Viral infection

The Role of Inflammation, Redox and Mitochondrial Health

Ray Griffiths MSc

Clinical Education Associate

pure encapsulations®

Webinar Disclosure

Ray Griffiths

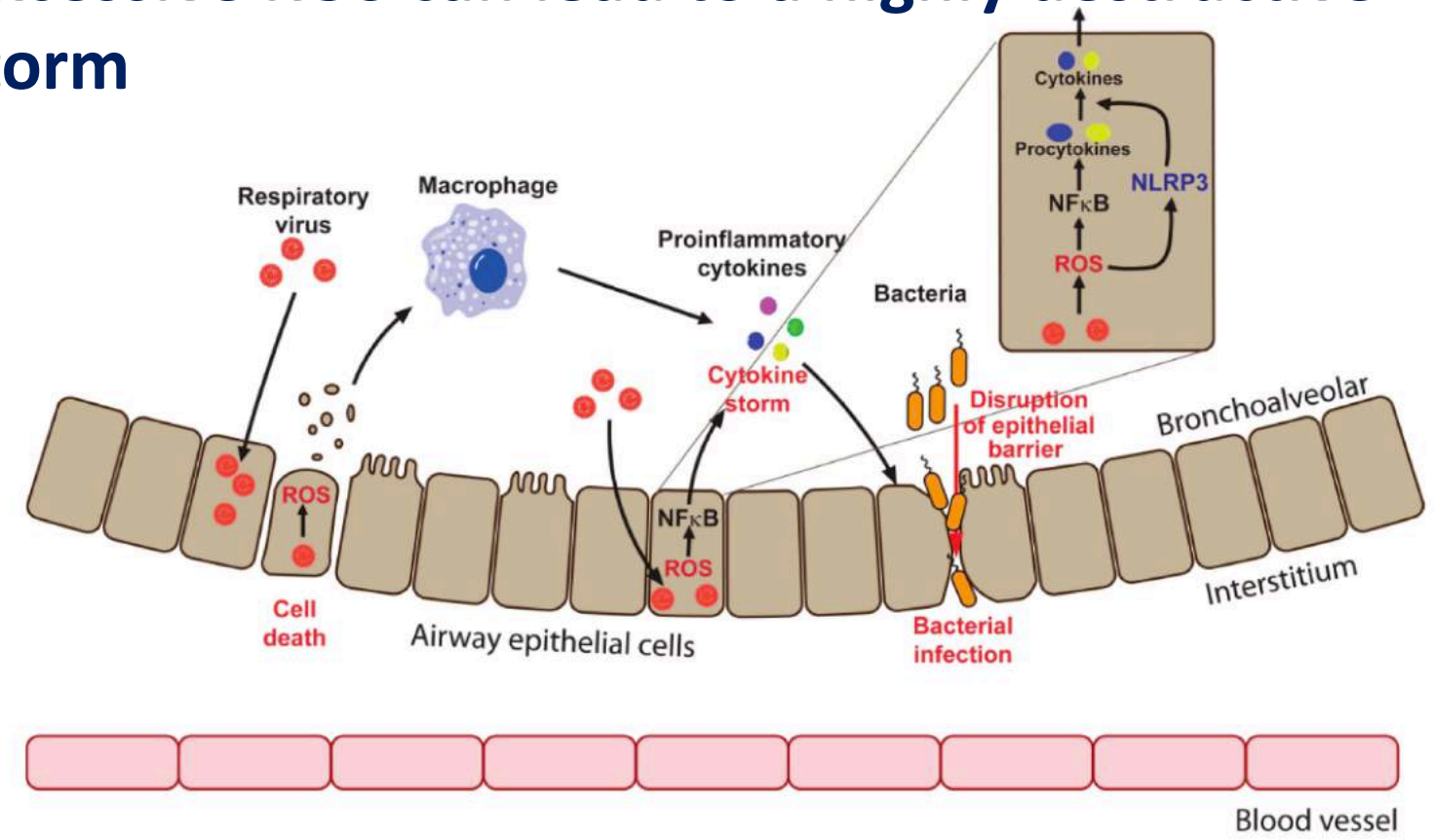
I am a paid clinical advisor for Pure Encapsulations and the author of 'Mitochondria in health and disease', Depression: The mind-body diet and lifestyle connection' and 'Parkinson's disease: An in-depth metabolic guide. I am a visiting lecturer for the College of Naturopathic Medicine and the Centre for Nutrition Education and Lifestyle Management.

Webinars such as this are for educational purposes only and are intended for health care practitioners.

These therapies are not substitutions for standard medical care. Practitioners are solely responsible for the care and treatment provided to their own patients.

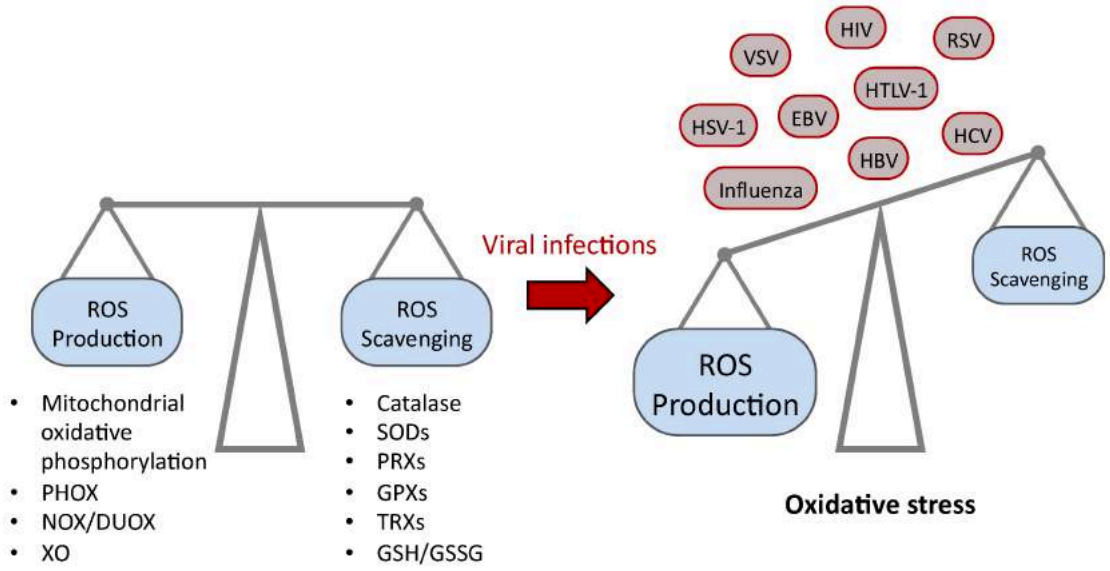
pure encapsulations

Fighting a viral infection requires regulated ROS production – however excessive ROS can lead to a highly destructive cytokine storm



Khomich, O.A., Kochetkov, S.N., Bartosch, B. and Ivanov, A.V., 2018. Redox biology of respiratory viral infections. *Viruses*, *10*(8), p.392.

Maintaining redox homeostasis during viral infection can help prevent tissue damage

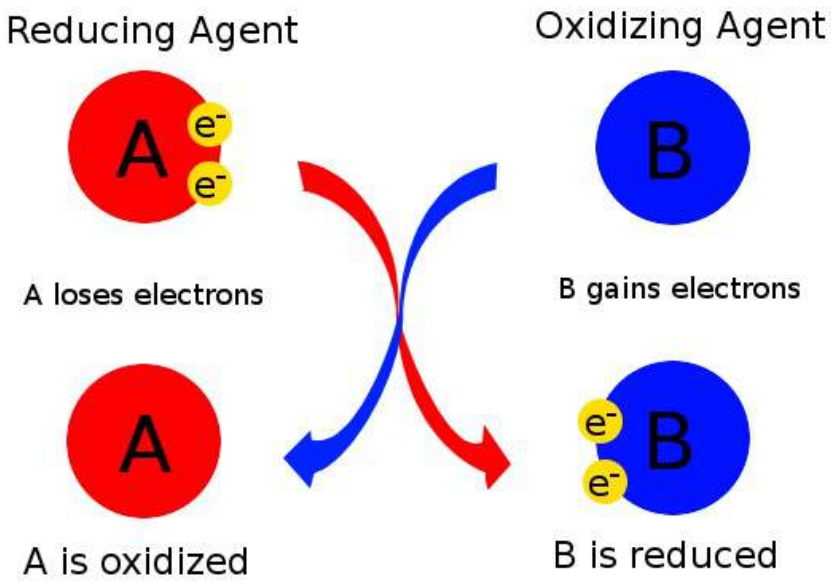


Changes in redox homeostasis in infected cells is one of the key events that is linked to infection with respiratory viruses and linked to inflammation and subsequent tissue damage

Khomich, O.A., Kochetkov, S.N., Bartosch, B. and Ivanov, A.V., 2018. Redox biology of respiratory viral infections. *Viruses*, *10*(8), p.392.
Guillin, O.M., Vindry, C., Ohlmann, T. and Chavatte, L., 2019. Selenium, selenoproteins and viral infection. *Nutrients*, *11*(9), p.2101.

What is Redox?

