Basics of Regenerative Medicine: from PRP to stem cells

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I have no conflicts of interest with regards to this presentation.

Objectives

- Pathophysiology of chronic orthopedic injuries
- Definition of regenerative medicine
- Definition of platelet rich plasma
- Definition of stem cells
- Benefits of orthobiologics

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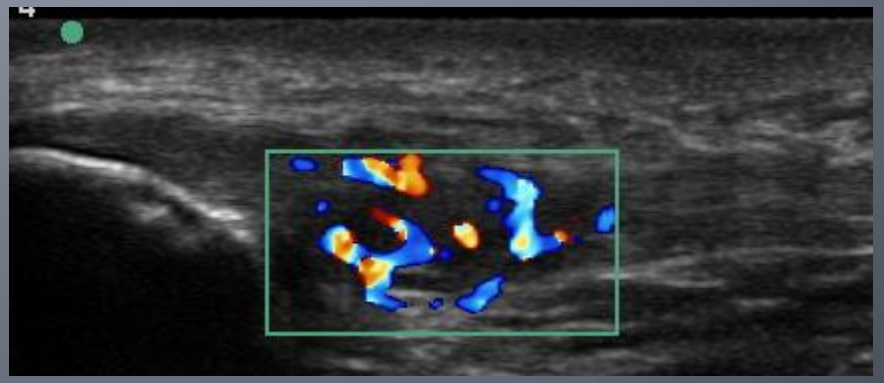
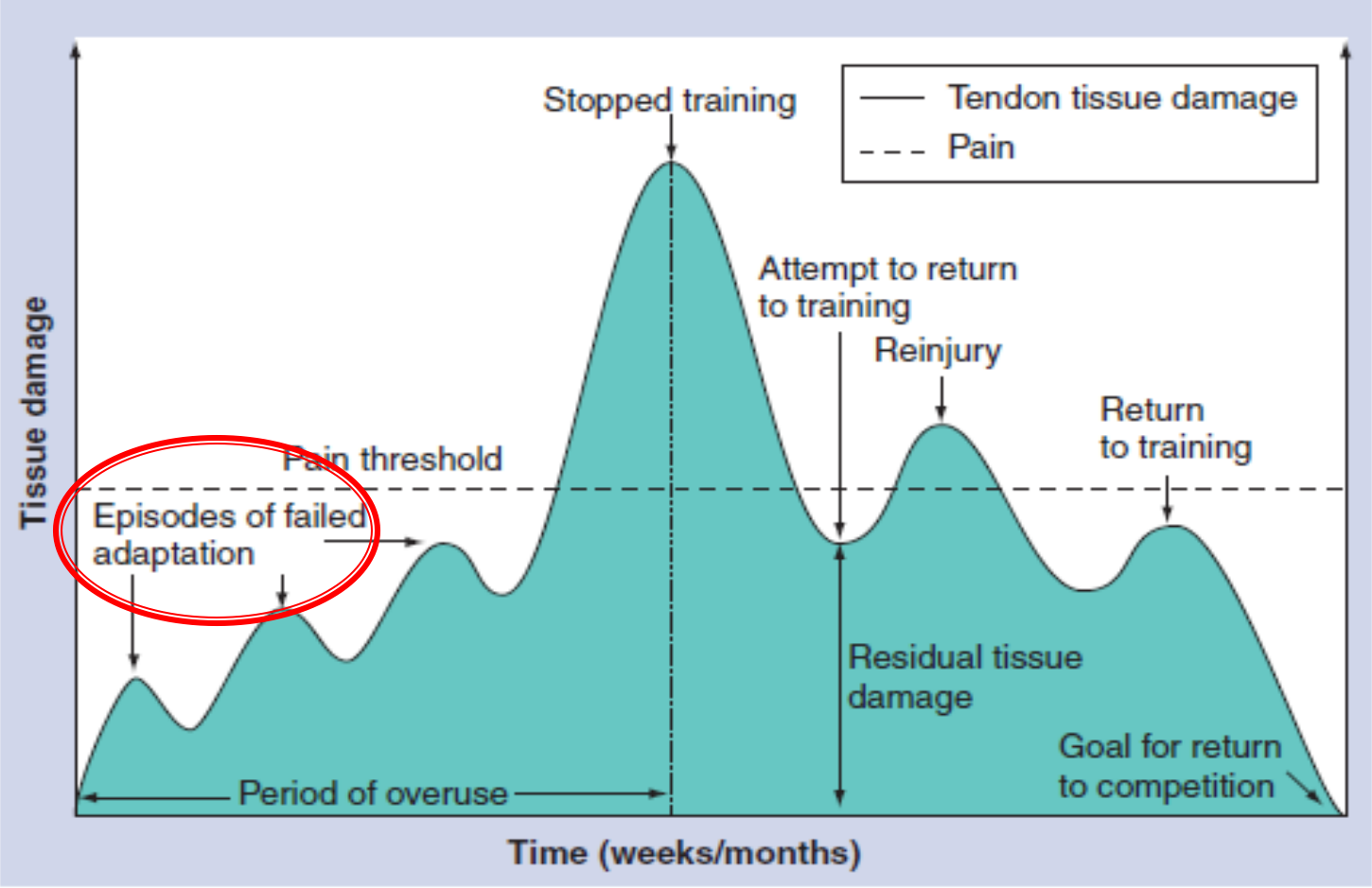
Pathophysiology of chronic orthopedic injuries



