دور الخلايا الجزعيه فى تقويم النسيج الغضروفى

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Role of Stem Cells Therapy in Cartilage Tissue Repair

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الملخص العربى

إن الغضروف السطحى المفصلى هو نسيج عالى التخصص يوجد فى المفاصل حيث يغطى نهايات العظام المكونه للمفصل. ويعمل الغضروف على خفض الإحتكاك بين نهايات العظام.

يتكون النسيج الغضروفى من خلايا الكندروسيت و شبكه من الكولاجين بينما لا توجد أوعيه دمويه بالغضروف؛مما يجعل قدرة الغضروف للتصليح الذاتى محدوده.

وتعد أمراض الغضاريف من الأمراض التى إزدادت فى العصر الحديث مع زيادة العمر المتوقع للفرد؛ حيث أن معظم أمراض الغضاريف تحدث نتيجة تآكل الغضروف الذى يحدث مع تقدم العمرالذى يعرف بالتهاب المفاصل الضمورى أو تحدث بعد إصابات المفصل.

لذلك يعد علاج وإصلاح المفاصل من التحديات المعاصره فى مجال جراحة العظام بسبب النتائج الغير مرضيه لطرق العلاج الجراحيه الحديثه؛ لذلك بدأ البحث فى هندسة النسيج الغضروفى دور العلاج بإستخدام الخلايا الجزعيه كبد يل مستقبلى ناجح لعلاج أمراض الغضروف.

الخلايا الجزعيه هى الخلايا الأم التى لها القدره على التطور والتحوّر لتكّون اى نوع من الانسجه؛ وتوجد هذه الخلايا فى النخاع العظمى و النسيج الدهنى والعضلات.

ومن المتوقع ان العلاج بإستخدام الخلايا الجزعيه يحدث طفره فى علاج مختلف الامراض الصعبه فى مختلف فروع الطب.

وقد تم إستخدام الخلايا الجزعيه لإصلاح تشوهات الغضروف المفصلى فى حيوانات التجارب وجارى البحث الآن لتطبيقه فى علاج التهاب المفاصل الضمورى ومختلف حالات التهتّك الغضروفى.

الهد ف من البحث

مناقشة الصعوبات فى علاج امراض الغضاريف مع إلقاء الضوء علي الاساليب الحديثه.

مناقشة دورالعلاج بإستخدام الخلايا الجزعيه فى علاج امراض الغضاريف.

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ABSTRACT

Articular cartilage is a specialized, avascular, aneural connective tissue that provides covering for the osseous components of diarthrodial joints. It serves as a load-bearing material, absorbs impact and is capable of sustaining shearing forces. The unique properties of this tissue are related to the composition and structure of its extracellular matrix, which is composed mainly of a high concentration of proteoglycans (aggrecan) entangled in a dense network of collagen fibers and a large amount of water. This tissue allows the frictionless motion of the joint, in which it absorbs and dissipates load. The articular cartilage is composed of a sparse population of cells, named chondrocytes, which are responsible for the synthesis and maintenance of the extracellular matrix.

Cartilage injury remains a major challenge in orthopedic surgery due to the fact that articular cartilage has only a limited capacity for intrinsic healing. Cartilage impaction is followed by a post-traumatic inflammatory response. Chondrocytes and synoviocytes are activated to produce inflammatory mediators and degradative enzymes which can induce a progredient cartilage self destruction finally leading to secondary osteoarthritis (OA). However, an anti-inflammatory compensatory response is also detectable in cartilage by up- regulation of anti-inflammatory cytokines, probably a temporary attempt by chondrocytes to restore cartilage homeostasis.

Current data demonstrate the efficacy of treatment of various pathologies with the use of MSCs. Their application seems to be safe, without complications and ethical issues. MSCs and other similar progenitor cells can be isolated from a wide variety of tissue sources, thereby avoiding additional damage to diseased/injured tissues.

MSCs are a multipotent cell type capable of differentiating towards a number of lineages of the musculoskeletal system, including bone, cartilage and fat. This multipotential capacity was first described over three decades ago, and since then, the potential use of MSCs for regenerative therapies has generated tremendous excitement and focus. The attractiveness of MSCs for tissue repair is self-evident: in addition to their ability to take on multiple phenotypes, MSCs are readily expandable in culture and retain their multipotential characteristics with expansion.

Recent advances in cell biology and material sciences have contributed to tissue engineering becoming a promising therapeutic modality for the treatment of osteoarticular disorders. Cell-based strategies have not only proved the feasibility of such approaches for cartilage repair but have also provided acceptable clinical results. However, the available protocols are still far from being able to generate a tissue that is comparable to native cartilage with respect to quality and stability. Nevertheless, more-sophisticated approaches, which will combine the delivery of chondrogenic progenitors, in particular MSCs and bioactive growth factors, together with a chondro-conductive scaffold, will be required to achieve a complete healing of cartilage lesions. The success of these strategies will rely on a better understanding of the complex molecular events that are involved in induction of chondrogenesis and in maintenance of the chondrocyte phenotype because these events, which take place during embryogenesis, will have to be reproduced in adult tissue repair. This will lead to the identification of the exact factors needed for hyaline cartilage repair, including their bioactive levels and kinetics of application. Moreover, because most of these factors have short half-lives as recombinant proteins, gene transfer techniques could be adopted to achieve the desired results. Finally, cartilage repair will also require a complete integration of the neocartilage and reconstitution of an appropriate zonal organization for successful cartilage patterning.

