Free Radicals and the Ageing Immune System: Friend or Foe? A Systematic Review.

Lucy Robinson, Cardiff University School of Medicine,
Contact: robinsonlh@cardiff.ac.uk. Acknowledgements: Dr Robert Santer.

Context: Free radicals (FRs) are vital signalling molecules within the immune system (IS).[1] Therefore can promoting antioxidant (AO) supplementation as a "miracle cure" for the "free radical problem," and associated "immune-mediated diseases" of the elderly, ever be justifiable?[2-3]

Introduction: Free radicals are uncharged molecules that have an unpaired valence electron. They are typically highly reactive and short lived.

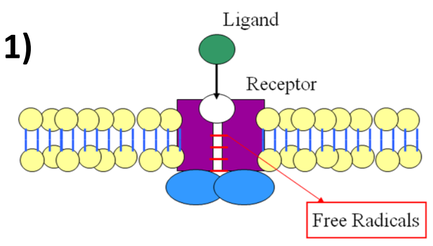
However, they play an important role in a variety of cellular signalling systems – the deregulation of which can result in disease.

Methodology: A systematic review of all relevant and accessible literature; identified through PubMed; using the search keywords: "free radical ageing immune system".

Free Radicals Physiology:

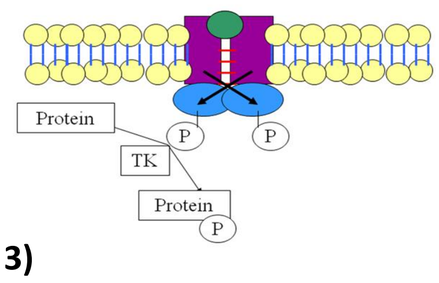
The majority of free radical signalling occurs via signals through tyrosine kinase phosphorylation cascades.[1]

1)



A ligand binds to the receptor which causes receptor dimerisation and oligomerisation. The reduction of sugar residues results in free radical production.

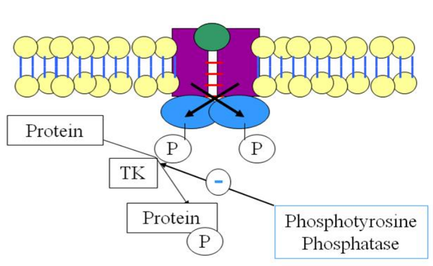
2)



Allosteric changes allow for autophosphorylation of the receptor and ultimately activation of intracellular tyrosine kinase cascades.

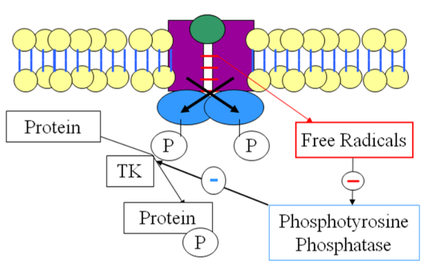
Subsequently phosphorylated proteins act as effector molecules within the cell.

3)



Phosphotyrosine phosphatases (PTPs) dephosphorylate tyrosine kinases thus limiting signal response.

4)



Free radicals, produced by ligand-induced receptor dimerisation or in response to cellular stress, inhibit PTPs and thus, prolong the duration of effect of the signal cascade.

Tyrosine kinase signalling is important for the regulation of cell proliferation, differentiation, motility and apoptosis.

Integrins, G-Protein coupled and Jak-Sat receptors trasnactivate tyrosine kinase signalling cascades and are therefore regulated in a similar manner.[1]

In-vivo and in-vitro excess of catalase results in a relative inactivation of all these signalling pathways.[1]

Redox Signalling:

Changes in cellular redox potential alters protein structures.
Low pKA proteins e.g. transcription factors are more redox susceptible.
Thus free radical levels affect protein synthesis.

↑ free radicals → oxidative dependent PTP inactivation
= ↑ cell proliferation and survival.[1]

↓ free radicals → reductive PTP activation
= ↓ receptor signals, ↓ cell growth, may ↑ apoptosis.[1]

References:
1. Winrow et al. 1993. Free radicals in inflammation: second messengers and mediators of tissue destruction. British Medical Bulletin. 49 (3): pp. 506-522.
2. Brambilla et al. 2008. The role of antioxidant supplement in immune system, neoplastic and neurodegenerative disorders: a point of view for an assessment of the risk/benefit profile. Nutrition Journal. 7 (29).
3. Peters et al. 2009. Reactive oxygen intermediate-induced pathomechanisms contribute to immunosenescence, chronic inflammation and autoimmunity. Mechanisms of Ageing and Development. 130: pp. 564-587.
4. Gomez et al. 2005. The ageing immune system. Current Opinion in Immunology. 17: pp. 457-462.
5. Fulop et al. 2004. Signal transduction and functional changes in neutrophils with aging. Ageing Cell. Pp 217-226.
6. Cannizzo et al. 2012. Age-Related Oxidative Stress Compromises Endosomal Proteostasis. Cell Reports, 2: pp. 136-149.