Why do tendons, ligaments and cartilage develop chronic injuries? The Overuse Theory



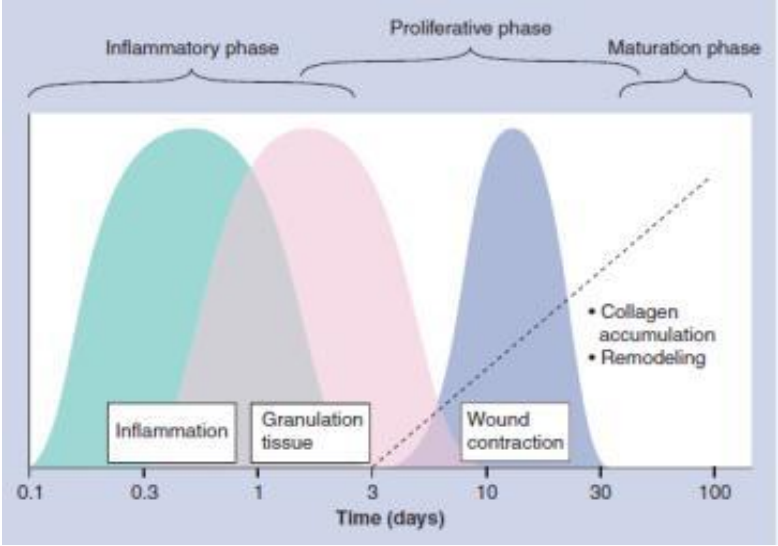
Historical Approach to Chronic Orthopedic Injuries

- The treatment of chronic injuries to this day still frequently focuses on treating perceived inflammation.
  - Oral anti-inflammatory medications, ice, etc.
  - Cortisone injections are commonly offered

    –> Provide short-term relief but may interfere with the tissue healing

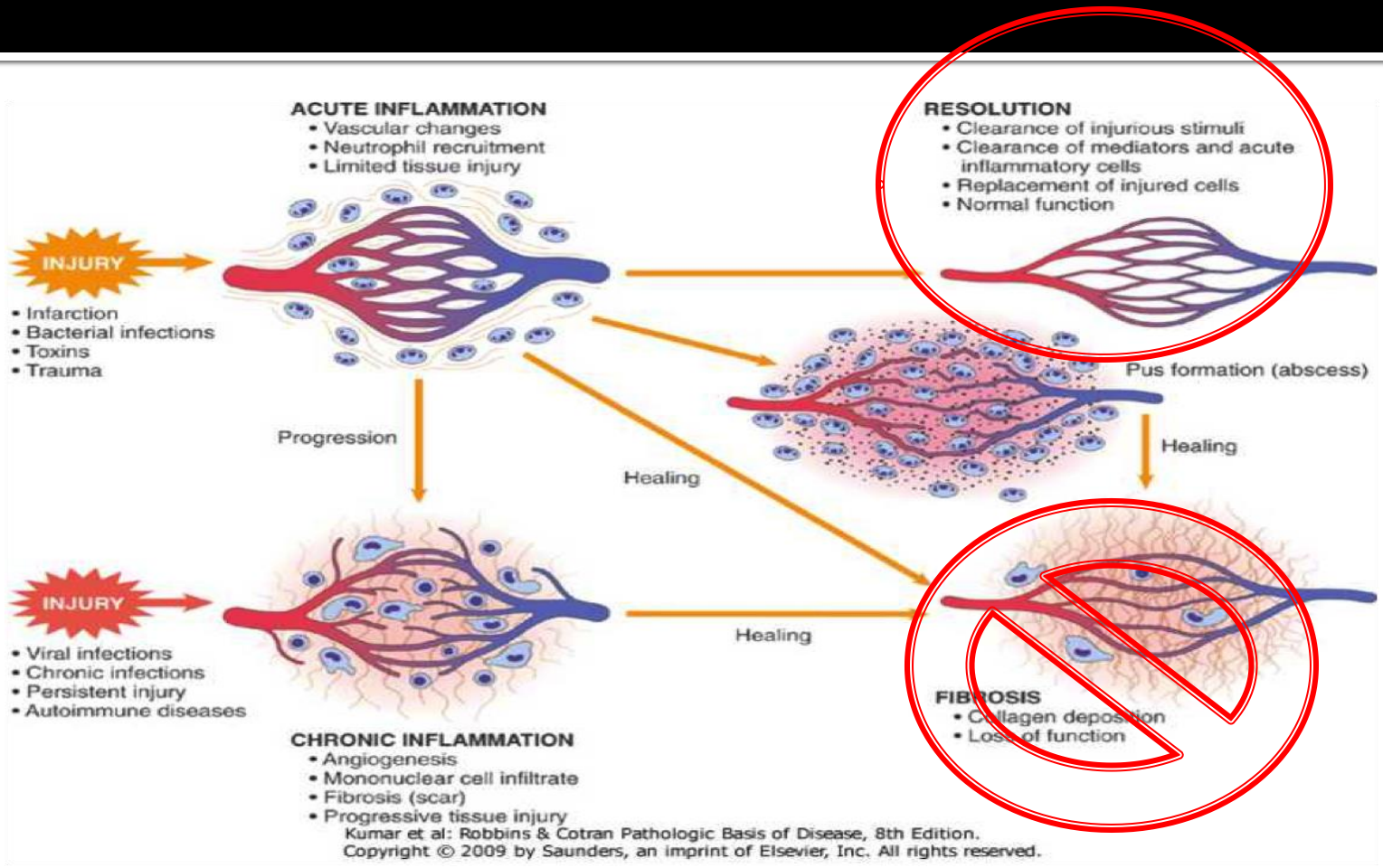
- Those considered cured (because their pain lessened) often have:
  - residual structural weakness
    - Tendon tears
    - Calcifications
    - Poor collagen deposit
  - Re-injury occurs with return to play

