# 英语学习与文献汇报

English learning & Literature reviewing

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2019-12-04

# *Association between cytokines and exosomes in synovial fluid of individuals with knee osteoarthritis*

膝关节骨性关节炎患者滑膜液中细胞因子与外泌体的关系


2019 Modern Rheumatology (IF 1.97)

# *The potential of exosomes in the therapy of the cartilage and bone complications; emphasis on osteoarthritis*

外泌体在骨与软骨相关疾病中的可能治疗作用：着重于骨关节炎

Life Sciences 236 (2019) 116861

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie


Review article

## The potential of exosomes in the therapy of the cartilage and bone complications; emphasis on osteoarthritis

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ARTICLE INFO

*Keywords:*
Extracellular microvesicles

ABSTRACT

Osteoarthritis is a prevalent worldwide joint disease, which demonstrates a remarkable adverse effect on the patients' life modality. Medicinal agents, exclusively nonsteroidal anti-inflammatory drugs (NSAIDs), have been

2019 Life Sciences (IF 3.448)

# *Introduction*

- Osteoarthritis (OA) affects about 10% of men and 18% of women over the age of 60. The symptoms of OA chiefly occur in the knee and hip bone as well as the soft-tissue framework in around the joint.
- Prevalent pharmacologic remedy for OA include some monoclonal an-tibody like as Tanezumab (against nerve growth factor) and acet-aminophen, sprifermin/recombinant human fibroblast growth factor-18, and Nonsteroidal anti-inflammatory drugs (NSAID)
- Not  suitable alternatives treatment for Surgery

# *Introduction*

- Various signaling pathways like paracrine and endocrine play a key role in retaining cellular and molecular homeostasis, and can lead to the onset and spread of many diseases.
- Some soluble factors like growth factors, chemokine and cytokines, are the main form of paracrine communication approaches between cells.
- Extracellular vesicles　Evs 细胞外载体
- Especially exosomes 外泌体, have been identified as another important intermediate cell mediator

# Evs 细胞外载体

**Table 1**
Classification of extracellular vesicles.

| Type of vesicles | Exosomes | Microvesicles | Apoptotic bodies |
|---|---|---|---|
| Origin | Endosomes from many cell types | Plasma membrane of many cell types | Plasma membrane from endoplasmic reticulum |
| Size | 40–100 nm | 50–1000 nm | 50–4000 nm |
| Density | 1.12–1.22 g/cm$^3$ | None | 1.17–1.29 g/cm$^3$ |
| Markers | CD9, CD63, CD81, CD82, Alix, TSG101, HSP 70, flotilin-1 | Integrin, CD40 metalloproteinase, Selectin, flotilin-2 | Phosphatidylserine and histones |
| Lipids | Ceramide, cholesterol, sphingomyelin and lysophosphatidic acid | Cholesterol | Phosphatidylserine |
| Molecular cargo | mRNA, miRNA, nc RNAs, mtDNAs | mRNA, miRNA, nc RNAs, mtDNAs | Nuclear fractions and cellular organelles |
| Reference | [7] | [8] | [9] |

外泌体——多种细胞类型的内含体

微囊泡——多种细胞的质膜

凋亡小体——来自内质网的质膜

# *Introduction*

- Exosomes can be used as potential biomarkers for early diagnosis of cancer, as well as drug carriers (for gene therapy) in the treatment of malignancies.
- In recent years, other applications has been introduced for exosome, including promoting the regeneration of tissues, bone and cartilage healing, and reducing the risks of direct stem cell transplantation (immune rejection and cell renewal capacity).
- cartilage and bone regeneration with the help of exosomes

# *Methodology*

- Criteria for considering studies for this review
- Types of studies
- 对观察性研究(前瞻性和回顾性)、实验研究和准实验研究、横断面研究
- 纳入标准为：(1)外泌体治疗软骨和骨并发症；(2)外泌体治疗骨关节炎；(3)外泌体治疗骨折愈合。
- Search strategy
- MEDLINE (PubMed)
- keywords
- “exosomes; osteoarthritis; cartilage and bone complications, bone fracture healing”.