Free Radical Pathology in the Ageing Immune System:

Immunosecescence describes the progressive decline in function of the immune system with age. Elderly patients exhibit chronic yet ineffective hyper-inflammatory responses and also increased susceptibility to infection, autoimmune diseases and neoplasias.

Free radical theory of ageing = accumulation of free radical oxidative damage → impairs cell and tissue function. Therefore removal of the free radical "problem" would prevent such degeneration.[4]

However FRs are vital for effective signalling and thus coordinated function of the IS. The three main roles of free radicals in the IS are ...

1) Free Radicals as Antimicrobial Agents:

In the innate immune system phagocytic cells produce reactive oxygen species for degradation of microorganisms within phagolysosomes. And eosinophils produce reactive nitrogen species to combat extra-cellular parasites.

In the elderly there is
↓ respiratory burst ,
= ↓FR production,
↓phagocytic efficiency
= ↑ infection susceptibility.[5]

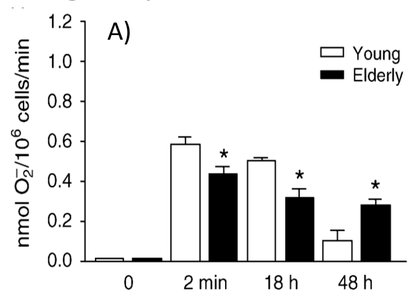


Fig A) Production of superoxide anion production by FMLP stimulated neutrophils.[5]

The adaptive immune system is then recruited by antigen-presenting cells. Failure of reactive oxidative proteolysis in the phagolysosome
= ↓ antigen presentation and lymphocyte recruitment in the elderly.[6]

2) Free Radical Coordination of Cellular Signalling:

Redox induced transcription of tissue factor activates the extrinsic pathway of the clotting cascade. Platelet aggregation is amplified by FR release. Deregulation of FR signalling in the elderly
= ↑ hypercoagulability and thus ↑thromboembolic disease.[4]

Redox induced transcription of stress proteins and signalling molecules in damaged cells initiate and potentiate cytokine release.
= Cytokine/chemokine production become ↑ irregular with age.[3-4]

Eiconisoids production is ↑ by FR activation of phospholipases. Prostaglandins, thromboxanes and leukotrienes ↑ inflammation whereas Lipoxins ↓inflammatory responses.

There is ↑ pro-inflammatory mediators and ↓ lipoxins with age
= "INFLAMM-AGEING".[3-4]

3) Free Radicals and Cellular Survival:

There is **↓ proliferation of epithelial cells in the elderly = weak physical barriers and ↑ invasion by pathogenic organisms.** Goblet secretion of mucus is also ↓ in the elderly.

Growth factor cytokines regulate immature leukocytes growth, proliferation, differentiation and survival

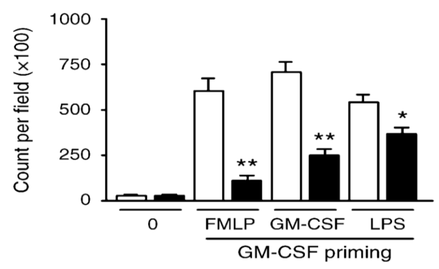


Fig B) Reduced neutrophil activity to chemoattractants and GM-CSF priming.

(all via free radical mediated cellular signalling pathways)!

There is **↓ lymphopoeisis (and ↓ antibody production) in the elderly**
but **↑ myelopoesis = ↑ risk of myeloproliferative disease.**

There is ↓ classical complement pathway activation and ↓ opsonisation due to ↓ antibody levels. This combined with ↓ antigen-presenation

= ↓ stimulation of tumour necrosis factor secretion by macrophages
= ↓ Fas ligand expression on T/NK cells
= thus ↓ cytotoxic apoptosis in the elderly.

Conclusion: Antioxidant supplementation as a preventative measure against age associated immune-mediated disorders has become increasingly popular over recent years. However the importance of FR signalling in the ageing IS must not be overlooked. There is a very real possibility of AO toxicity from overdose and interactions which must be more fully understood before AOs can be prescribed as reliable therapeutics.