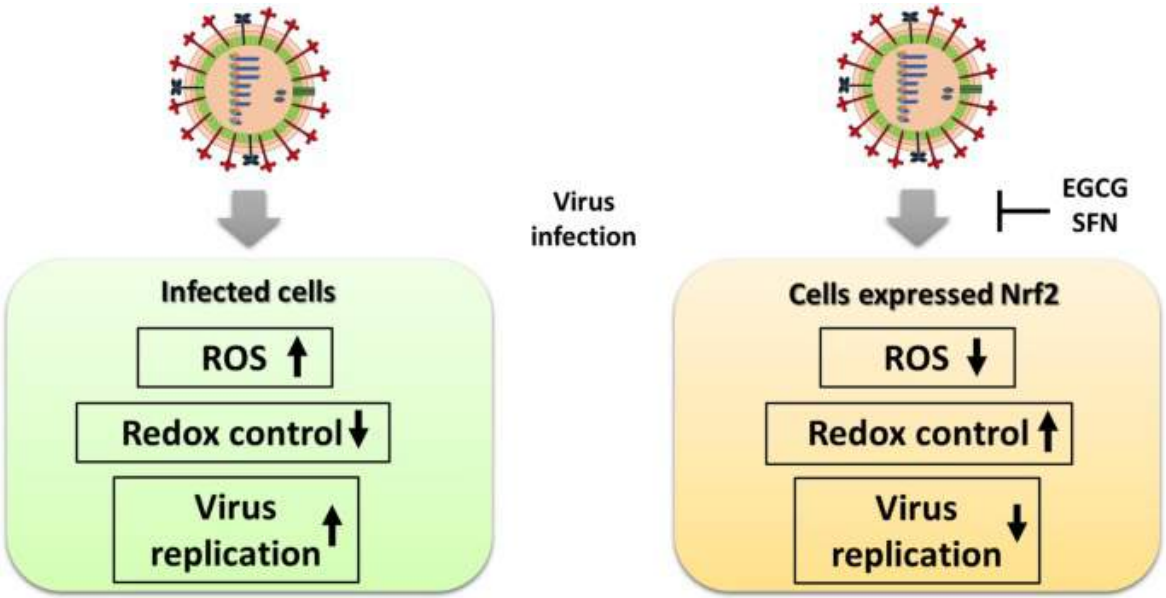
Redox biology embraces events involving shift of balance between reactive oxygen or nitrogen species (ROS and RNS) production and their scavenging



http://chemwiki.ucdavis.edu/Core/Analytical_Chemistry/Electrochemistry/Redox_Chemistry/Oxidizing_and_Reducing_Agents

Khomich, O.A., Kochetkov, S.N., Bartosch, B. and Ivanov, A.V., 2018. Redox biology of respiratory viral infections. *Viruses*, *10*(8), p.392.

Redox control is upregulated by phytonutrients which activate the transcription factor Nrf2



Chen, K.K., Minakuchi, M., Wuputra, K., Ku, C.C., Pan, J.B., Kuo, K.K., Lin, Y.C., Saito, S., Lin, C.S. and Yokoyama, K.K., 2020. Redox control in the pathophysiology of influenza virus infection. *BMC microbiology*, *20*(1), pp.1-22.

Redox control is upregulated by phytonutrients which activate the transcription factor Nrf2

pure encapsulations

THE AMAZING HEALING POTENTIAL OF NATURAL NRF2 ACTIVATORS
http://www.integratedhealthblog.com/category/enzymes/

Glucoraphanin from broccoli protective in respiratory viral infection - Nrf2 involvement

Capsules of broccoli seeds containing glucoraphanin (precursor to Nrf2 inducing sulforaphane) were being taken before the onset of respiratory infection and were continued daily for over a month after the first symptoms. They were found to reduce many of the symptoms rapidly and for a duration of 6–12 h by repeated dosing

600 mmol per day of glucoraphanin was used in the trial – more studies are needed to assess the safety of this high dose

pure encapsulations

World Allergy Organization Journal. 2020 Dec 9:100498.

Vitamin D

- Vitamin D upregulates Nrf2 and reduces oxidative stress
- Vitamin D increases the antiviral activity of bronchial epithelial cells
- Vitamin D downregulates inflammatory cytokine expression, and so helps protect against a cytokine storm

Chen, L., Yang, R., Qiao, W., Zhang, W., Chen, J., Mao, L., Goltzman, D. and Miao, D., 2019. 1, 25-Dihydroxyvitamin D exerts an antiaging role by activation of Nrf2-antioxidant signaling and inactivation of p16/p53-senescence signaling. *Aging Cell*, *18*(3), p.e12951.

Missouri Medicine. 2021 Jan;118(1):68

Telcian, A.G., Zdrenghea, M.T., Edwards, M.R., Laza-Stanca, V., Mallia, P., Johnston, S.L. and Stanciu, L.A., 2017. Vitamin D increases the antiviral activity of bronchial epithelial cells in vitro. *Antiviral research*, *137*, pp.93-101.

Therapeutic potential of resveratrol against emerging respiratory viral infections

Over the last few years, resveratrol has acquired importance for its therapeutic potential against respiratory viral infections

Filardo, S., Di Pietro, M., Mastromarino, P. and Sessa, R., 2020. Therapeutic potential of resveratrol against emerging respiratory viral infections. *Pharmacology & therapeutics*, p.107613.

Quercetin acts as an antiviral agent by inhibiting Influenza A virus

Quercetin is thought to exert its antiviral activity via interaction with viral hemagglutinin which inhibits virus entry into a cell

Quercetin is found in: apples, berries, cruciferous vegetables, capers, grapes, onions, shallots, tea, tomatoes, as well as many nuts and seeds

Wu, W., Li, R., Li, X., He, J., Jiang, S., Liu, S. and Yang, J., 2016. Quercetin as an antiviral agent inhibits influenza A virus (IAV) entry. *Viruses*, *8*(1), p.6.
Li, Y., Yao, J., Han, C., Yang, J., Chaudhry, M.T., Wang, S., Liu, H. and Yin, Y., 2016. Quercetin, inflammation and immunity. *Nutrients*, *8*(3), p.167.

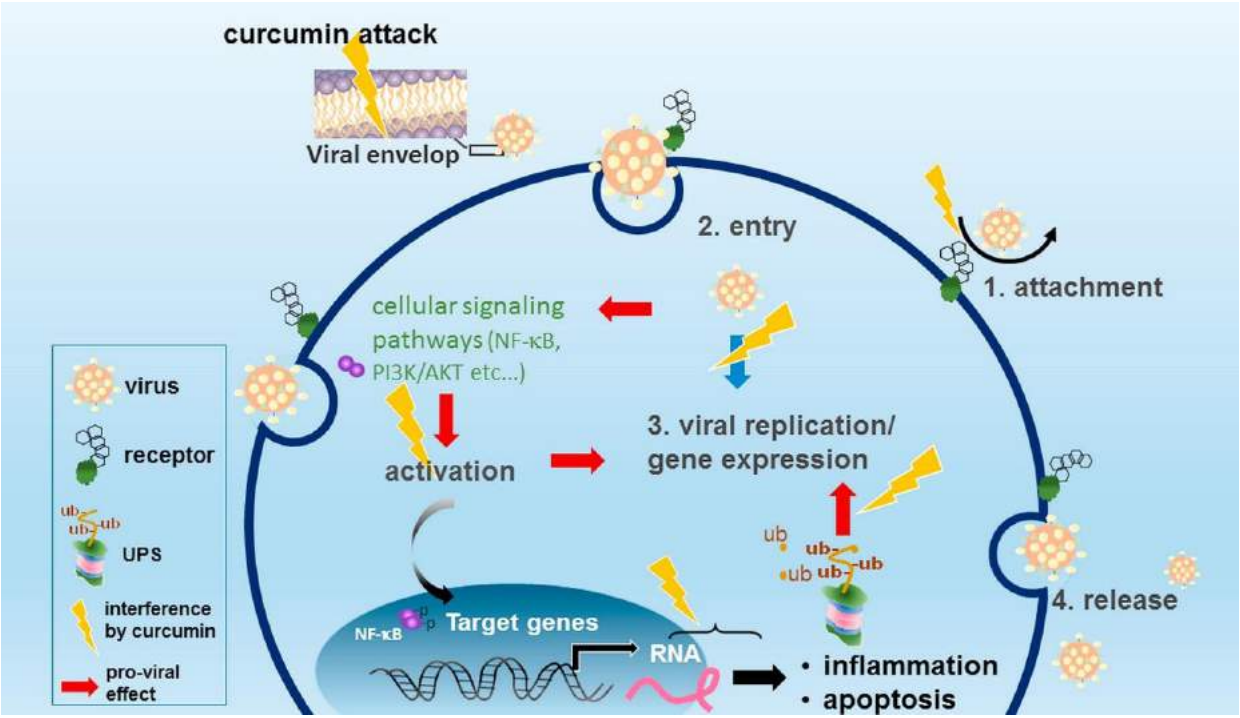
Quercetin reduces the risk of upper respiratory tract infection (URTI) – but only in older physically fit individuals

Older physically fit individuals ingesting 1000 mg/day quercetin experienced a one-third reduction in total number of URTI sick days and URTI severity

Additionally, ascorbate and niacin were supplemented to increase quercetin absorption

Heinz SA, Henson DA, Austin MD, Jin F, Nieman DC. Quercetin supplementation and upper respiratory tract infection: A randomized community clinical trial. Pharmacol Res. 2010 Sep;62(3):237-42. doi: 10.1016/j.phrs.2010.05.001. Epub 2010 May 15. PMID: 20478383; PMCID: PMC7128946.