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List of abbreviation

ACI: Autologous Chondrocyte Implantation

ACL: Anterior Cruciate Ligament

AMP: Adenosine monophosphate

AOT: Autologous Osteochondral Transplantation

AP: Alkaline Phosphatase

ARNT: Aryl hydrogen Receptor Nuclear Translocator

AT: Adipose tissue.

ATP: Adenine triphosphate

BDNF: Brain-Derived Neurotrophic Factor

BM: Bone Marrow

BMC: Bone Marrow-Derived Mononuclear Cells

BMPs: Bone Morphogenic Proteins

CD: Cluster of differentiation

CDMP1: Cartilage-Derived Morphogenetic Protein

CD-RAP: Cartilage-Derived Retinoic Acid-Sensitive Protein

CFU-f: Colony Forming Unit-Fibroblast

COMP: Cartilage Oligomeric Protein

COX-2: Cyclooxygenase -2

DNA; Deoxy Nucleic Acid

ECM: Extracellular matrix

ESCs: Embryonic stem cells

FGF: Fibroblast Growth Factor

GAGs: Glycosaminoglycans

GVHD: Graft-Versus-Host Disease

HA: Hyaluronic Acid

HIF: Hypoxia Inducible Factor

HRE: Hypoxic Responsive Element

HSCT: Hemopoietic Stem Cell Transplantation

ICRS: International Cartilage Repair Society

IGF: Insulin-Like Growth Factor

Ihh: Indian hedgehog

IKDC: International Knee Documentation Committee.

IL-1b: Interleukin-1b

iPSCs: induced Pluripotent Stem Cells

MMPs: Matrix metalloproteinases

MRI: Magnetic Resonance Imaging

mRNA: messanger Ribonucleic Acid

MSCs: Mesenchymal stem cells

NO: Nitric oxide

NOS: Nitric oxide synthase

PBC: Peripheral Blood-Derived Mononuclear Cells

PDGF: Platelet-Derived Growth Factor

PPAR-γ: Peroxisome proliferator-activated receptor-gamma

PTHrP: Parathyroid Hormone-related Protein

RA: Rheumatoid arthritis

ROS: Reactive oxygen species

SCID: Severe Combined Immunodeficiency

SOX9: Sry-related HMG(high mobility group) box-9

TGF-β: Transforming growth factor -β

TIMPs: Tissue inhibitors of metalloproteinases

TNF: Tumor necrosis factor

UCB: Umbilical cord blood

VAS: Visual Analogue Scale

VEGF: Vascular Endothelial Growth Factor

Wnt: Wingless family

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Introduction

Articular cartilage is a highly specialized tissue that reduces joint friction at the extremities of long bones. It consists of chondrocytes, some progenitor cells and an extracellular matrix (ECM) that is composed of a network of collagens, in particular type II collagen, which gives the tissue its shape and strength, and proteoglycans, which give resistance to mechanical stress[1]. When damaged, the articular cartilage has a limited capacity for repair due to the absence of vasculature, which would allow progenitor cells from the blood or the bone marrow to enter the tissue.

Repair of full thickness articular cartilage defects remains a major challenge in the field of orthopedic surgery because of the unsatisfactory outcomes of current surgical strategies, mainly chondrectomy, subchondral drilling, periosteal or perichondrial resurfacing and transplantation of autochondrocytes [2]. Each of these treatments has its own limitations and in most cases the repaired tissues are fibrocartilage rather than hyaline cartilage, which usually results in degenerative changes with pain after a long-term follow-up. As an alternative to those current therapies, tissue engineering has been demonstrated to own promising therapeutic advantages in restoring both the structure and function of the damaged articular cartilage.[3]

Mesenchymal stem cells (MSCs) are non-hematopoetic, pluripotent, stromal cells that exhibit multi-lineage differentiation capacity being capable to give rise to diverse tissues, including bone, cartilage, adipose tissue, tendon and muscle[4]. They can rapidly divide and form colonies. MSCs are present in many adult mesenchymal tissues, such as synovium, muscle, adipose tissue and bone marrow. MSCs are usually isolated from bone marrow, but may be obtained from muscle, adipose or synovial tissues and can be amplified ex vivo without loss of phenotype or multi-potentiality. [5]

MSCs have been used in vivo to repair full-thickness joint cartilage defects in animal models using various carrier matrices [6]. Recently, autologous bone-marrow-derived MSCs have been applied to patients with osteoarthritis. MSC therapy for cartilage repair, which probably requires both cartilage regeneration and MSC immunoregulatory effect, may play a role in reducing arthritis signs and symptoms due to inflammatory reaction [7]. Finally, MSCs have been successfully used for intervertebral disc regeneration in a rat model .[8]

The aim of this review is:

1- To discuss challenges in treatment of cartilage injury and degeneration and the role of emerging strategies of tissue engineering.

2- To discuss the possible future role of stem cell therapy on treatment of degenerative cartilage diseases.