The three stages of tissue healing



- The inflammatory cascade (the first 3 days) stimulates the healing process of the injured tissue.
- If the Inflammatory Phase is blocked, then the tissue will not enter the proliferative phase and maturation phase of tissue healing.
- If the injury is past the Inflammatory Phase, why do we treat with NSAIDs and CSI?

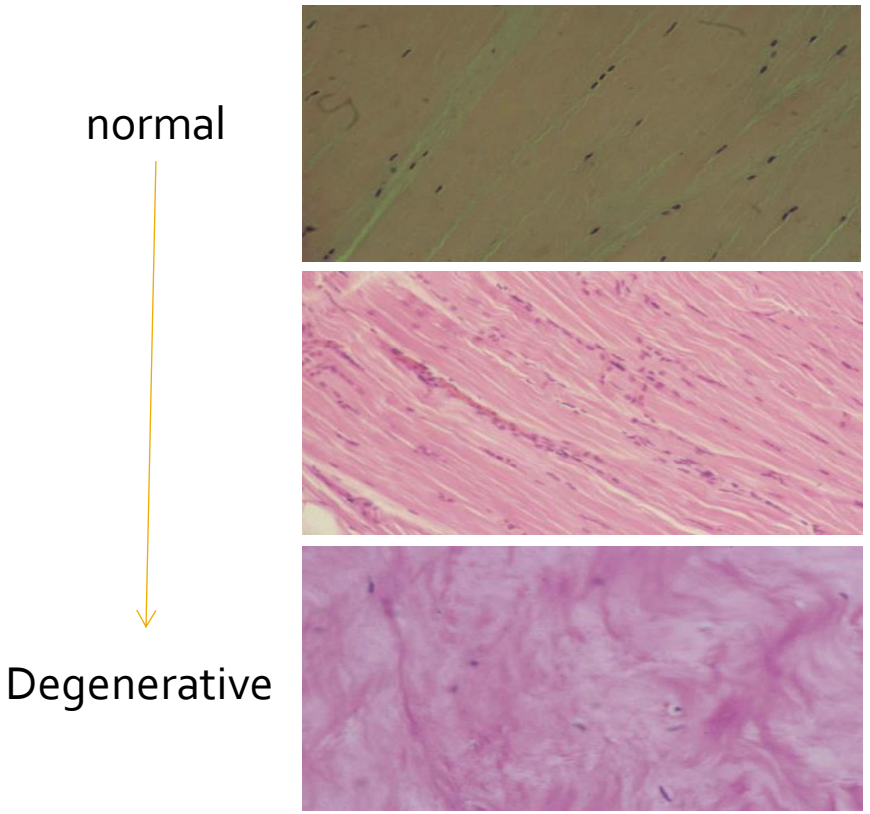
Pathologic Tissue Changes



- Tendons with impaired healing develop scar tissue fibrosis, pathologic neovessels, and degenerated collagen that hinder the normal tissue function.

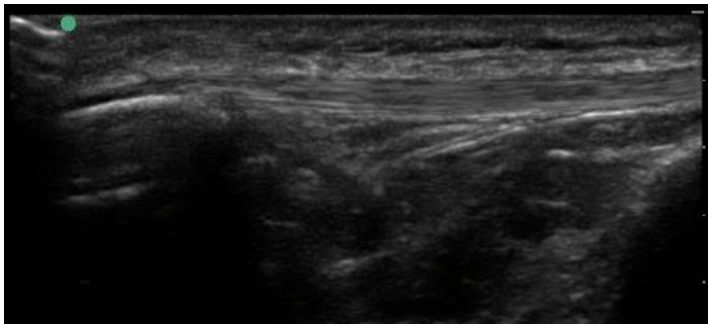
Histology of Tendinosis

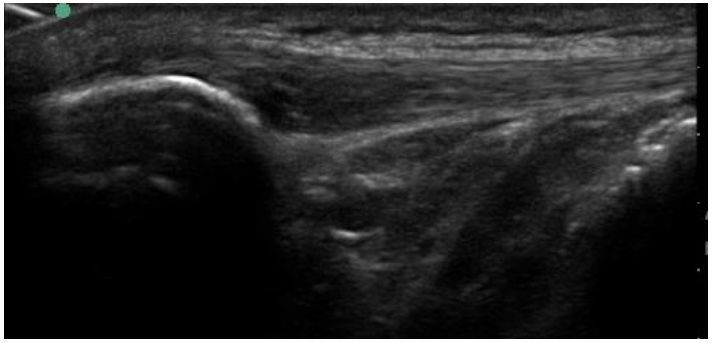
- Chronically injured tendons develop:
  - Degenerated collagen
  - Fibrosis and calcifications
  - Neovessels
  - Lack of inflammatory cells