Antiviral potential of curcumin



Curcumin plays an inhibitory role against infection of numerous viruses. These mechanisms involve either a direct interference of viral replication machinery or suppression of cellular signaling pathways essential for viral replication

Mathew, D. and Hsu, W.L., 2018. Antiviral potential of curcumin. *Journal of functional foods*, *40*, pp.692-699.

Ginkgolic acid from ginkgo biloba can inhibit the fusion and synthesis of viral proteins

In addition to its antiviral properties, ginkgo suppresses inflammation, protecting against acute lung injury

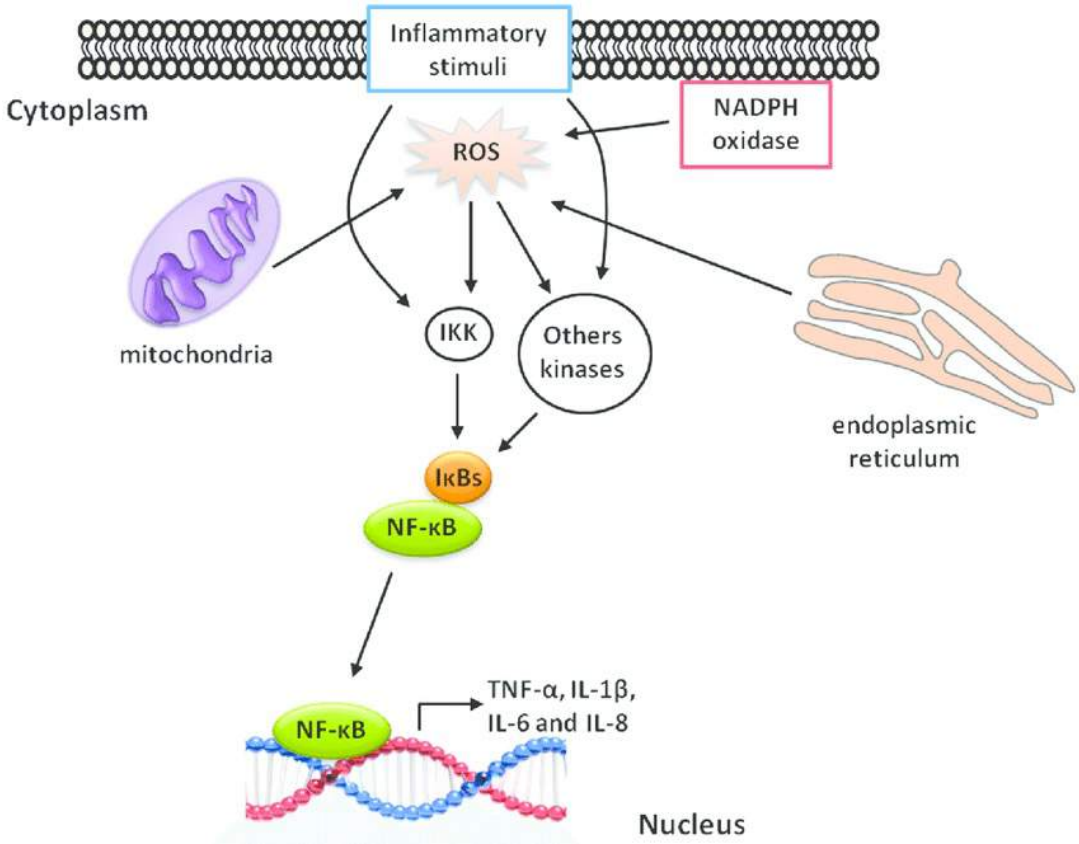
Journal of Basic and Clinical Physiology and Pharmacology. 2021 Feb 16

NF-κB activation is central to the acute respiratory RNA virus-induced cytokine storm

Blocking the activation of the inflammatory transcription factor NF-κB has the potential to reduce the ferocity of a cytokine storm

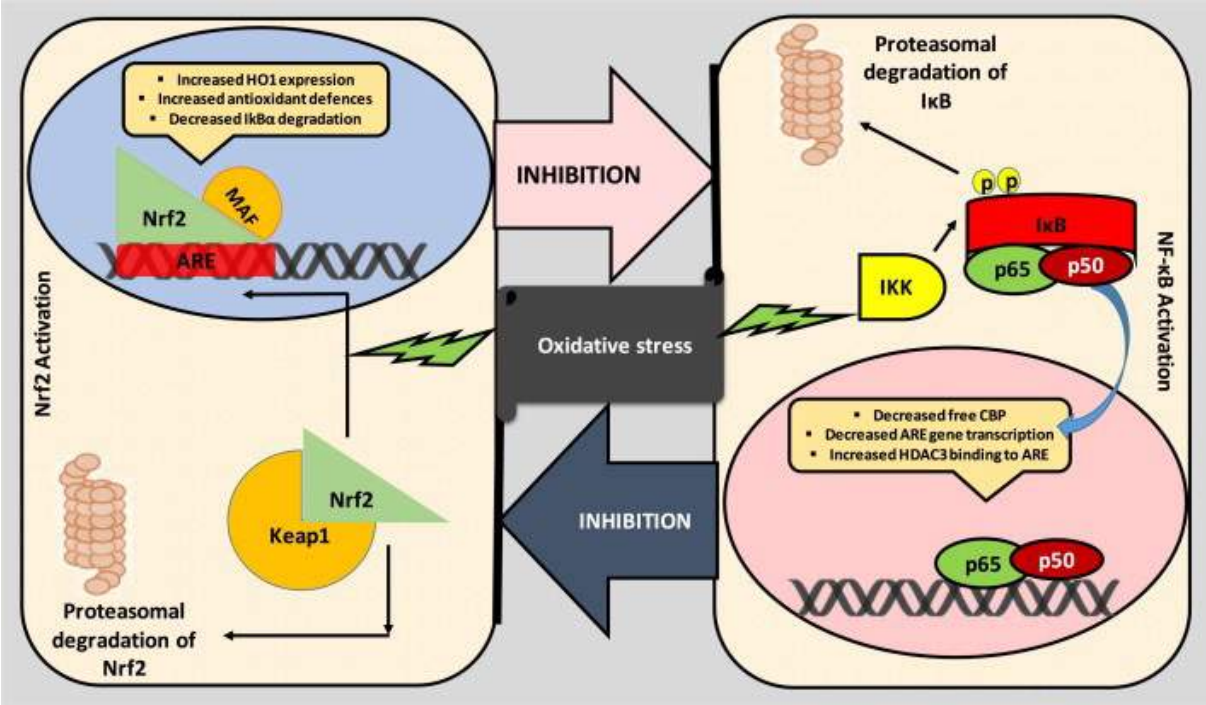
Inflammopharmacology. 2020 Nov 7:1-0.
Frontiers in immunology. 2020;11.

The inflammatory transcription factor NF-κB is sensitive to changes in redox



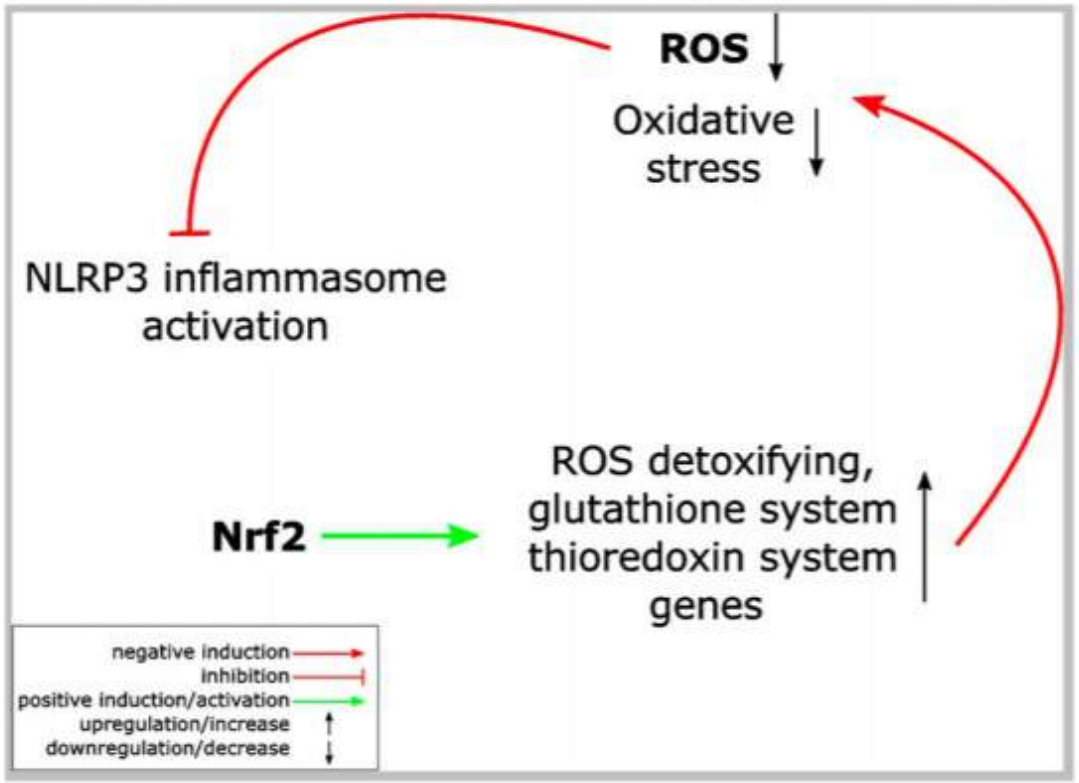
Minatel, I.O., Francisqueti, F.V., Corrêa, C.R. and Lima, G.P.P., 2016. Antioxidant activity of γ-oryzanol: A complex network of interactions. *International journal of molecular sciences*, *17*(8), p.1107.

