**Soft Tissue Healing in Injuries Affecting the Knee Joint**

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**Topic Areas**

- Review general phase model of tissue repair
- Identify the key issues in each of the inflammatory, proliferative and remodelling stages
- Consider the factors that influence repair
- Consider the potential impact of ‘therapy’ on these processes and events and possible additional biochemical / bioelectric influences

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**Inflammation**

- **TISSUE DAMAGE & BLEEDING**
  - Macrophages
  - Neutrophils

- **CHEMICAL RESPONSE**
  - Increased vascular permeability
  - Increased capillary volume
  - Increased capillary leak

- **TISSUE DAMAGE**
  - Release of mediators that stimulate PROLIFERATION phase

- **Phagocytes seeking and finding bacteria**

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**Tissue Repair Phases and Timescale**

- **Bleeding**
- **Inflammation**
- **Proliferation**
- **Remodelling**

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**Tissue Repair Phases and Timescale**

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**Phagocytes seeking and finding bacteria**
Tendon healing is a complex and highly-regulated process that is initiated, sustained and eventually terminated by a large number and variety of molecules. Growth factors represent one of the most important of the molecular families involved in healing, and a considerable number of studies have been undertaken in an effort to elucidate their many functions.

Five growth factors are reviewed whose activities have been best characterised during tendon healing: insulin-like growth factor-I (IGF-I), transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF).


Examples of Mediators Influenced by Therapy

- Ostrowski et al (2000) - link between exercise and Interleukin-6 (IL-6) production
- Leung et al (2006) - link between ultrasound and TGF-β in knee ligament healing
- Zhang et al (2004) - demonstrated link between electroacupuncture and peripheral inflammatory responses
- Bjordal et al (2006) - link between laser therapy and altered prostaglandin levels in the tissue (Achilles tendon)
Migrate into damaged tissue from adjacent areas
Proliferate and increase activity
Collagen laid down
Angiogenesis (formation of new local circulation)
Myofibroblasts initiate early wound contraction

Collagen production by the Fibroblasts is driven by cytokines and other mediators from the inflammatory phase and is an Oxygen dependent (aerobic) process
Myofibroblasts initiate early wound contraction

The angiogenic response is essential for effective repair material construction and is driven by mediators derived from the inflammatory events
Myofibroblasts initiate early wound contraction

Review
The vasculature and its role in the damaged and healing tendon
Shane A Fenwick, Bhaskar Halasyamani and Graham P Riley

... Tendon is a comparatively poorly vascularised tissue that relies heavily upon synovial fluid diffusion to provide nutrition...

... During tendon injury, as with damage to any tissue, there is a requirement for cell infiltration from the blood system to provide the necessary reparative factors for tissue healing...

... The angiogenic response is essential for effective repair material construction and is driven by mediators derived from the inflammatory events...

Fenwick et al (2002) contd

- Review the response of the vasculature to tendon damage in a number of forms, and how and when the revascularisation or neovascularisation process occurs.
- Also review on the revascularisation of tendon during its use as a tendon graft in both ligament reconstruction and tendon-tendon grafting...
Vascular physiology and long-term healing of partial ligament tears
Robert C. Bray*, Catherine A. Leonard, Paul T. Salo

Looked at BLOOD FLOW and LIGAMENT RESPONSE to injury (rabbit model)
Various models for ACL and MCL trauma including control, sham operated, partial MCL, partial ACL and complete PCL transection giving rise to knee joint instability

In control animals, the baseline blood flow for the MCL was not significantly different from that of the ACL
Sham operation did not induce any significant change in ligament blood flow at 16 weeks
Both MCL and ACL showed significant increases in blood flow 16 weeks after hemisection (389% and 421% of control, respectively).
Both ligaments therefore demonstrate the ability to adapt to the requirements of tissue remodelling with changes in vascular physiology.