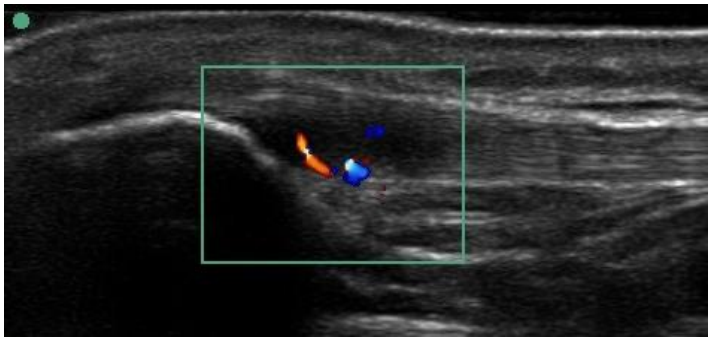


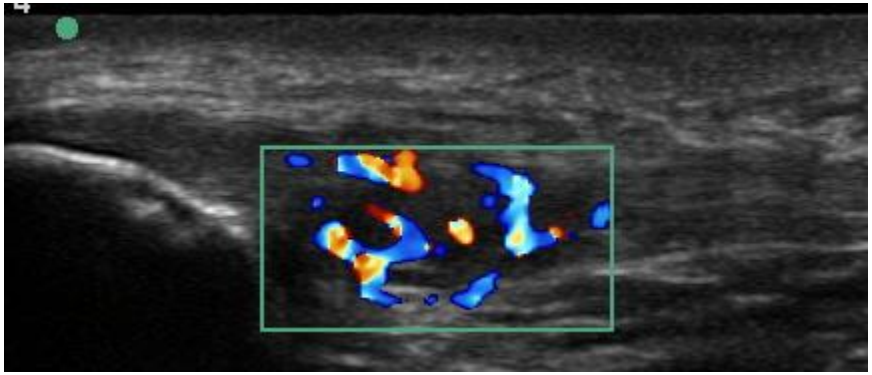
J.D. Rees et al. *Rheumatology*, May 2006

Ultrasound of Abnormal Neovessels

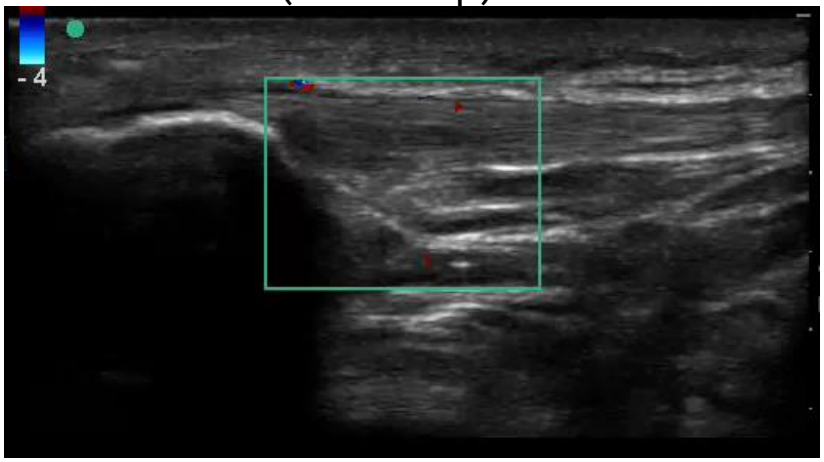






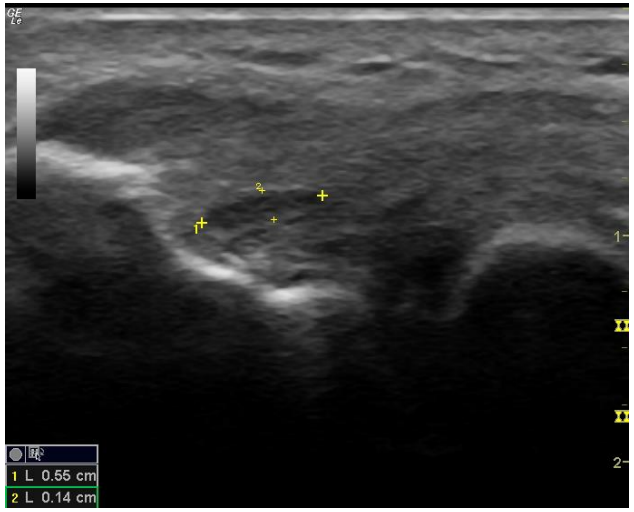


(video clip)



56 y/o male with an intra-substance tear at the lateral epicondyle

- The tear probably occurred from one of the steroid injections performed, injecting into the injured tendon.
  - Similar cases are seen with "greater trochanter bursitis" that progress to partial gluteus medius tendon tears after consecutive cortisone injections. It was probably tendinitis/osis from the beginning…