Nrf2 and NF-κB – in balance they both ensure low inflammation and low levels of oxidative stress



Yerra, V.G., Negi, G., Sharma, S.S. and Kumar, A., 2013. Potential therapeutic effects of the simultaneous targeting of the Nrf2 and NF-κB pathways in diabetic neuropathy. *Redox biology*, *1*(1), pp.394-397.

Nrf2 negatively regulates inflammation by inhibiting reactive oxygen species-induced inflammasome activation



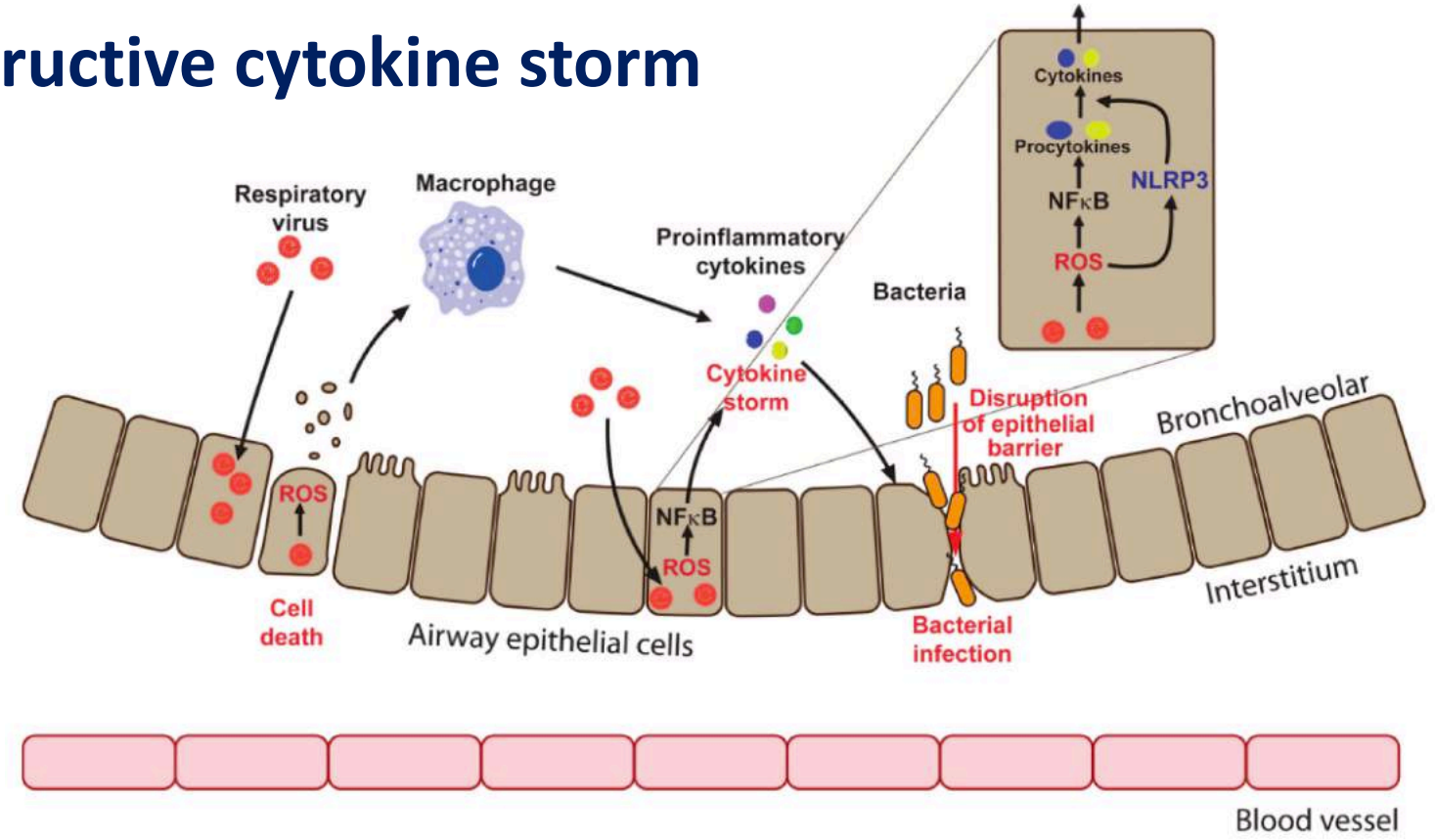
Liu, X., Zhang, X., Ding, Y., Zhou, W., Tao, L., Lu, P., Wang, Y. and Hu, R., 2017. Nuclear factor E2-related factor-2 negatively regulates NLRP3 inflammasome activity by inhibiting reactive oxygen species-induced NLRP3 priming. *Antioxidants & redox signaling*, *26*(1), pp.28-43.

Hennig, P., Garstkiewicz, M., Grossi, S., Di Filippo, M., French, L.E. and Beer, H.D., 2018. The crosstalk between Nrf2 and inflammasomes. *International Journal of Molecular Sciences*, *19*(2), p.562.

In addition to Nrf2 activation quercetin, resveratrol and curcumin are all inhibitors of NF-κB

Natural Product Communications, *15*(12), p.1934578X20976293.
Abba, Y., Hassim, H., Hamzah, H. and Noordin, M.M., 2015. Antiviral activity of resveratrol against human and animal viruses. *Advances in virology*, *2015*.
Xu, Y. and Liu, L., 2017. Curcumin alleviates macrophage activation and lung inflammation induced by influenza virus infection through inhibiting the NF-κB signaling pathway. *Influenza and other respiratory viruses*, *11*(5), pp.457-463.

Fighting a viral infection requires a regulated proinflammatory response – however excessive immune activation can lead to a highly destructive cytokine storm



Khomich, O.A., Kochetkov, S.N., Bartosch, B. and Ivanov, A.V., 2018. Redox biology of respiratory viral infections. *Viruses*, *10*(8), p.392.

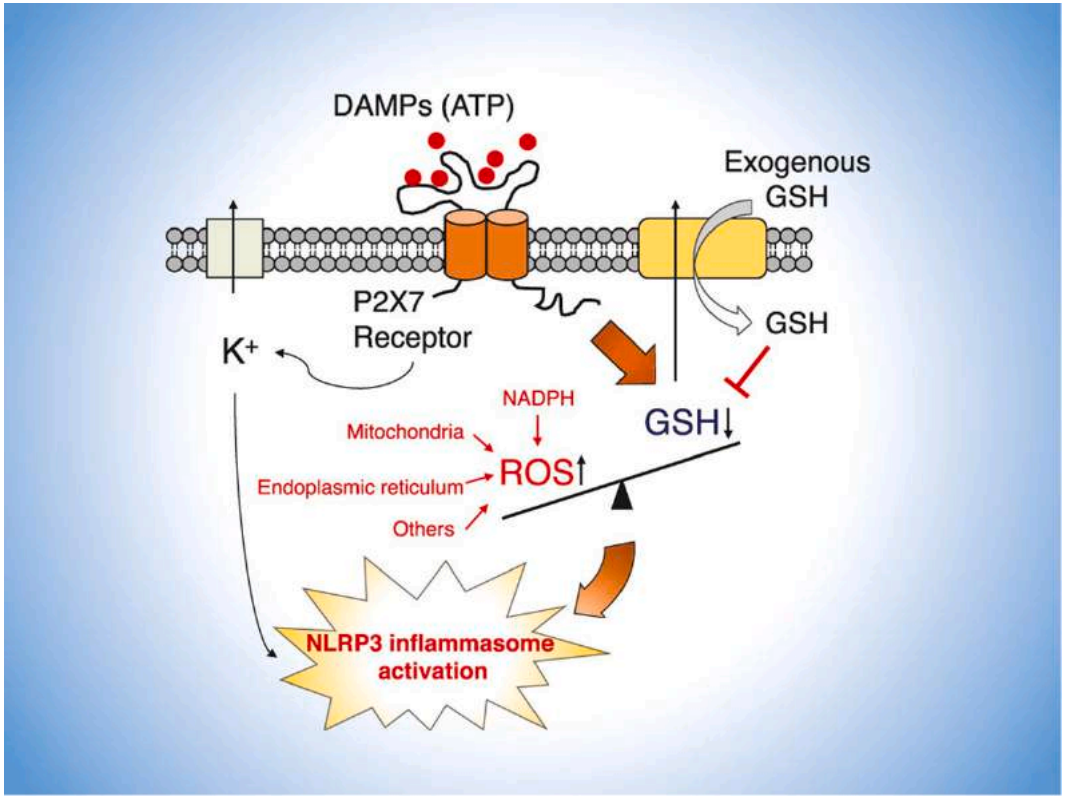
Correct or aberrant inflammasome activation during viral infection

Both inflammasome activation and the subsequent inflammation play significant roles in defending against viral infections

