Do we rebuild a real ligament?

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Ligamentization

- Still a matter of debate

Basic science

Graft healing

- Inflammatory phase
  - Proliferative phase (4-12th wk.)
  - Ligamentization phase (12- ... th wk.)

Amiel et al. J Orthop Res 1986

Basic science

- Early healing phase
  - Central acellularity and necrosis
  - Influx of host cells
    - Inflammatory cells
    - Fibroblasts
  - Complete replacement of viable graft cells by host cells around 2-4 weeks in animal models
  - No revascularization

Kobayashi et al. Trans Orthop Res 2005

Basic science

- Proliferation phase (4-12 wks)
  - Increased cellularity with proliferation of fibroblasts - myofibroblasts
  - Loss and reformation of collagen crimp
  - Revascularization
    - Increased collagen type III / fibrinectin
    - Increase smaller diameter collagen fibrils
    - Increased GAG content

proliferative

reparative
**Basic science: Proliferation phase (4-12 wks)**

- Recellularization (4-12 wks)

**Basic science: Revascularization (4-12 wks)**

- Revascularization (4-12 wks)

**Basic science: Proliferation phase (p-12 wks)**

- Revascularization

**Basic science: Ligamentization phase (12-... wks)**

- Remodeling phase:
  - Structural and mechanical adaptation
  - Increased in collagen content
  - Non-reducible/reducible cross-link ratio increase

Kirkendall et al. J Orthop Res 1986
Scheffler et al. Arthroscopy 2008

**Biology**

- Favorable vascularization
- Cellular repopulation
- Matrix remodeling
- The ultimate small diameter collagen fibril orientation
- Final cross-sectional area of the graft

**Original ACL versus graft**

- Similar macro-morphology within 6 to 12 months
- More type III collagen in the graft
- Unimodal pattern of small collagen fibers
- Crimp frequency remain increased in the graft
- In animal model, graft strength could never surpass 50-60% of the intact ACL

Ahn et al. Arthroscopy 1995
Jackson MR, Crenshaw MB 1995
Scheffler et al. Curr Orthop 2000
**Original ACL versus graft**

- Collagen crimp pattern
- Sheep model
- Polarized light microscopy x200

**In human**

- Some healing phases:
  - Graft necrosis, recellularisation, revascularization, ligamentization
  - Remodeling is reduced
  - Less necrosis (no more than 30%)
  - Not all intrinsic grafts cells replaced by extrinsic cells
  - Large area of normal collagen alignment and crimp pattern
  - No excessive revascularization

**Biological process**

- In animal models, the graft undergoes a process of adaptation rather than full restoration of the intact ACL's biological properties.

  - Law of functional adaptation
  - William Bauce:
    - An organ will adapt itself structurally to an alteration, quantitatively and qualitatively in function

**What we know!**

- MECHANICAL ENVIRONMENT
  - Placement of the graft
  - Tensioning
  - Rehabilitation
  - Patient compliance
  - It takes time...

**How about "bundles"**

- V. H. basketball player 29 y old
  - ACL BPTB
| V. H. basketball player 29 y old ACL BPTB, 5 years post-ACL rec |
| V. J. 38 y old capoeira, 4 years post ACL-rec, partial ACL rupture |

### How about “bundles”

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### In summary

- The ligamentization process is an adaptative transformation of the graft which does not lead to a full restoration of the intact ACL’s biological properties.
- Biological response is related to the biomechanical and biochemical environment into which the graft is placed.
Epidemiology
- 1 ACL reconstruction/2000 inhabitants in US
- 200'000 ACL rupture/year in US
- 120'000 TKR/year
  Steinert et al Orthop Res Society San Francisco 2008
- 31'000 ACL reconstructions/year in France
  Symposium French Society of Arthroscopy Lyon 2007

ACL failure
- Functional instability with sports or activities of daily living
- Increased pain
- Loss of motion
- Recurrent episodes of giving way
- SSD diff. > 5 mm, Lachman et pivot positive

Graft necrosis
- Released of cytokines
  - Matrix metalloproteinase (MMP-3)
  - Tissue inhibitor metalloproteinase-1 (TIMP)-1
  - Interleukin-6 and 8 (IL-6, IL-8)
  - Tumor necrosis factor alpha (TNF-α)
  - IL-1
  - Nagash et Orthop Med 2006
- Extended necrosis
- Collagen disturbance
- Myxoid degeneration
- Interfering process of revascularization

Vascularization
- Overtensioning of the graft
- Patients habits:
  - Smoking, cocaine consumption
  - Diabetes
- Choice of the graft
- Hypoxia
  - Period of avascular necrosis – decrease in VEGF expression

Cells repopulation
- Vascularization
- GF cascade: TGF-β, b-FGF, PDGF
- Age?
- Genetic background?
  - Fast healer?
  - Slow healer?
  - Kuroda et al KSSTA 2000
Matrix remodeling

- GF cascade: TGF-β, b-FGF, PDGF
- Vascularization
- Cell repopulation
- Age ?
- Genetic background ?
  - Fast healer ?
  - Slow healer ?

Kurita et al. KSSTA 2000