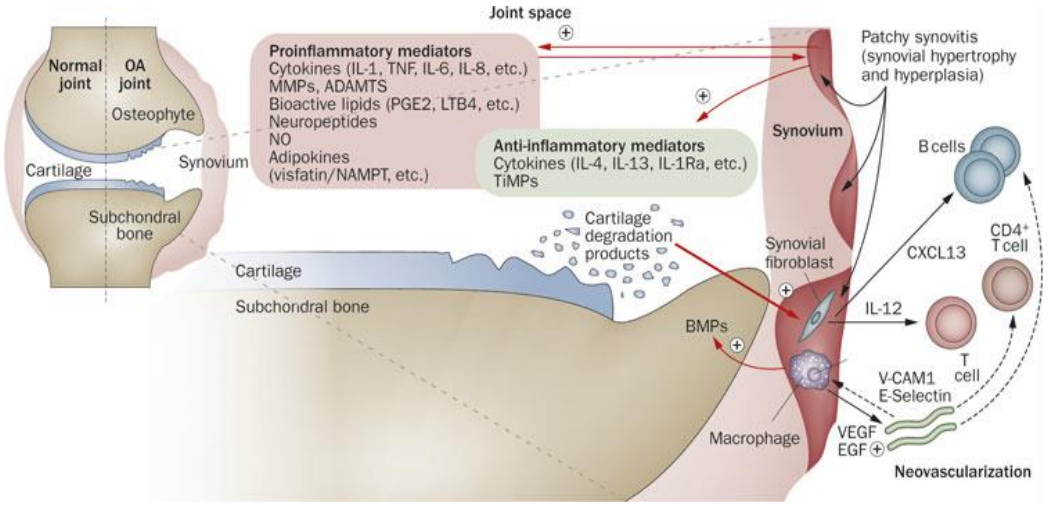
Cortisone no longer recommended

- Dong, Wei, et al. "Injection therapies for lateral epicondylalgia: a systematic review and Bayesian network meta-analysis." *British journal of sports medicine.* 2016 Aug;50(15):900-8.
  - Conclusion: Injection therapies such as platelet-rich plasma and autologous blood injection can be considered treatment options for lateral epicondylitis, but corticosteroid is not recommended.

Cortisone no longer recommended

- Wernecke C, Braun HJ, Dragoo JL. "The Effect of Intra-articular Corticosteroids on Articular Cartilage: A Systematic Review." *Orthopedic Journal of Sports Medicine*. 2015 Apr 27;3(5). eCollection 2015.
  - **METHOD:** Systematic review of corticosteroids on cartilage health. Preliminary searches yielded 1929 articles, and final analysis included 40 studies.
  - **RESULTS:** Methylprednisolone, dexamethasone, hydrocortisone, betamethasone, prednisolone, and triamcinolone displayed dose-dependent deleterious effects on chondrocytes in both in vitro and in vivo models.
    - At low doses (<3 mg/dose), increased cell growth and recovery from damage was observed.
    - At higher doses (>3 mg/dose) and longer exposure, corticosteroids were associated with significant gross cartilage damage and chondrocyte toxicity.
  - **CONCLUSION:** Corticosteroids have a time- and dose-dependent effect on articular cartilage, with beneficial effects occurring at low doses and detrimental effects at high doses and durations. The lowest efficacious dose should be used.

Osteoarthritis – Is the pain from loss of cartilage or from chronic synovitis?



- "Why do many patients with lateral knee OA complain of medial knee pain?" → Could it be chronic medial knee synovitis?
- PRP and stem cells are thought to modulate this reactive synovitis by stimulating the production of anti-inflammatory mediators and inhibiting the proinflammatory mediators.
  - Cortisone blocks the inflammation but does not stimulate the bioactive proteins that promote tissue healing and restoration of the joint's homeostasis

Healing potential

- Other non-pharmacologic factors that impede healing:
  - overuse of the injured site
  - Improper biomechanics (ex. Genu valgum deformity due to lateral compartment OA leads to a chronic strain of the MCL and chronic synovitis)
  - Decreased vascularity, especially at sites of friction or compression
  - Systemic co-morbidities that impair healing

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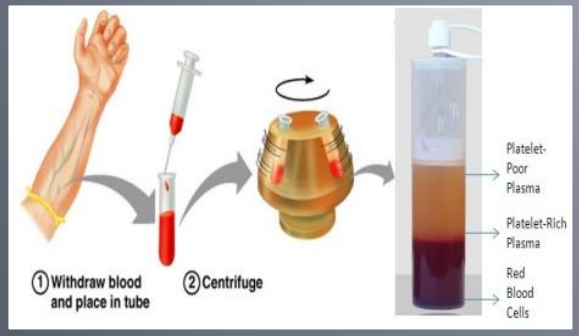
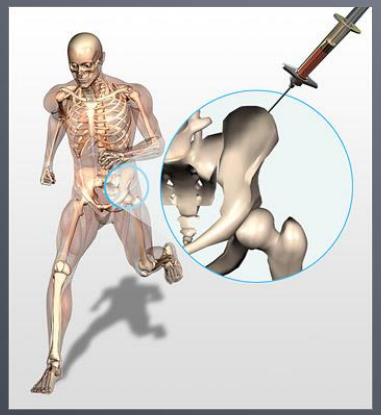
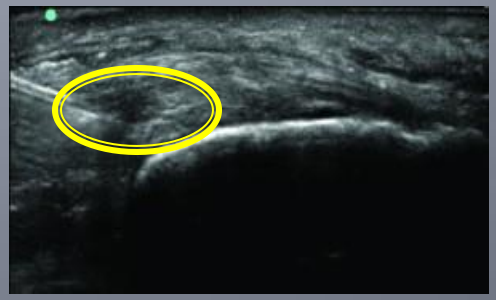
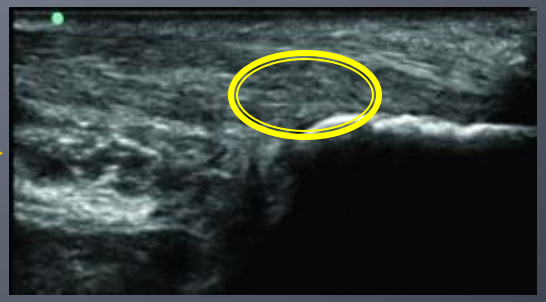
Definition of regenerative medicine