# 3个方面

- 1. Characteristics of exosomes
- 外泌体的特征
- 2. The potential of exosomes in treatment of OA
- 外泌体在OA治疗中的潜力
- 3. Bone fracture healing by exosomes
- 外泌体在骨折愈合中的应用

# *Characteristics of exosomes*

- The production of exosomes initially begins with the penetration of micro domains with a clathrin coating on the cell membrane.
- Exosomes stem from the endosomes, which originate from endocytosis of the cytoplasmic membrane. Then a number of substances, such as the coating of two-layer lipid-enriched with cholesterol, sphingomyelin, and ceramide, are added to these vesicles and, eventually exosomes are released.

# Characteristics of exosomes

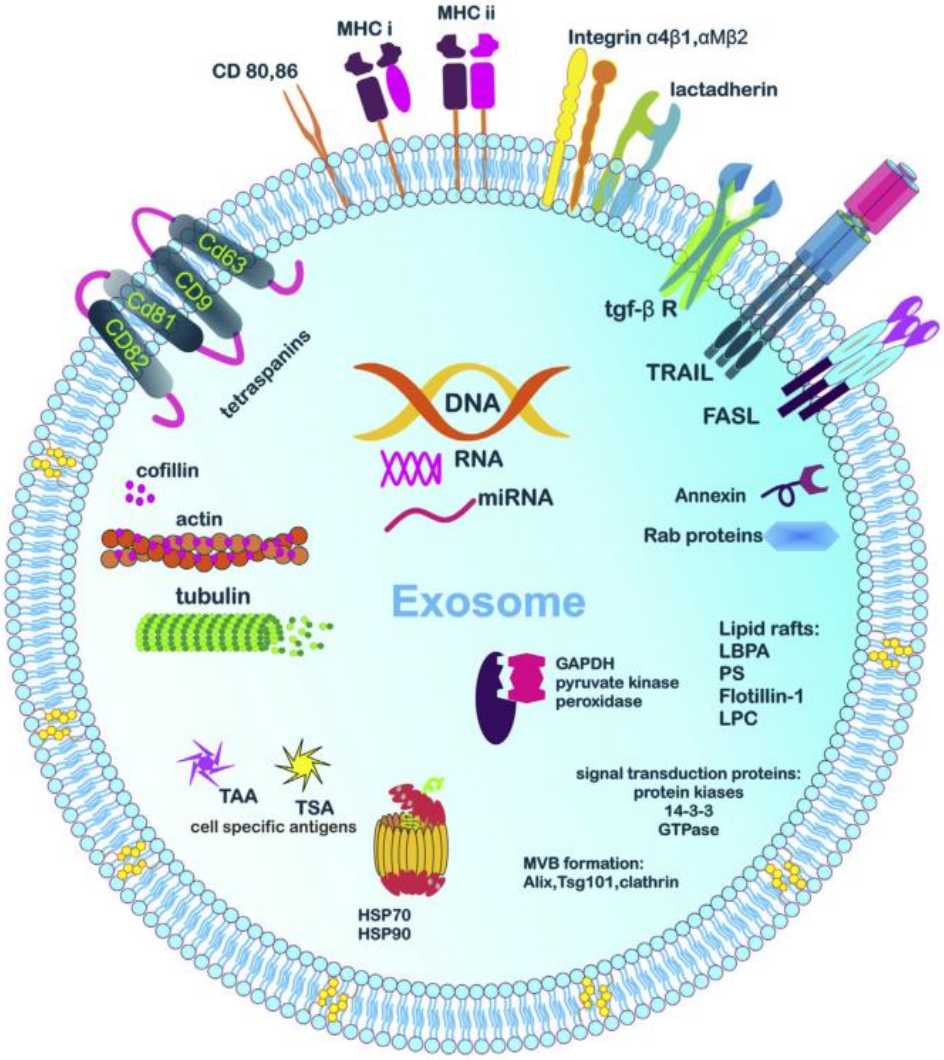



**Fig. 1.** Exosome molecular composition.

# *Characteristics of exosomes*

- At first, exosomes were considered as useless cellular metabolic waste, and then, with subsequent studies, more functions were discovered.
- Exosomes impress the target cells by several approaches.
- Exosome secretion can be accelerated by various chemical substances, environmental conditions (low pH and oxygen), and mechanical excitation.

