Future of Cartilage Surgery

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CURRENT TREATMENT OPTIONS AND LIMITATIONS

Early Treatment Options & Limitations

Treatment	Limitation
Lavage / Debridement	Palliative only, No repair tissue
Marrow stimulation (microfracture)	Fibrocartilaginous repair, Deterioration with time
Osteochondral autograft transplantation	Technically demanding, Deterioration with time, Donor site morbidity
Osteochondral allograft transplantation	Expensive, Histocompatability, Disease transmission, Ethical consideration
Autologous chondrocyte implantation (ACI)	Invasiveness, Necessity of 2 stage procedures, Long postoperative rehabilitation, Donor site morbidity
: 1st generation ACI	Adverse effects: graft delamination, hypertrophy Chondrocyte dedifferentiate during culture

Newly-developed Treatment Options : Cartilage Tissue Engineering

1) Scaffold-associated chondrocyte implantation: 2nd generation ACI
2) Characterized chondrocyte implantation (CCI): 3rd generation ACI
3) Cartilage autograft implantation
4) Neocartilage Implantation
5) Osteochondral graft substitute

Limitations / Challanges for tissue engineered cartilage[1-4]

: *remains controversial, unpredictable, imprecise indication, and at times impractical*

1) Invasiveness, donor site morbidity
2) Need 2-step procedures that include an arthroscopic biopsy, cell cultivation, and subsequent implantation
3) Limited to small cartilage lesion
4) None of the current treatment options have regenerated persistent, long-lasting hyaline cartilage tissue
5) Biological obstacles1,2
   : Differentiation insufficiency, loss of transplanted cells or tissues, matrix destruction, integration failure

FUTURE PERSPECTIVES

1. Bioactive factors

- Gene therapy concept
- Candidate factors
  - morphogens and transcription factors: promote differentiation along chondrogenic lineages
  - growth factors: promote matrix synthesis, inhibitors of osteogenic, hypertrophic differentiation,
  - antagonists: inhibit apoptosis, senescence or responses to catabolic cytokines
- Toward 1-step surgery: avoids the first surgery for cartilage biopsy and chondrocyte cultivation
- Problems: "*Drug Delivery*"
  - getting high enough concentrations of substrate to the local tissue for a prolonged time
  - appropriate factors being delivered at the correct time

  ➜ Needs proper scaffold-created controlled release of biological factors
- Combination of multiple growth factors?
  - To enhance cartilage growth, factors commonly work in tandem with TGF-βs[5]
  - TGF-βs + BMP-6[6], IGF-1[6], FGF-2/PDGF[7] → chondrogenesis ↑
  - cf. combined effect of multiple growth factors is not always favorable[8-10]
- Which is the best bioactive factor

2. Nanotechnology

- Nanofibers: morphological similarities to natural ECM → promise as a scaffolding material

- Superior physiochemical properties
  - surface area
  - surface roughness
  - surface area to volume ratios
- "Zonal cartilage tissue engineering"[11,12]
  - Artificially mimic the zonal organization of articular cartilage
  - Employing organ printing technique[11-13]
- Carbon nanotube composite → support chondrocyte proliferation and ECM synthesis[14]
- MSC chondrogenesis within an electrospun polycaprolactone nanofibrous scaffold[15]
- Multilayer gradient nano-composite scaffold → chondrogenesis ↑ with/without chondrocyte[16]

3. Stem cells

- Primary chondrocytes
  - Limited supply, need for a surgical procedure
  - Unstable in monolayer culture
  - Old chondrocytes have much lower ability to build cartilage than young ones[17]
- MSCs: Bone marrow, adipose tissue, muscle, periosteum, synovium
- Ease of availability, relatively non-invasive, high capacity of in vitro expansion
- Toward 1-step, less-invasive surgery
- Scaffold-free tissue engineered construct[18,19]
  - Human synovial MSCs cultured in medium with Asc-2P → self-supporting mechanical properties
  - Advantages: safe, cost-effective, less-invasive and quick surgical time
- Major advantage: simplicity, low cost[4]
- Embryonic stem cells
- Induced pluripotential stem cells[20]
  : Somatic cells reprogrammed to pluripotent cells via transfection of stem cell-associated genes

4. Platelet-Rich Plasma (PRP)

- "Biological solution for biological problems"[21]
- Natural cocktail of growth factors in concert to accelerate healing and restoration of damaged tissues[22]
- Potential for a "one-stop", intraoperative, cost-effective, practical method for

introducing and capturing "growth factors" within an operating room setting

- Conservative biological treatment for OA?
- Intra-articular injection of PRP→chondrogenesis ↑ [21,23]
  cf. PRP/chondrocyte composite in goat model[24]
  - Implanted beneath periosteal flaps: hyaline-like tissue
  - Not implanted under the periosteal flap: dislodged
  ➜ Essential need for mechanical stability (scaffolds)

* PRP + stem cells: acting as a sources of growth factors and "working cells"[25]

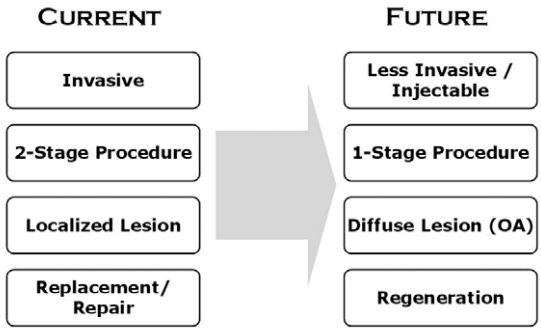
5. Cartilage tissue engineering for degenerative joint disease

- Currently, outcomes of tissue engineering methods in degenerative joint disease is inferior[26]
- Not only a problem of cartilage → must be focused also to inflammation and mechanical issue[27]
- Persistent high levels of synovial fluid markers after cartilage repair → resurfacing alone cannot stop the disease progress[28]
- Conservative treatment and joint reconstruction before applying tissue engineering technology[29]
- Needs to promote the anabolic events over the catabolic degenerative mechanisms
  - BMP-7: strong pro-anabolic / anti-catabolic activity → highest clinical potential at the moment[30]
  - PRP: sustained growth factors release → preventive effects against OA progression[31]
  - Stem cells: intra-articular injection of MSCs to an OA knee → regeneration of articular cartilage[32]

6. Novel approaches with less-invasive procedure[33]

- Magnetically labeled MSCs injected
  → Accumulated to the desired osteochondral defect site under the direction of an external magnetic field

From laboratory to clinic: should be safe, efficient, and as simple as possible



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