Inflammatory Response of Human Tendon Fibroblasts to Cyclic Mechanical Stretching
Zhaozhu Li, MD, Guoguang Yang, MD, Matthew Khan, MD, David Stone, MD, Stanco L-Y. Xue, PhD, and James H-C. Wang, PhD
- Looked at effect of fibroblast stretching on 2 mediators - leukotriene B4 and prostaglandin E2
- Both related to inflammatory events and tissue repair
- Human patellar tendon fibroblasts
- Also considered influence of NSAID

Zhaozhu et al 2004 (contd)
... CONCLUSION ...
Cyclic stretching of human tendon fibroblasts increases the production of prostaglandin E2 and leukotriene B4 which enhance repair process
Also demonstrated that NSAID has adverse effect and that its use might contribute to the development of tendinopathy

Angiogenic Influence of existing Therapies
- Azuma et al (2001) demonstrate that LIPUS influences angiogenesis in relation to # healing
- Reher et al (2002) demonstrate influence of ultrasound in relation to NO and PGE2 production
- Zhao et al (2004) demonstrate link between electrical stimulation and angiogenic enhancement by means of VEGF mediated response
From Hinz & Gabbiani (2003)
Mechanisms of force generation and transmission by myofibroblasts
Current Opinion in Biotechnology 14:538-546


- Fibroblastic cells acquire contractile features during healing, modulating into myofibroblasts
- Myofibroblasts synthesize extracellular matrix components such as collagen types I and III
- The transition from fibroblasts to myofibroblasts is influenced by mechanical stress, TGF-beta and cellular fibronectin.

Fibroblastic cells acquire contractile features during healing, modulating into myofibroblasts. Myofibroblasts synthesize extracellular matrix components such as collagen types I and III. The transition from fibroblasts to myofibroblasts is influenced by mechanical stress, TGF-beta and cellular fibronectin.

Connective tissue cells align in response to stretch. Studies have shown these responses occur within 12-14 h of initiation of stretch, but do not identify the time at which this orientation occurs. Nor whether the orientation continues after cessation of stretch. Study to establish the earliest times at which fibroblast orientation occurs, using cultured primary human fibroblasts on deformable culture dishes and stretched them for up to 24 h. (1 Hz, 8% uniaxial strain)

Cells photographed for up to 24 h after cessation of stretch. The fibroblasts began to orient by 2-3 h and orientation appeared nearly complete by 24 h.

Cultures stretched for 2 or 3 h continued to exhibit greater degrees of orientation (compared to controls) for 2 or 3 h respectively after cessation of stretch.

Conclude that fibroblasts begin to orient within 3 h of initiation of stretch, and that they continue to orient for several hours after cessation of stretch.

Cyclic strain influences the expression of the vascular endothelial growth factor (VEGF) and the hypoxia inducible factor 1 alpha (HIF-1α) in tendon fibroblasts.

Neovascularization is involved in beneficial and detrimental processes of tendon pathology. We investigated the influence of repetitive motion on the expression of the most important angiogenic factor, the vascular endothelial growth factor (VEGF). These results demonstrate that mechanical factors are involved in the regulation of VEGF expression in tendon tissue.
Collagen Bonding

- X Links (bonds)
  - within triple helix structure
  - between collagen filaments
- MORE BONDS:
  - more strength
  - more stiffness
  - less mobility
  - less extensibility

IMMOBILISATION & IMMObILITY

- Increases number of bonds
- Decreases lubrication
- therefore:
  - decreased mobility
  - decreased flexibility
  - decreased extensibility
- Akerson et al 1977

Evans & Stanish (2000)
The basic science of tendon injuries
Current Orthopaedics 14;403-412

Collagen Biomechanics

- Collagen fibre orientation such as to resist tension throughout its length
- non linear stress - strain relationship
- during normal physiological activity tendon / ligament is subjected to <25% of its ultimate stress
Collagen Stress / Strain Curve