However, aberrant inflammasome activation or chronic inflammation can also lead to severe pathological injury

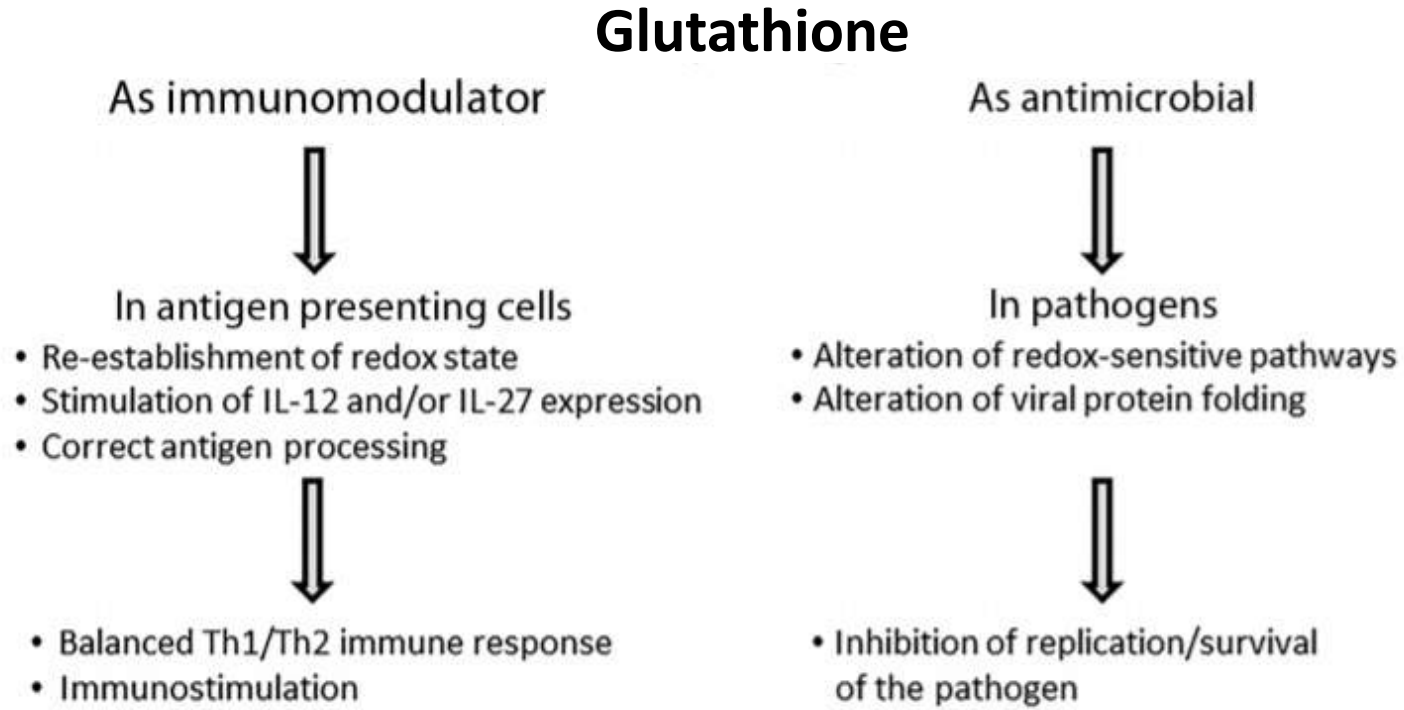
Zhao, C. and Zhao, W., 2020. NLRP3 inflammasome—a key player in antiviral responses. *Frontiers in immunology*, *11*, p.211.

Glutathione is able to restore redox homeostasis and inhibit the inflammasome



Zhang, T., Tsutsuki, H., Islam, W., Ono, K., Takeda, K., Akaike, T. and Sawa, T., 2021. ATP exposure stimulates glutathione efflux as a necessary switch for NLRP3 inflammasome activation. *Redox biology*, p.101930.

Glutathione restoration of redox supports antiviral strategies



Fraternale, A., Brundu, S. and Magnani, M., 2017. Glutathione and glutathione derivatives in immunotherapy. *Biological chemistry*, *398*(2), pp.261-275.

NAC has antiviral and anti-inflammatory effects via its support of glutathione synthesis, Nrf2 activation and NF-κB inhibition

Antioxidants, *10*(2), p.272.

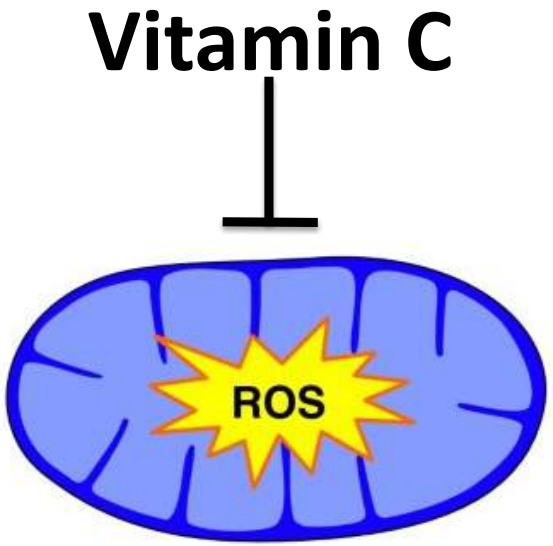
Glutathione and glutathione precursors – Protection against cytokine storm

Glutathione, NAC and alpha lipoic acid may represent a novel treatment approach for blocking NF-κB and addressing “cytokine storm syndrome” and respiratory distress

Respiratory medicine case reports. 2020 Jan 1;30:101063.

Mitochondrial ROS are needed for Inflammasome activation

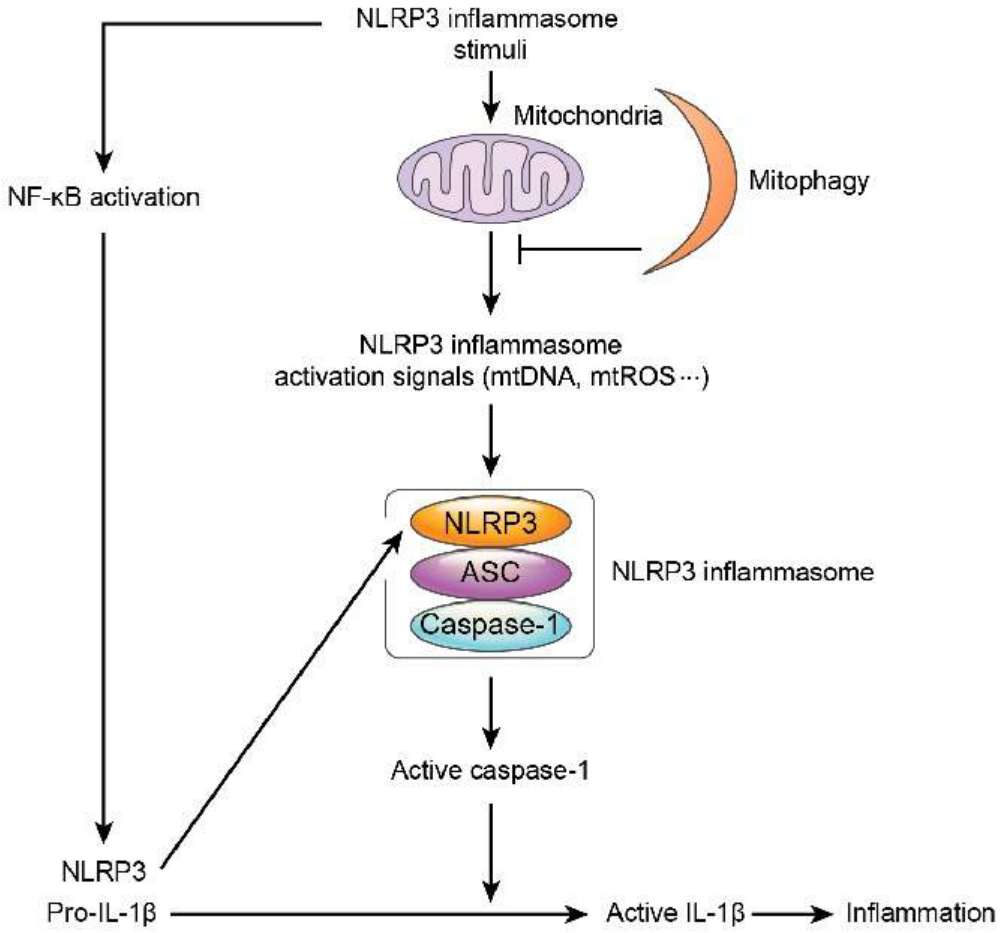
Vitamin C inhibits the activation of the inflammasome by scavenging mitochondrial ROS



Sang, X., Wang, H., Chen, Y., Guo, Q., Lu, A., Zhu, X. and Meng, G., 2016. Vitamin C inhibits the activation of the NLRP3 inflammasome by scavenging mitochondrial ROS. *Inflammasome*, *2*(1), pp.13-19.

