Fat, Inflammation and Ageing

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Acute vs Chronic Inflammation

- A strong Acute inflammatory response favours survival. Protects against lethal infections, severe trauma e.g. shark bite. Etc

- A strong chronic systemic inflammatory response favours degenerative disease

- Antagonistic Pleiotropy – beneficial and detrimental effects from the same gene
Chronic Inflammation

- If tissue health is not restored or in response to stable low-grade irritation, inflammation becomes a chronic condition that continuously damages the surrounding tissues.

- Tissue injury and healing proceed simultaneously.

- The collateral damage caused by this type of inflammation usually accumulates slowly, sometimes asymptotically for years and may eventually lead to severe tissue deterioration.
Innate Immunity

- First line of defense
- Germ cell-encoded proteins recognise molecular patterns common to pathogens and express a small number of highly active genes. Proinflammatory genes
- Effective in minutes to hours
- When the threat has passed anti-inflammatory genes produce the anti-inflammatory cytokines that reverse the response and stabilise the system
The Common Cytokines

Cytokines
Message molecules that allow cells to communicate and alter one another's function

Proinflammatory
- Interleukin-1 IL-1
- Interleukin-6 IL-6
- Tumour Necrosing Factor-alpha TNF-alpha

Anti-inflammatory
- Interleukin-10
Resistin – The New Cytokine

Resistin is a recently described, low-molecular-weight, cysteine-rich secretory peptide also known as adipocyte-specific secretory factor. Animal studies show that resistin is produced mainly in white adipose tissue and may be the linkage between obesity and insulin resistance. There is evidence that resistin has proinflammatory properties and is abundant in inflammatory diseases (for instance, rheumatoid arthritis (RA) and Crohn’s disease. In humans, resistin is expressed in inflammatory cells, leukocytes, and macrophages and has the potency of inducing production of interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α). Resistin is accumulated in inflamed joints of patients with RA and has the capacity to induce arthritis in mice. There are also data indicating that resistin levels are inversely associated with renal function and possibly contribute to a low-grade inflammation in patients with chronic renal dysfunction.

The performance of monocytes, macrocytes, chemokines, cytokines and T-lymphocytes declines with age but strength of inflammatory response increases with age because the production of proinflammatory cytokines is higher.
The inflammatory response to chronic antigenic stress appears to be the triggering mechanism that drives tissue damage associated with age-related diseases such as Alzheimer's disease, atherosclerosis, diabetes, sarcopenia and cancer.

Tissue damage is happening at the cellular and molecular level, causing the accumulation of molecular and cellular scars.
Conditions That Promote Inflammatory Cytokines

- Declining sex steroids
  - Testosterone, oestrogen, androstenedione, also growth hormone (Anabolic)
- Obesity
- Smoking
- Subclinical and overt infections
- Increasing BMI
- Arteriosclerosis
- Diet
  - Glucose
  - Excess calories
There is evidence to suggest that repeated infections at a young age will increase the levels of inflammatory proteins increasing the risk of heart attack and other degenerative diseases in older age.


This reinforces the value of vaccinations. It also supports the early use of antibiotics to control bacterial infection quickly.
Inflammation And Mortality

Low grade increases in inflammatory markers are strong predictors of all cause mortality risk in several longitudinal studies of elderly cohorts.

Markers used included TNK-α, IL-1, IL-6, CRP and low levels of albumin and HDL cholesterol.


Frailty and Sarcopenia

**Frailty** has been defined as an age-related decline in lean body mass, decreased muscle strength, endurance, balance and walking performance, low activity and weight loss accompanied by a high risk of disability, falls, hospitalisation and mortality overproduction of catabolic cytokines and by the diminished availability or action of anabolic hormones.

**Sarcopenia** is the loss of muscle mass and strength that occurs with normal ageing.
Metabolic Syndrome

- Metabolic syndrome may be detected by 5 clinical diagnostic criteria
- Abdominal adiposity
- Hypertriglyceridemia
- Low high density lipoprotein
- Hypertension
- Fasting hyperglycaemia
There is a lot of evidence to say that inflammation causes the metabolic syndrome and that as obesity is reversed the expression of inflammatory cytokines such as TNF-α subsides and the metabolic syndrome resolves.


