, scaffold needs to fulfill several requirements. High porosity and adequate pore size are needed to facilitate cell seeding and nutritional diffusion across the structure of the cells. Biodegradable traits are often important as scaffolds preferably absorbable by surrounding tissues without the need for surgery. The degradation rate should align with the tissue formation rate; meaning when the cells are forming, the cellular natural matrix structures are present around the cells. Scaffold should provide structural integrity in the body and finally leave behind neotissue - a newly-formed tissue that will then cover the mechanical weight of the body.

The criteria of good scaffolds are high porosity rate, adequate pore size that enables nutritional and cellular diffusion all around the structure, and degradable trait - an important criteria as scaffolds are expected to be absorbed by surrounding tissues without additional surgeries. It is expected to be degraded after cells formed a binding matrix that is able to provide structural support and tissues are formed. Numerous materials have been

used, and most, have been used in the medical, one of which is surgical suture threads that is usually collagen or aliphatic polyester. Some materials for scaffolds were taken from synthetic sources, while some others were taken from natural sources. Most materials were widely known in the medical field before tissue forming techniques were known as research topics.

Scaffolds can also be made from natural materials, such as different derivates from the extracellular matrix, that have been studied to evaluate its ability to support cell growth. Proteic materials, such as collagens or fibrins, and polysaccharidic materials such as chitosan and glysoaminoglycans (GAG), are proven to be compatible as scaffolds, but potentially cause troubles in immunogenicity. Other forms of scaffolds that are currently being investigated include decellularized tissue extract, in which residual cellular/extracellular matrix is used as scaffolds.

Mesenchymal Stem Cells

Mesenchymal stem cells (MSC) are multipotent cells with the capacity to reproduce (independently) and differentiate into osteocytes, chondrocytes, and other types of mesodermal cells. MSC also releases pro-regenerative growth factors and cytokines that modulate immunity. MSC was first illustrated the 1960s by Friedenstein et al as cells from bone marrow that is able to replicate and form into new bones. It is only after 1991 International Society for Cellular Therapy (ISCT) the term ‘mesenchymal stem cells’ was introduced as derivable from fat, cartilage, and muscle isolates. ISCT defined a minimum of 3 criteria for MSC, which are: attached in the surface of plastic in standard culture , express CD105, CD73, and CD90 markers, do not express CD45, CD34, CD14 or CD11b, CD79α or CD19, and surface molecule HLA-DR, and able to differentiate into osteoblasts, chondroblasts and adipocytes in in vitro experiments.

Since then, MSC has been known to exist in blood vessels in almost every tissue in the body, including subcutaneous fat and adipose tissues. Other than fulfilling all the ISCT criteria, each MSC has different kinds of characteristics that show their origins, e.g. MSC from bone marrows in TGF-β-rich environment will differentiate into chondrocytes and form extracellular matrix of cartilages, while SPM in environments with TGF-β and BMP-6 will differentiate into cartilage.

CONCLUSION

Biological approach has been widely known for a while for orthopedic surgeons, but currently, it seems that this approach is slowly being left behind. It is shown from how many orthopedic surgeons only focus on mechanical problems without considering biological and other problems. When faced with musculoskeletal cases that involve massive loss of tissues, an orthopedic surgeon should employ comprehensive thinking and consider every modalities possible according to the problem. The importance of biological approach in treating bone fracture patients should be a shared concern and discussion, so there will not be any failure in therapy and treatment.