Dysfunctional mitochondria drive excessive inflammasome activation via release of mtDAMPS or mtROS

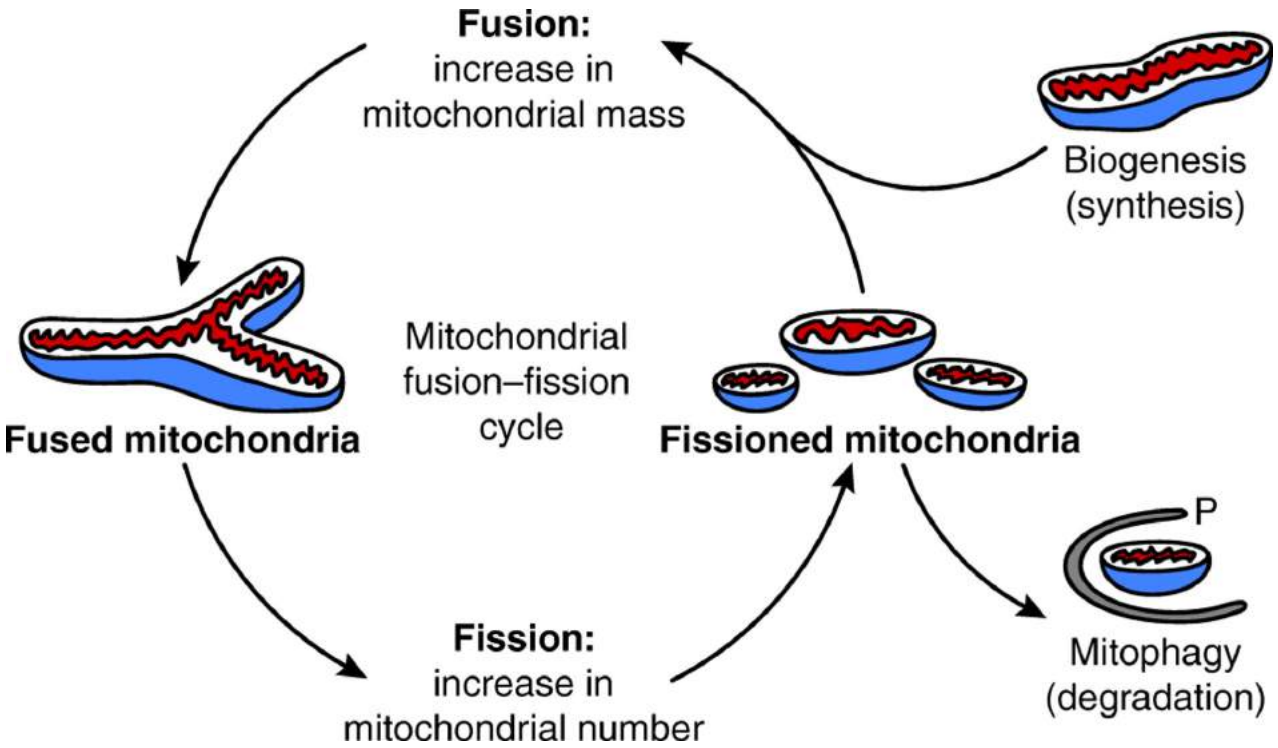
Mitophagy maintains mitochondrial integrity to limit inflammasome activation



DAMPs = Damage-associated molecular patterns

Kim, M.J., Yoon, J.H. and Ryu, J.H., 2016. Mitophagy: a balance regulator of NLRP3 inflammasome activation. *BMB reports*, *49*(10), p.529.

Mitochondrial dynamics (including mitophagy) enable the maintenance of high quality, efficient mitochondria



Insulin resistance undermines mitochondrial dynamics and leads to mitochondrial dysfunction

Mitochondrial fusion is required for efficient antiviral signaling

Seo, A.Y., Joseph, A.M., Dutta, D., Hwang, J.C., Aris, J.P. and Leeuwenburgh, C., 2010. New insights into the role of mitochondria in aging: mitochondrial dynamics and more. *Journal of cell science*, *123*(15), pp.2533-2542.

Sergi, D., Naumovski, N., Heilbronn, L.K., Abeywardena, M., O'Callaghan, N., Lionetti, L. and Luscombe-Marsh, N., 2019. Mitochondrial (dys) function and insulin resistance: From pathophysiological molecular mechanisms to the impact of diet. *Frontiers in physiology*, *10*, p.532.

Quality control of mitochondria and the inflammasome

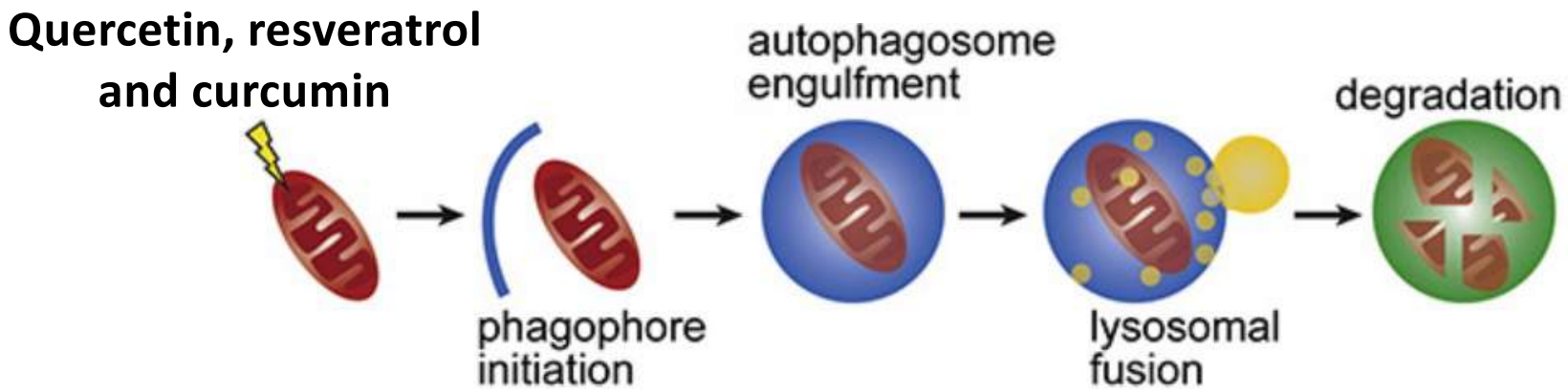
In combination with lessened ATP production, there is a decrease in mitophagy as a person ages, which contributes to unregulated inflammasome activity and inflammation

Mitophagy is a protective function of the cell that keeps inflammation at a manageable level by removing damaged mitochondria, that could contribute to hyper inflammation, especially among already susceptible older patients.

Without autophagy or mitophagy, levels of ROS rise and cause oxidative stress and related tissue damage

Ganji R, Reddy PH. Frontiers in Aging Neuroscience. 2020.

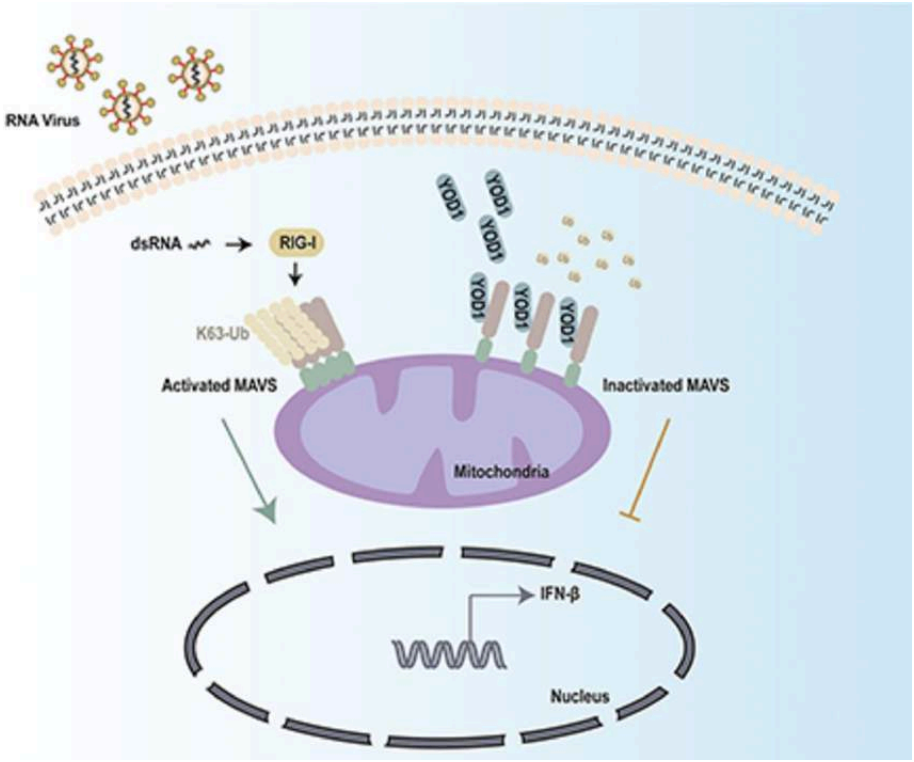
Quercetin, resveratrol and curcumin all support mitophagy to help improve mitochondrial integrity



Tan, S. and Wong, E., 2017. Mitophagy transcriptome: mechanistic insights into polyphenol-mediated mitophagy. *Oxidative medicine and cellular longevity*, *2017*.
Evans, C.S. and Holzbaur, E.L., 2020. Quality control in neurons: mitophagy and other selective autophagy mechanisms. *Journal of molecular biology*, *432*(1), pp.240-260.