# *Characteristics of exosomes*

- Isolation of exosomes is a challenge and it is necessary to achieve an optimal purity before any therapeutic application.
- The EVs isolation is carried out by several methods including, density gradient, commercially kits, centrifugation, and then are recognized through particular biomarkers.
- After isolation, exosomes are used in several ways in regenerative medicine.

# Characteristics of exosomes

**Table 2**
Comparison of exosome isolation techniques.

| Isolation technique | Ultracentrifugation based techniques | Exosome precipitation |
|---|---|---|
| Isolation principle | Density, size, and shape based | Altering the solubility of exosomes |
| Advantage | Cost-effective and feasible for Large sample and yields have great quantities of exosomes | Easy and does not need advanced equipment, Potential for high capacity utilization |
| Disadvantage | Costly equipment, time-consuming, low portability, not available everywhere, high speed centrifugation may affect the exosomes | Co-sedimentation of other non-exosome such as proteins and polymeric materials, time-consuming and need pre-and post-cleanup |

| Size-based techniques | Microfluidics based technique | Immunoaffinity capture-based techniques |
|---|---|---|
| Entirely based on the size diversity between exosomes and other extra cellular particle | Based on a variety of exosomes features like immunoaffinity, size, and density | Based on specific interaction between exosomes membrane-bound antigens and immobilized antibodies |
| Fast, does not need advance equipment, good portability, high-purity yield | Fast, low costs, portable | Appropriate for specific exosomes isolation, extremely purified yield much better than other techniques |
| Moderate exosomes purity, Entering shear stress, exosomes loss owing to sticking to the membranes, need precise equipment, not suitable for large volumes | In general, it is not a standard method and is not suitable for large-scale experiments on clinical specimens | High reagent cost, low capacity and yields, the antigenic epitope may be blocked or masked. |

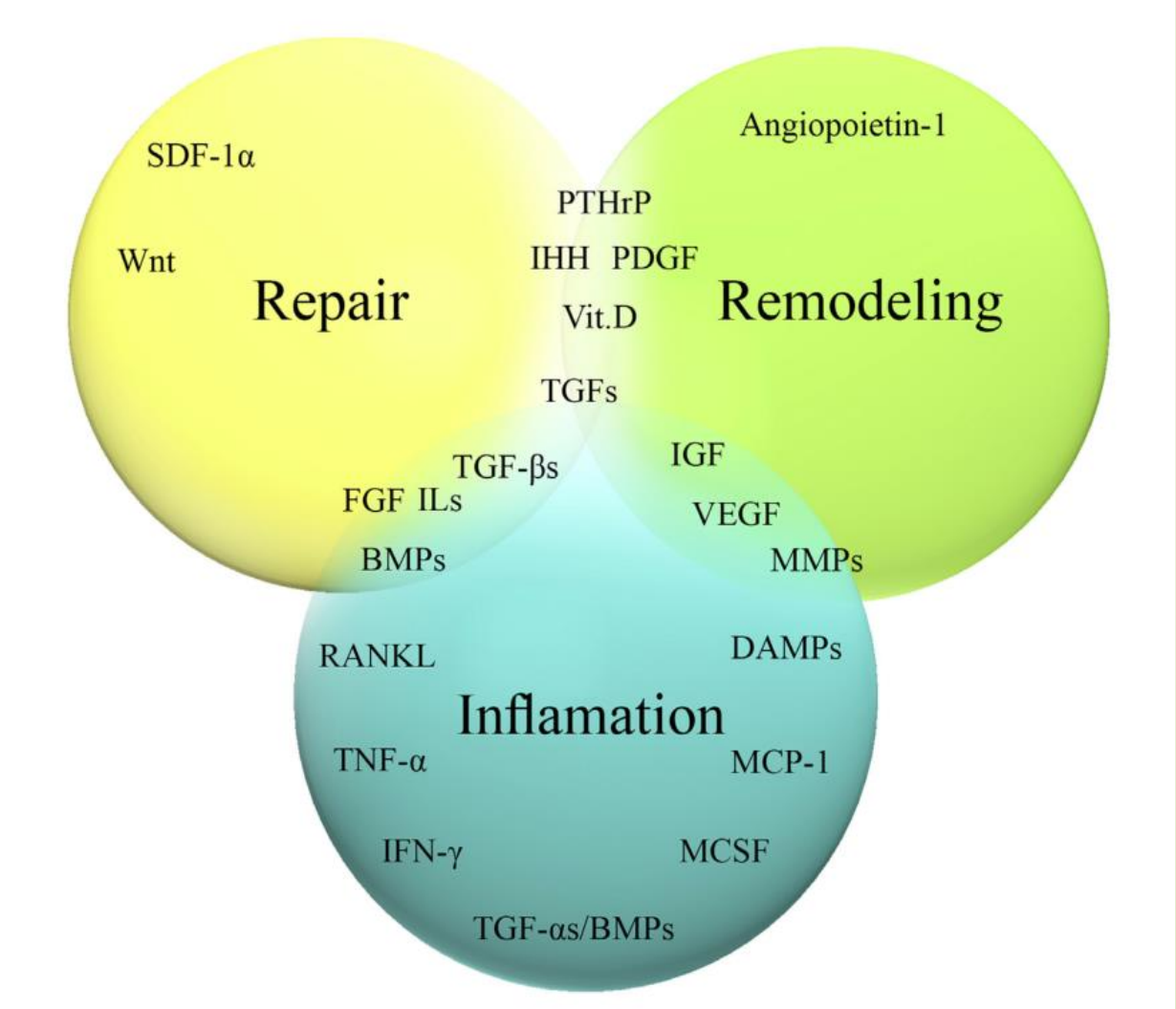
# *The potential of exosomes in treatment of OA*