**TOE**
- early stress
- increase in length with minimal force applied
- relate to CRIMPS and possible FILAMENT SLIDING

**Unloaded ligament** (x1000) **Loaded ligament**


**LINEAR**
- almost linear increase in resistance as the load is increased

**FAILURE**
- progressive failure beyond a certain point
- fibres begin to fail
- eventual and rapid onset of complete failure at yield point
Clinical Correlates (after Noyes 1977)

Suggested that ‘normal’ physiological activity only uses approximately 25% of tissue capacity (Noyes 1977, Riley 2004)

Injury

• Bone - tendon - ligament ADAPT to the demands put on them
• Increased stress - become stronger and stiffer
• Decreased stress - become weaker and less stiff

Effect of Exercise

• Evidence that the use of exercise can increase tendon tensile stress
  • Tipton et al 1967, 1970
• Evidence that the use of exercise can increase ligament / bone junction strength

Evans & Stanish (2000)
The basic science of tendon injuries
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Exercise
Exercise-induced structural and metabolic adaptations include:
- increased tissue blast activity;
- accelerated collagen synthesis;
- increased collagen fibre thickness, cross links and crystallography;
- improved stress orientation of fibres;
- larger diameter and total weight.

These changes improve mechanical properties, producing a tendon with increased stiffness and ultimate strength, capable of absorbing a larger amount of energy before failure. The tendon becomes larger, stronger, and more resistant to injury.
**Effect of Exercise**

- Evidence that the collagen bundle diameter increases with stress / exercise
- Immobilisation / immobility reduces the tensile strength of ligament / tendon

**Noyes (1977)**

- Monkey ACL research
- Had previously demonstrated 40% reduction in ACL strength following 6/52 immobilisation
- 8/52 immobilisation in POP
- POP off - followed by reconditioning programme (exercise)
- 5/12 later, ligaments still 20% reduced strength
- 12/12 - 'almost' same as the controls (90%)

**Remodelling**

- Orientation of Collagen Fibres
- Reabsorption of Type III Collagen
- Replacement with more Type I Collagen
- Structure of final scar as similar as possible to parent tissue

**Influences of Therapy on Remodelling**

- Also link with fibroblast responses to mechanical stress
- Other therapies - e.g. Ultrasound, laser therapy and electrical stimulation have been shown to influence these events (e.g. Nussbaum, 1998, Huys et al, 1992 and Byl et al, 1996)

Light micrograph illustrating ruptured collagen fibres with no regular crimp pattern 1cm from the macroscopical rupture site in the ruptured Achilles tendon (mag x400) Jarvinen et al (2004) J Orthop Res 22;1303-1309
Implications for Therapy

- Mechanical stress influences not only the mechanical but also the biochemical environment of repairing tissue
- Therefore exercise and manual therapy have the POTENTIAL to influence repair at a level not usually described
- Of course, more research needed in order to ‘fill the gap’

Bioelectric Potential

- Bioelectric influences could act in addition to the mechanical, neurological and biochemical influences of manual and exercise therapy
- Relationships between therapy intervention and bioelectrics need further investigation

Bioelectricity

- Human natural bioelectric phenomena
- Relations between tissues injury, healing and bioelectric events
- Voluntary control over bioelectric events

Lower Limb Bioelectricity after Injury

- Normal Bioelectric Pattern
- Injured Bioelectric Pattern
Summary and Conclusion

Tissue repair

- The process of repair is a highly regulated and complex cascade of events
- The division into ‘phases’ is convenient rather than ‘real’
- The increased understanding of the effect of mediators in this scenario offers an opportunity to further influence the events and enhance the processes

Repair and Therapy

- In addition to the ‘known’ effects of exercise, electrotherapy and manual therapy, new possibilities are arising with current findings
- Existing therapies have effects that have not been previously determined
- Opportunity to exploit these further and to have even greater potential to enhance the process of repair

Thank You

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