Mitochondria and viral immunity

In the event of a viral infection, mitochondria contribute to immunity by engaging the antiviral interferon system

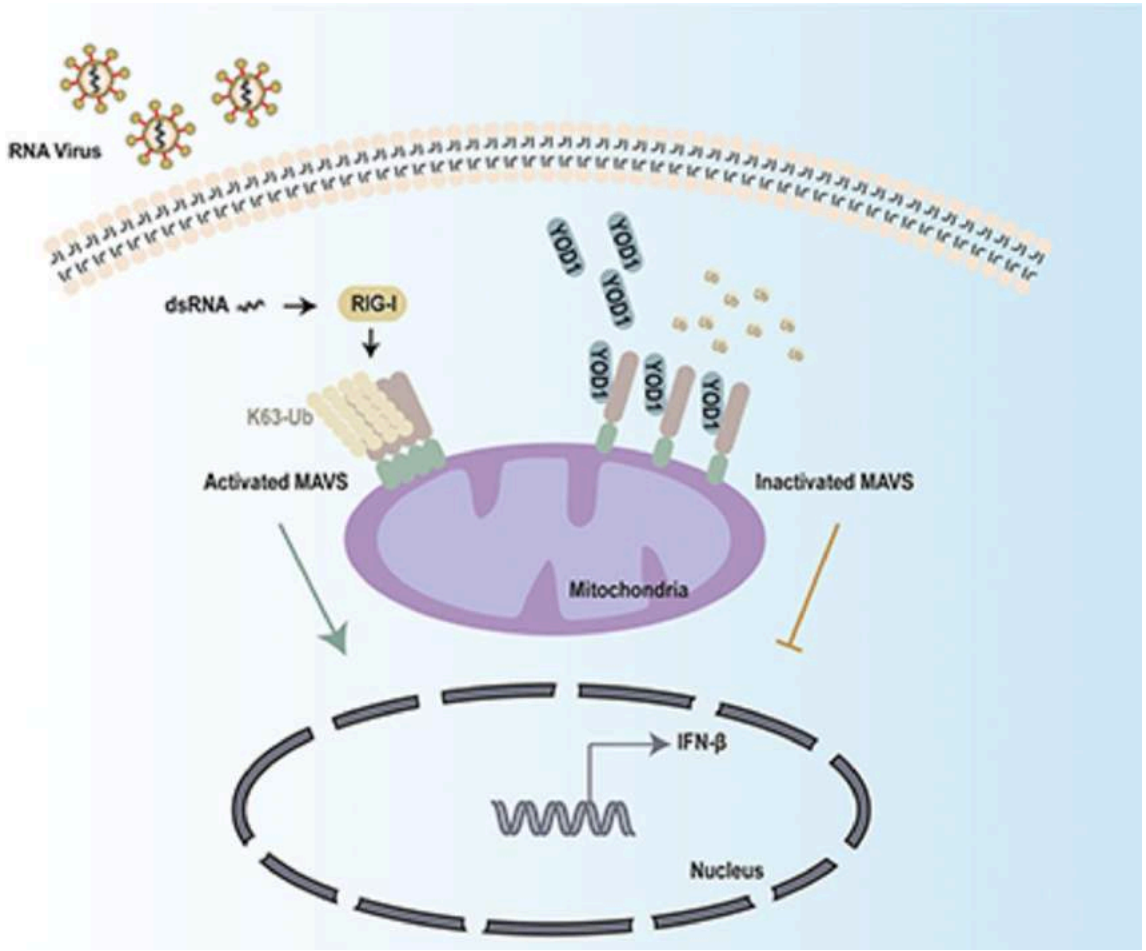


Ganji R, Reddy PH. Frontiers in Aging Neuroscience. 2020.

To fight a virus mitochondrial antiviral signalling (MAVS) proteins need to come into play

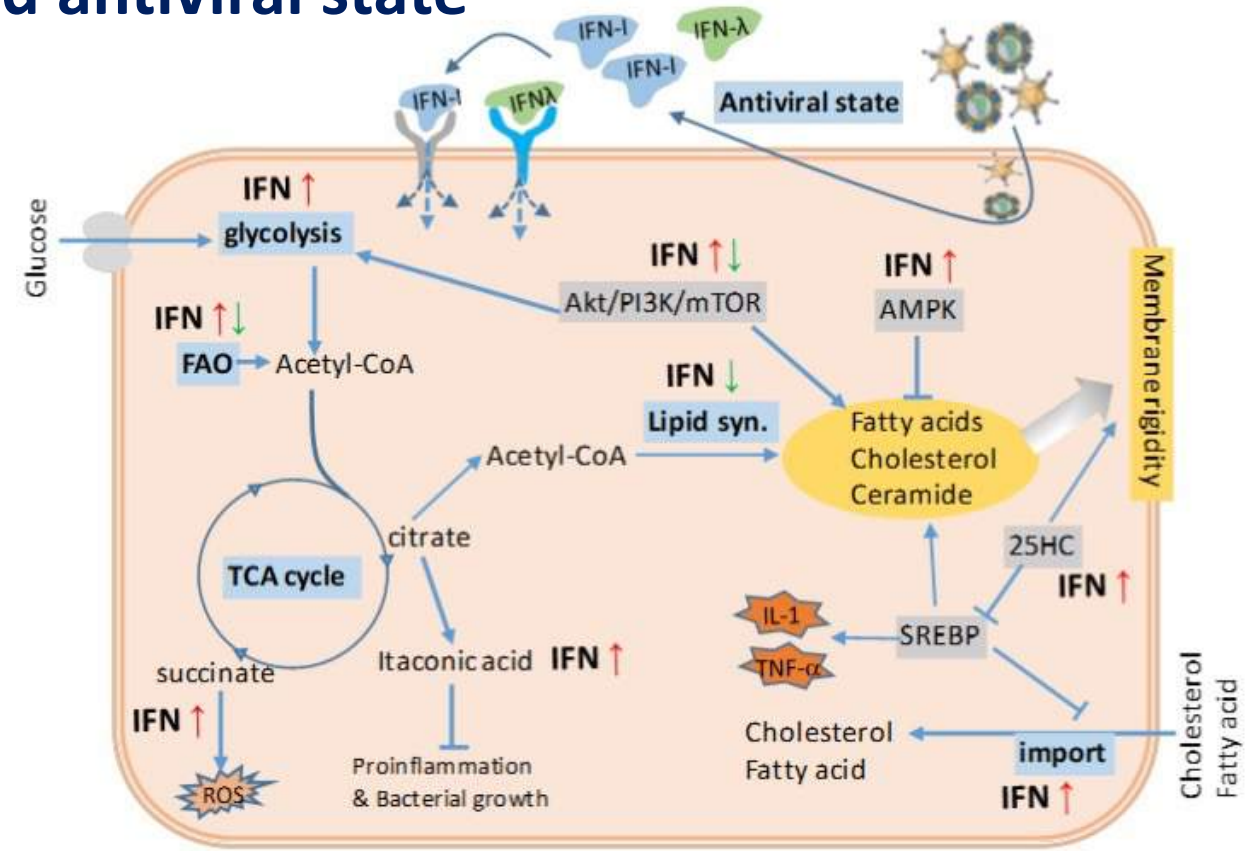
It is MAVS proteins which signal to DNA to express interferon β, to help fight the viral infection

Retinoic acid induced-gene 1 (RIG-1) is required for MAVS activation - vitamin A increases the expression of RIG-1 during viral infection



Liu, C., Huang, S., Wang, X., Wen, M., Zheng, J., Wang, W., Fu, Y., Tian, S., Li, L., Li, Z. and Wang, X., 2019. The otubain YOD1 suppresses aggregation and activation of the signaling adaptor MAVS through Lys63-linked deubiquitination. *The Journal of Immunology*, *202*(10), pp.2957-2970.
Clinical and Experimental Pharmacology and Physiology. 2020 Oct;47(10):1765-7.
Soye, K.J., Trottier, C., Richardson, C.D., Ward, B.J. and Miller Jr, W.H., 2011. RIG-I is required for the inhibition of measles virus by retinoids. *PloS one*, *6*(7), p.e22323.

Interferon β and α place a cell into a fully prepared antiviral state



Tian, Y., Jennings, J., Gong, Y. and Sang, Y., 2019. Viral infections and interferons in the development of obesity. *Biomolecules*, *9*(11), p.726.