Kern PA, Saghizadeh M, Ong JM, Bosch RJ, Deem R, Simso RB:
Insulin resistance may precede diabetes by 10 to 20 years

Inflammation linked to insulin resistance


CRP, fibrinogen and PAI-1 are predictors of diabetes


CRP with Fasting insulin is the test of choice in the presence of a normal blood glucose.
Genetic Predisposition

Subclinical inflammation is linked to insulin resistance in people with a positive family history for diabetes


The Garvin Institute in Sydney recently published a trial in which they increased the calorie intake of two groups for 28 days. The group with a family history of diabetes gained 50% more weight than the group without a family history of diabetes.
Glucose Is Inflammatory

Glucose and excessive food intake cause oxidative stress and inflammation


- post-prandial dysmetabolism, induces immediate oxidant stress, which increases in direct proportion to the increases in glucose and triglycerides after a meal
- Post-prandial dysmetabolism is an independent predictor of future cardiovascular events even in nondiabetic individuals.
- Improvements in diet exert profound and immediate favorable changes in the post-prandial dysmetabolism. Specifically, a diet high in minimally processed, high-fiber, plant-based foods such as vegetables and fruits, whole grains, legumes, and nuts will markedly blunt the post-meal increase in glucose, triglycerides, and inflammation. Additionally, lean protein, visceral fat, fish oil, tea, cinnamon, calorie restriction, weight loss, exercise, and low-moderate-dose alcohol each positively impact post-prandial dysmetabolism

Cancer

- Age is a marker of duration of exposure to carcinogenic factors

- Chronic inflammation induced by either biological, chemical, mechanical or physical injuries has been associated with increased incidence of cancer in different human tissues

- CRP measured before or after surgery predicts outcome

- Polymorphisms of genes involving inflammatory cytokines such as IL-6 and IL-10 may influence susceptibility to and prognosis in neoplastic diseases
Atherosclerosis

- More than half of patients with atherosclerosis do not show classical risk factors, such as hypercholesterolemia, hypertension, history of smoking, diabetes, obesity and sedentary life style.

- A fundamental role for innate immunity in mediating all stages of this disease.

- Levels of CRP or IL-6 have been suggested as significant predictive risk factors for future development of cardiovascular events.

Inflammatory Genes

Differences in the genetic regulation of inflammatory processes may explain why some people get atherosclerosis with or with the traditional risk factors of obesity, smoking, sedentary lifestyle, cholesterol or diabetes.

Inflammation occurs in pathologically vulnerable regions of the Alzheimer brain. Highly insoluble Aβ42 peptide deposits and neurofibrillary tangles increase inflammation.


Long term NSAIDs may protect against Alzheimers.


CRP may reflect cerebral disease mechanisms related to dementia and this is measurable long before clinical symptoms appear, and might be used to monitor disease progression.

Antagonistic Pleiotropy

- Polymorphisms are fairly common in the general population so there is a fairly high probability that individuals will inherit one or more high risk allele. This will help decide whether high cholesterol will be directly associated with cardiovascular disease for individuals.

- Obesity, smoking, infection and physical inactivity promote inflammation

- Controlling inflammation promotes longevity

- Antagonistic pleiotropy – one gene controls for traits that are beneficial and detrimental

'It is interesting to note that 'in vitro' addition of IL-1 and TNF-α to fibroblasts induced an accelerated senescent phenotype which was rescued by antioxidant addition.'


This demonstrates in a culture dish that premature ageing from inflammation can be reversed by taking anti oxidants.
Mature adipocytes in culture secrete cytokines that promote the differentiation of preadipocytes to adipocytes. The greater the number of mature adipocytes present the stronger this effect is.


It has been postulated that when fat cells reach critical mass they secrete cytokines to recruit precursors. This may be the mechanism for fat cell hyperplasia and regeneration of fat after Lipectomy.

Faust, et al, Adipose tissue regeneration following lipectomy. Science 197, 391-396
Systemic Illness?
Twins

"Non-Smoker"

"Five Year Smoking History"
(2 pack per day)
Sun And Cigarettes