- Pathological symptoms include bone destruction, bone margin expansion or along joint margins (osteophytes), increased subchondral bone thickness, and inflammatory conditions. These diseases may also disbalance bone regeneration, which increases the risk of bone fractures.
- The precise etiology of OA is unknown, but there is evidence that loss of cartilage matrix ingredients structural macromolecules, such as proteoglycans (PGs) and collagens due to an excessive activation of extracellular proteinases, and decreased synthesizing of new matrix for repair, is involved.

# *The potential of exosomes in treatment of OA*

- Osteoclasts have a key role in bone resorption. Two cytokines such as macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor-κB ligand (RANKL) are involved in osteoclastogenesis.
- Osteoclast-derived exosomes cause the formation of osteoclasts in vitro and also prevention of osteoclastogenesis process.
- Various transcription factors, signaling pathway, and co-regulators play an essential role in modulation of osteoblastogenesis.
- Osteoblasts-derived exosomes improved bone regeneration via upregulating Runx2 and alkaline phosphatase.

# *The potential of exosomes in treatment of OA*



# *The potential of exosomes in treatment of OA*

- If specific miRNAs could reduce inflammation or tissue destruction in OA, they could be packaged in exosomes or nanoparticles to treat OA patients.
- Human synovial mesenchymal stem cells-derived exosomes (hSMSCs) obviously stimulated chondrocyte proliferation and migration.
- Exosomes derived from MSCs had immunosuppressive properties, which lead to declining T and B lymphocyte proliferation, and also inducing regulatory T (Treg) cell differentiation.

# *The potential of exosomes in treatment of OA*

- Mao and colleagues observed that miR-92a-3p in exosomes cargo interfered with the cartilage growth and degradation through Wnt5a signaling pathway.
- Other studies have found that miR-92a-3p correlates with SRY-box 9 (SOX9) and collagen type II alpha 1 chain (COL2A1) overexpression, and also cause a delay in the progression of OA through ADAMTS4 and ADAMTS5 inhibition.

# *Conclusion*

- This review paper concentrated on the recent methods towards the exosome's application in the cartilage and bone repairing procedure. In recent years, the studies that have been done in this regard are very promising, while some problems are still existing.
- The use of natural carriers like as exosomes has some advantages and disadvantage than synthetic carrier agents (liposomes or any kind of nanoparticles).

# Conclusion

- 外泌体与合成载体制剂（脂质体、纳米颗粒）
- 毒性或免疫源性较低、稳定、可长期维持、免疫排斥反应风险低
- 外泌体具有很高的临床给药潜力
- 合适的细胞源获得外泌体
- 高效的、适合再生、大量可用、大规模分离提纯的可能性、储存条件


感谢各位老师、师兄弟的收听，欢迎提问！