Achilles Tendon partial tear



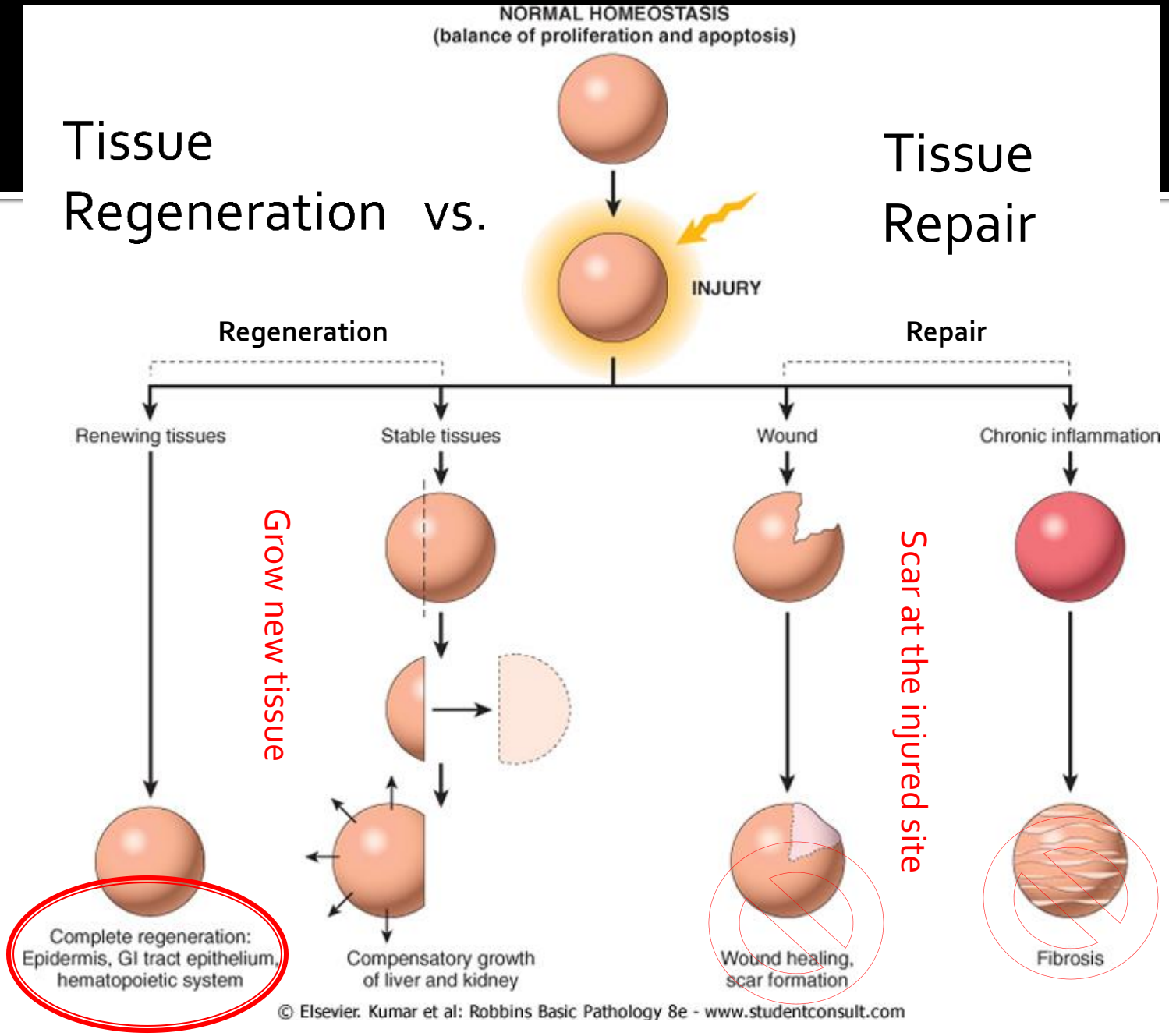


3 months later

What is Regenerative Medicine?

- Treatment of musculoskeletal injuries should promote the regeneration of the injured tissue.
- Platelet-rich plasma (PRP) and stem cell therapy stimulates the regenerative process of tendon, muscle and joint injuries.
- The term "orthobiologics" is frequently used interchangeably with "Regenerative Medicine products".

Tissue Regeneration vs. Tissue Repair



How does it work?

- Growth factors found in stem cells as well as in the α-granules and dense-granules in platelet cells activate the natural regenerative response in one's own body.

- These cells also release chemo-attractants and bioactive proteins, such as stromal-derived factor-1a, which are responsible for attracting white blood cells such as macrophages and fibroblasts.
  - This promotes removal of degenerated tissue and enhances tissue regeneration.

