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Chronic Inflammation and Chronic Disease

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INFLAMMATION

- To 'set on fire'
- Symptoms: swelling, redness, heat
- Maintenance and restoration of tissue homeostasis

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Acute Inflammation

- Pathogenic organisms breaching the body defenses or tissue damage instigates a cascade of immune responses – innate immunity
  - Cellular
  - Chemical
- Immunizing B- and T- cells kill pathogens and remove damaged cells
  - Cytokines down regulate the response once the clean up is completed
- Cure vs. death
  - Intervene or REST?!

CYTOKINE:
'cell' 'movement'
Signalling molecules
E.g. Interleukins, Interferons
Growth factors

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Chronic Inflammation

- Occurs when acute inflammation remains present in a tissue or becomes systemic:
  - Untreated cases of acute inflammation e.g. infection, injury
  - Long term exposure to irritants e.g. pollutants, chemicals, drugs
  - Autoimmune disease
  - Cancer requires it and produces it locally
  - Leaky gut – microbiome damage
- Contributing factors:
  - Second hand smoke – smoking (humans)
  - Alcohol (humans)
  - Obesity
  - Chronic stress

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Secondary Disease

- In chronic inflammation, the inflammatory response can:
  - Damage healthy cells, tissues, organs
  - Cause DNA damage
  - Create internal scarring and functional loss e.g. cirrhosis
- Chronic inflammation can lead to the development of:
  - Cancer
  - Autoimmune disease
  - Obesity
  - Asthma
  - Neurodegenerative disease

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Extracellular Matrix ECM

- Made up of secreted products of many cell types
  - Voluminous, highly insoluble, proteins
- Organised scaffold for cell support
- 3 dimensional ultra-structure
  - highly conserved sequences and arrangements
  - Independent structural domains
- Two basic forms:
  - Basement membranes
    - Type IV collagen, laminins, nidogen and heparan sulphate proteoglycan - Perlecan
  - Interstitial matrix
    - Fibrils containing Type I, III, V and/or XI collagen interspersed with supra-structural elements e.g. non collagenous glycoproteins such as fibronectin, vitronectin, chondroitin, keratan-sulphate proteoglycans
    - CNS is different
- Specialised mix of the two : reticular fibre network of the secondary lymphoid tissue
- Sulphated glycosaminoglycan chains – negative charge

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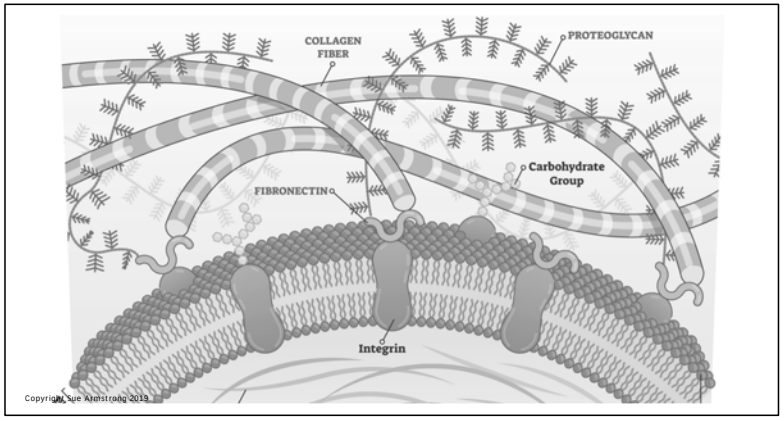

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Extracellular Matrix (ECM)

- Biophysical properties:
  - Immune cell signaling
  - Extravasation points
    - post capillary venules (except lungs)
  - Activation and proliferation of immune cells
  - Cell differentiation
- In chronic inflammation – 2 way changes
  - Inflammatory cytokines and proteases alter the ECM
    - E.g. TNF alpha – inflammatory cytokine reduces sulphate levels
  - The ECM signaling to immune cells alters their migration and behaviour

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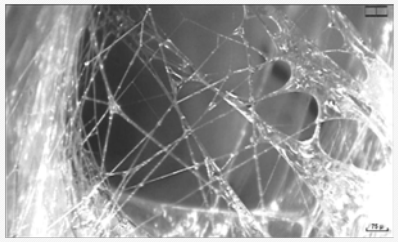
Fascia - ECM and Physical therapies

"We can no longer look at the body as a collection of cell based organs held together by connective tissue - instead we must look at it as a fibrillar framework in which locally adapted cells form our musculoskeletal system."
(Dr Jean Guimberteau)

Fascia now redefined to include all the collagenous based soft tissue in the body including the cells that create and maintain the ECM



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Mitochondria and Chronic Inflammation

- Immune cells employ a molecular machine, NLRP3 inflammasome, to keep tabs on inflammation
- NLRP3 is inactive in healthy cells
- Switched on when mitochondria are damaged by stress or exposure to bacterial toxins
- NLRP3 inflammasome can get stuck on the on position
  - Contributes to many chronic inflammatory conditions e.g. osteoarthritis
- Target for therapeutics
  - Choline kinase inhibitors inhibit choline from being incorporated into the mitochondrial membrane triggering the cell to remove them as 'damaged'
  - This inhibits NLRP3 inflammasome activation

Multiprotein oligomer
Promotes maturation and secretion of IL-1β and IL-18
Promotes pyroptosis – proinflammatory cell death