Biology of platelet cells

- Platelets are formed from megakaryocytes that originate from the bone marrow's hematopoetic stem cells.
  - They contain 30 bioactive proteins that play a role in hemostasis and tissue healing.
- Platelets initiate all wound healing by actively secreting from their granules 7 fundamental protein growth factors :
  - insulin-like growth factor-I (IGF-I)
  - transforming growth factor beta (TGFβ)
  - vascular endothelial growth factor (VEGF)
  - platelet-derived growth factor (PDGF)
  - basic fibroblast growth factor (b FGF)
  - epidermal growth factor (EGF)
  - connective tissue growth factor (CTGF).

Fundamental growth factors for tissue healing

Growth Factor	Biological Actions
IGF-1	Anabolic effects including protein synthesis, enhancing collagen, and matrix synthesis in the early inflammatory phase.
PDGF(αβ)	Assists in proliferation of growth factors by attracting stem cells and progenitor cells to stimulate tissue remodeling.
TGF (α-β)	A pro-inflammatory immunosuppressant that aids in cell migration, expression of collagen, and helps control angiogenesis and fibrosis.
VEGF	Promotes angiogenesis and neovascularization in the late inflammatory phase.
FGF	Promotes angiogenesis and neovascularization and appears to help in the regulation of cell migration and stimulate endothelial cells to produce granulation tissue during the late inflammatory phase.

All these growth factors work together as the chemical mediators that influence the cell migration and proliferation vital to regenerative tissue repair.

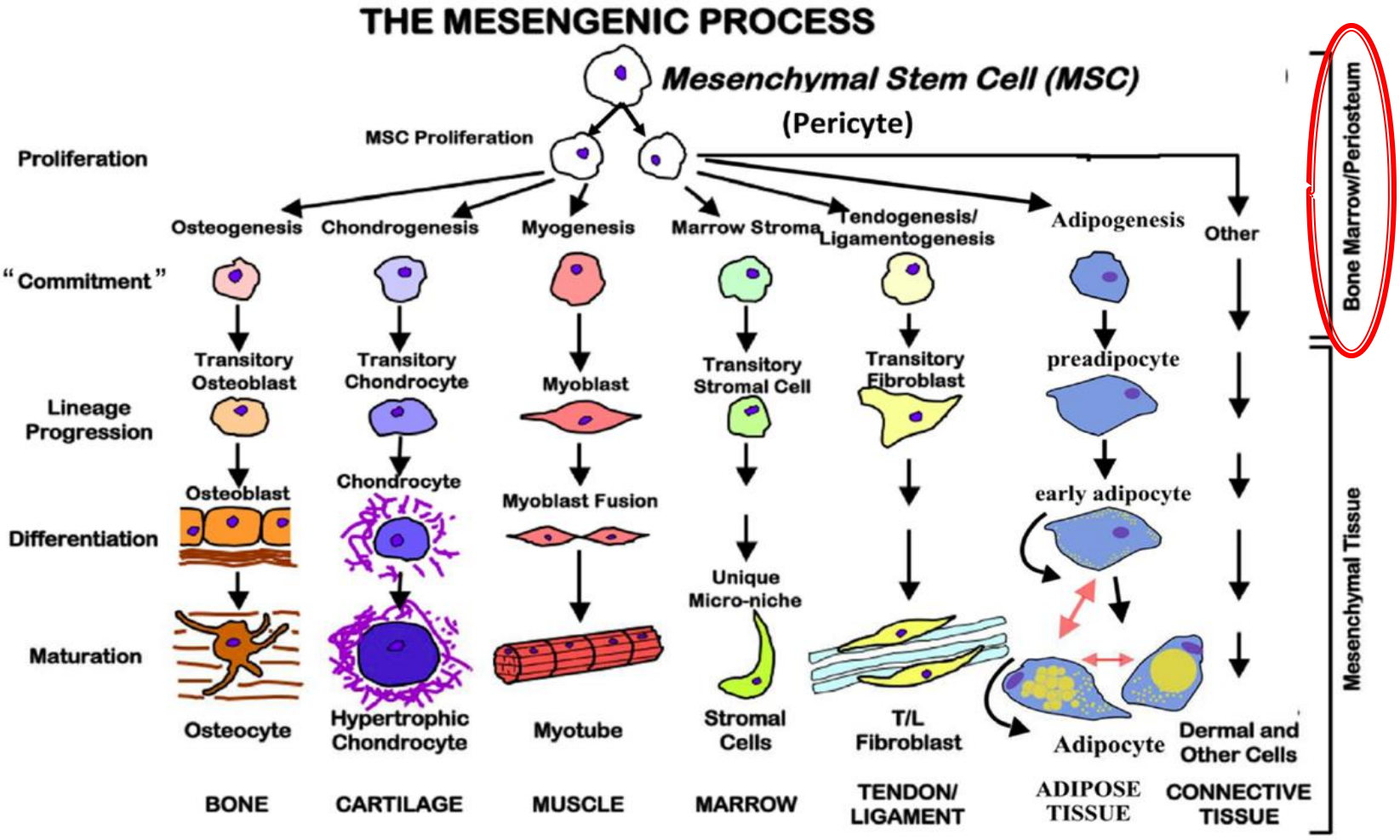
What are stem cells?