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Autophagy

- Cellular waste management
  - Cellular housekeeping – breaks down and recycles damaged or harmful elements
  - Prevents defective proteins from accumulating in the cell
- Chaperone mediated autophagy (CMA)
  - Specialised proteins chaperone old and damaged proteins to the lysosomes for digestion or eliminates them from the cell
- Autophagy is impaired in age related diseases e.g. Alzheimer's and Parkinson's in man – mutant proteins accumulate in these diseases
- Foods that can activate autophagy (Humans)
  - Pomegranates, red grapes, pears, mushrooms, lentils, soybeans and green peas
  - (Dr Nezis, Warwick's School of Life Sciences)

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Chronic Inflammation in Cancer

- Chronic inflammation can promote all the stages of tumorigenesis that are now clearly identified:
  - Evasion of apoptosis
  - DNA damage
  - Limitless replication
  - Sustained angiogenesis
  - Insensitivity to anti-growth signalling
  - Tissue invasion/metastases
- Cancer cells can generate and maintain a chronic inflammatory state themselves regardless of pre-existing chronic inflammation
- Malignant cancer cells have significantly raised CMA (chaperone mediated autophagy) levels as they have such a high rate of growth needing high levels of nutrients and efficient recycling of their components
  - Potential for therapeutics to block CMA - research has shown the ability to shrink malignant tumours by blocking CMA

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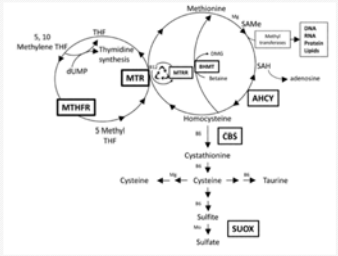
Treating Chronic Inflammation

- Pay attention to any inflammatory source
- Avoid and treat obesity
  - Chicken and egg?!
- Nutrition
  - Antioxidants
  - Plant Polyphenols
  - Short and Medium Chained Fibre
- Micronutrients:
  - Magnesium
  - Vit D
  - Vit E, zinc and selenium
  - Omega 3 fish oils
  - B12
  - SAMe



Methylation - transulphuration

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Treating chronic inflammation cont..

- Herbal supplements
  - Curcumin
  - Ginger
  - Hyssop
  - Harpagophytum procumbens (cats claw)
- Physical exercise
- Physical therapies
  - Acupuncture
  - LLLT
- Conventional therapeutics:
  - Metformin
  - NSAID's
  - Statins
  - Steroids
- Stress reduction – sleep management
- Future therapeutic targets:
  - Mitochondrial support
  - Autophagy promotion (blocking in malignancy)

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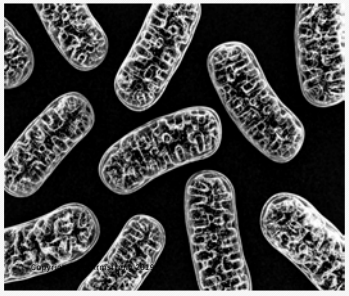
Low Level Laser Therapy LLLT



Mechanisms of Action of LLLT

- Light absorption in the mitochondria
- Mitochondria make energy (ATP) from oxygen and pyruvate
- In stressed or ischaemic tissue mitochondria make nitric oxide (mtNO) which competes with oxygen by binding to cytochrome c-oxidase (CcO)
- This results in:
  - Reduced ATP production
  - Increased oxidative stress
  - Leading to inflammation

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Effects of LLLT

1. Absorption by Cytochrome c-oxidase (= a chromophore)
   - Triggers a series of downstream effects
2. Modulation of ATP, nitric oxide & reactive oxygen species
   - Nitric oxide released from the enzyme allowing oxygen back into position
   - ATP production is therefore increased
   - Oxidative stress reduced
3. Downstream intracellular responses (gene transcription, and cellular signaling)
4. Extracellular, indirect, distant effects
   - Tissues that have not absorbed photons can be affected indirectly by secretions from other cells that have absorbed light.
   - Bystander effects: endocrine, paracrine, autocrine

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Wavelength

It is the structure of cytochrome c-oxidase and its redox state that determines which wavelengths of light will be absorbed

Most LLLT devices are within 600nm - 1000nm

There are many absorption peaks for cytochrome c-oxidase within this range - the laser light wavelength needs to coincide with one of these peaks

These wavelengths penetrate tissue well

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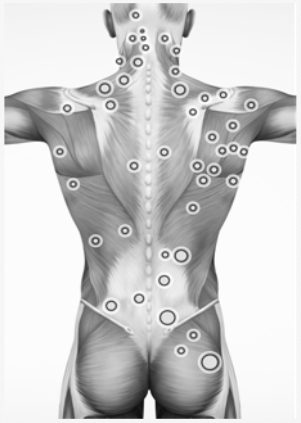
OTHER EFFECTS

Oedema/Lymphatic Flow
- Improves lymph flow
- Reduces oedema

Analgesia
- Inhibitory effect on Aδ and C pain fibres

Myofascial Trigger Points
- Palpable nodules in taut muscle bands and contraction of muscle fibres that lead to muscle spasms and limited joint movement
- Reduced electrical activity at the motor end plates that are implicated in the production of MTP's (become hyper-irritable)

Acupuncture Point Stimulation



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Other known effects:

- Increased neovascularisation
- Increased collagen and protein synthesis (wound healing)
- Decreased prostaglandin levels
- Improvement of the immune system
  - Increased leukocyte phagocytosis
- Increased DNA and RNA synthesis

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