- Definition:
  - Cells that have not differentiated into a particular tissue
  - They can reproduce and become tissue or organ-specific cells
  - Found in human tissues in either active or dormant states

- History:
  - 1920's: The earliest work on stem cells is attributed to Alexander Maximow at the University of Chicago
  - 1970's: Arnold Caplan started applying stem cells to cartilage repair
  - 1981: Isolation of embryonic stem cells from mouse embryos.
  - 1998: Isolation of stem cells from human embryos and grow the cells in the laboratory.
  - 2006: Reprogrammed adult cells to assume a stem cell-like state = Induced pluripotent stem cells (iPSCs)

http://stemcells.nih.gov/info/basics/pages/basics7.aspx

Mesenchymal Stem Cell differentiation



Sources of stem Cells

- Various methods of obtaining stem cells
  - Autografts (Adult cells):
    - **Bone marrow**
    - Adipose (fat) tissue
    - Other soft tissue
  - Allografts (embryonic cells):
    - Amniotic and chorionic membrane
    - Umbilical cord
    - Embryon (i.e. Blastocyst)

Stem Cell Therapy

- Adult stem cells replace cells that are lost through normal wear and tear, injury, or disease, such as in the bone marrow and the skin.
  - Stem cells generate the cell types of their tissue lineage
    - For example, a hematopoetic (blood-forming) stem cell in the bone marrow gives rise to blood cells.
    - A blood-forming cell in the bone marrow cannot give rise to the cells of a very different tissue, such as nerve cells in the brain.
    - Mesenchymal stem cells are the precursors of the musculoskeletal cells so they can differentiate into bone, muscles, tendons and ligaments

Stem cells from the Bone Marrow

- Bone marrow contains at least two kinds of stem cells
  - Hematopoietic stem cells -
    - forms all the types of blood cells in the body.
  - Bone marrow stromal (mesenchymal) stem cells –
    - can generate bone, cartilage, and fat cells.
    - They make up a small proportion of the cell population in the bone marrow.
- Theories on how they work:
  - They may be able to transform and regenerate injured tissue
  - The high load of growth factors in them can stimulate the injured tissue cells to reproduce and regenerate.

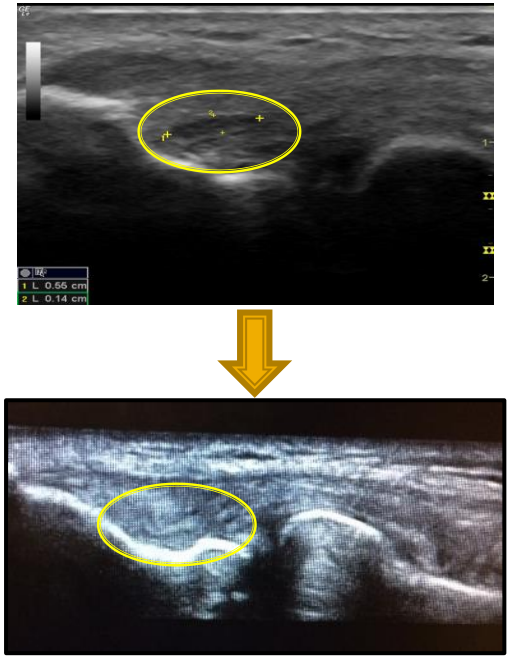
Benefits of Orthobiologics

Favored by patients since it is produced from the patient's own blood or bone marrow. The risk of adverse effects is minimal.

- The risk of acquiring a transmitted blood-born infection or suffering an anaphylactic reaction is extremely low.
- No major complications or tendon ruptures have been reported with these procedures
- Orthobiologics have been shown to inhibit the growth of bacteria, decreasing risk of infection at the treated site
- Orthobiologics are frequently less expensive than surgical management, which is the last resort for chronic injuries.
- Surgical management of recalcitrant tendinopathies lacks reliable evidence
- Orthobiologics impose fewer risks of complications compared to surgical options such as a knee replacement

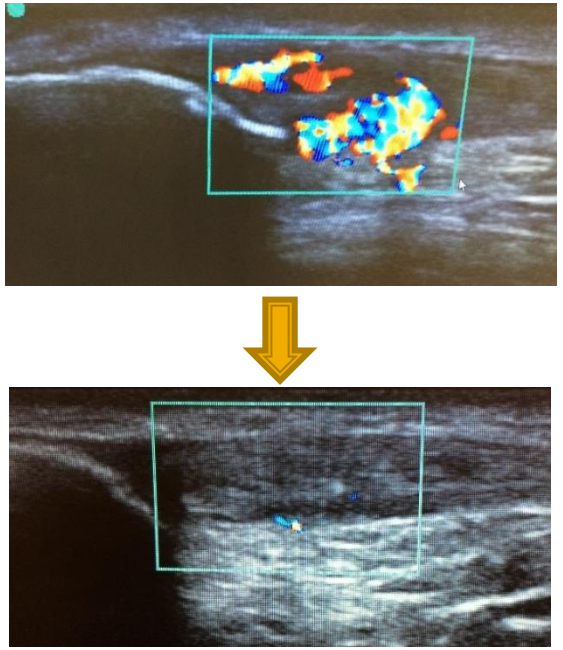
Could it be "placebo effect"?

59 y/o male tennis player with a tennis elbow tendon tear



5 years later

17 y/o male soccer player with a high grade partial patella tendon degenerative tear.



3 months later

Conclusions

- Patients with chronic tendon and cartilage lesions that have failed conservative treatments, especially those related to degenerative joint disease, have limited options.
  - Ex. Joint replacements carry significant risks
  - Regenerative injections carry minimal risks
- However, are we delaying the inevitable?

- Evidence-based outcomes should be discussed with the patient with full transparency about the reported success rates

Thank You!

Questions?

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