Interferon β and α place a cell into a fully prepared antiviral state

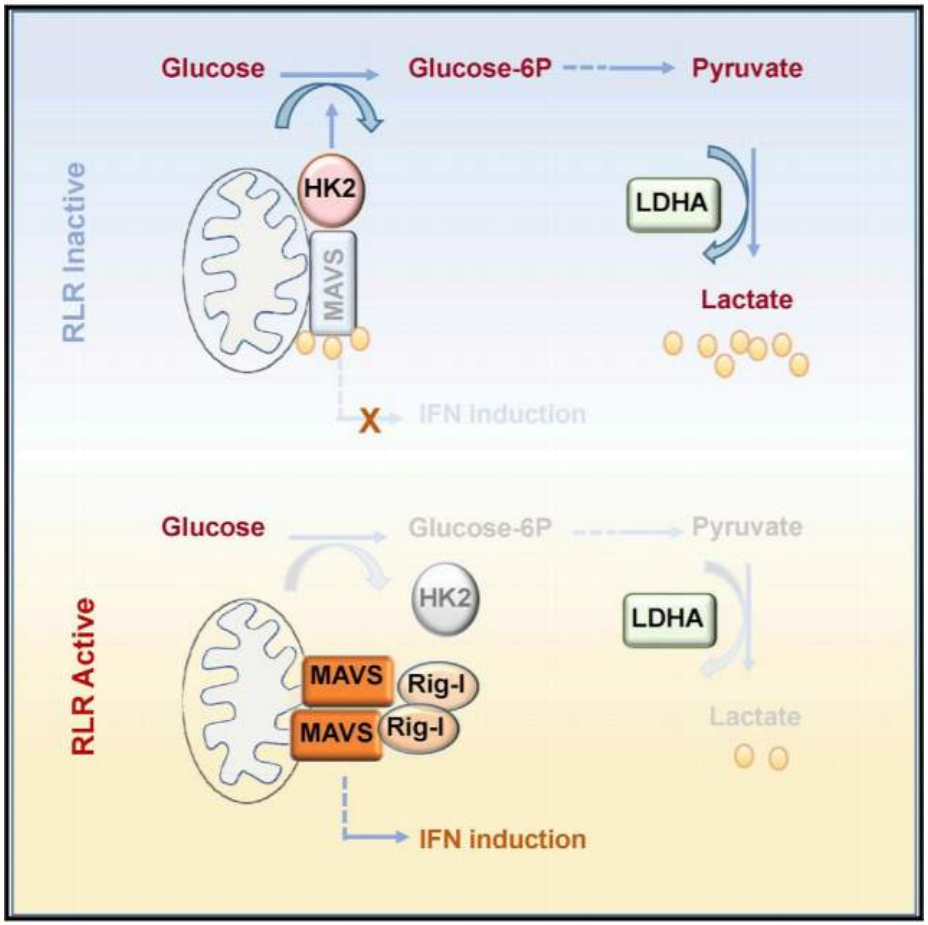
IFN-β modulates glucose metabolism

This regulation of metabolism appears important for the induction of an effective antiviral response

Burke, J.D., Platanias, L.C. and Fish, E.N., 2014. Beta interferon regulation of glucose metabolism is PI3K/Akt dependent and important for antiviral activity against coxsackievirus B3. *Journal of virology*, *88*(6), pp.3485-3495.

High lactate levels, seen in obesity, inhibit the operation of Retinoic acid induced-gene 1 and MAVS

This inhibits antiviral interferon β production



Zhang, W., Wang, G., Xu, Z.G., Tu, H., Hu, F., Dai, J., Chang, Y., Chen, Y., Lu, Y., Zeng, H. and Cai, Z., 2019. Lactate is a natural suppressor of RLR signaling by targeting MAVS. *Cell*, *178*(1), pp.176-189.

Post viral Fatigue

Post viral Fatigue

Sickness behaviour syndrome modulates the immune system and enhances recovery, the interplay between the immune system and central nervous system is an essential part of the overall host defence against pathogenic microorganisms

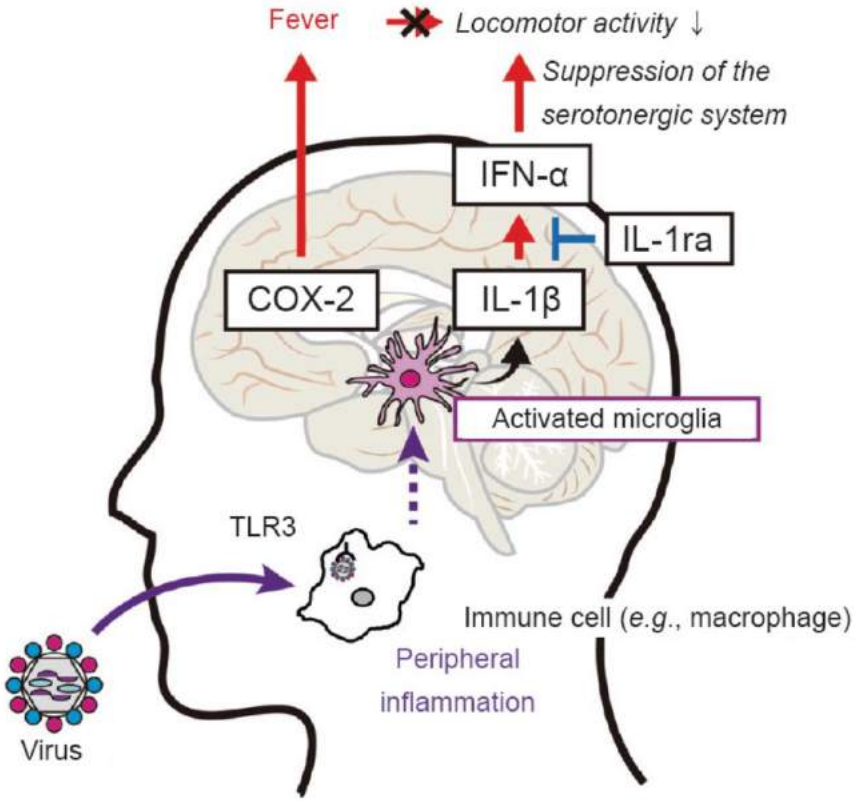
Symptoms of sickness behaviour are social avoidance, fatigue, reduced appetite, and inactivity during disease happen due to the need to contain an individual infection and the body's decision to prioritise rest and healing

Herz, J. and Kipnis, J., 2016. Bugs and brain: how infection makes you feel blue. *Immunity*, *44*(4), pp.718-720.
Johnson, R.W., 2002. The concept of sickness behavior: a brief chronological account of four key discoveries. *Veterinary immunology and immunopathology*, *87*(3-4), pp.443-450.

Post viral Fatigue

Viral infections such as influenza cause the occurrence of acute inflammation, and pro-inflammatory cytokines including interleukin 1β, which is produced by the activation of Toll-like receptors (TLR)

Microglia are activated by TLRs, triggering the symptoms of sickness behaviour and fatigue

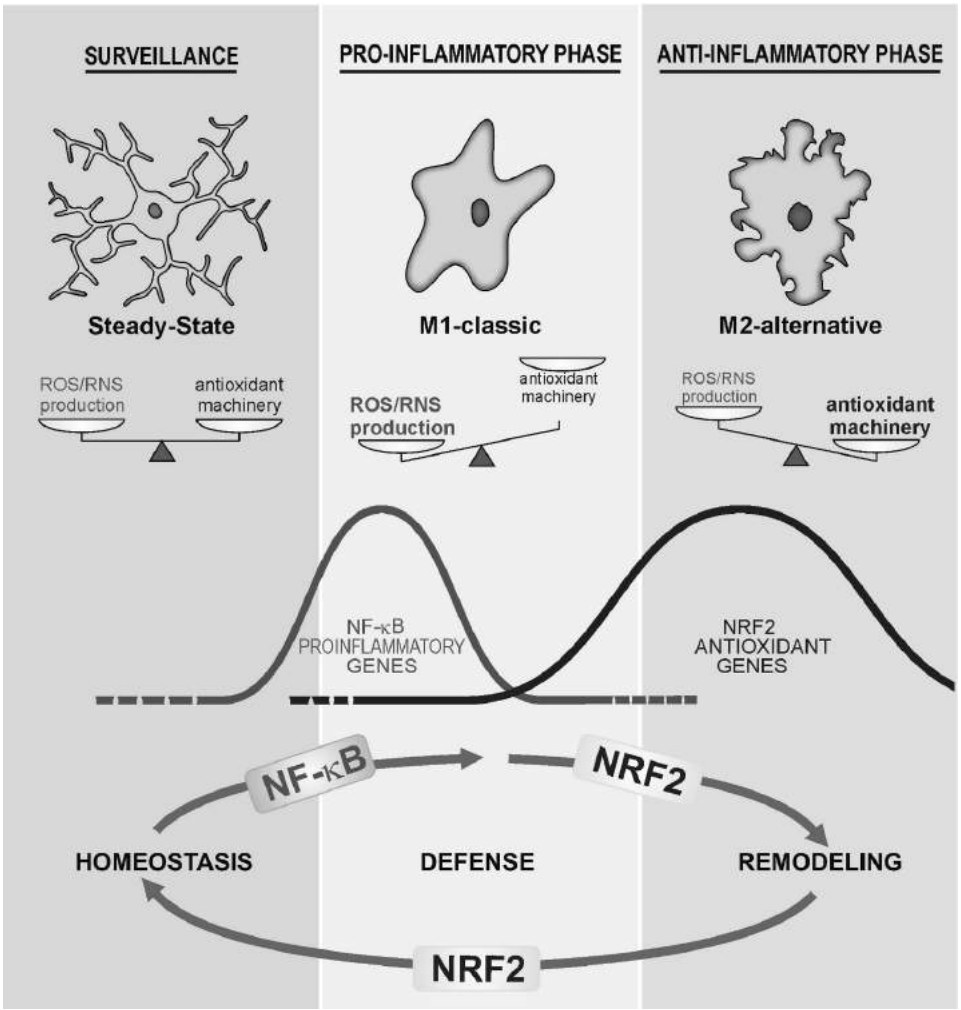


Yamato, M. and Kataoka, Y., 2015. Fatigue sensation following peripheral viral infection is triggered by neuroinflammation: who will answer these questions?. *Neural regeneration research*, *10*(2), p.203.

NF-κB activates M1 microglia

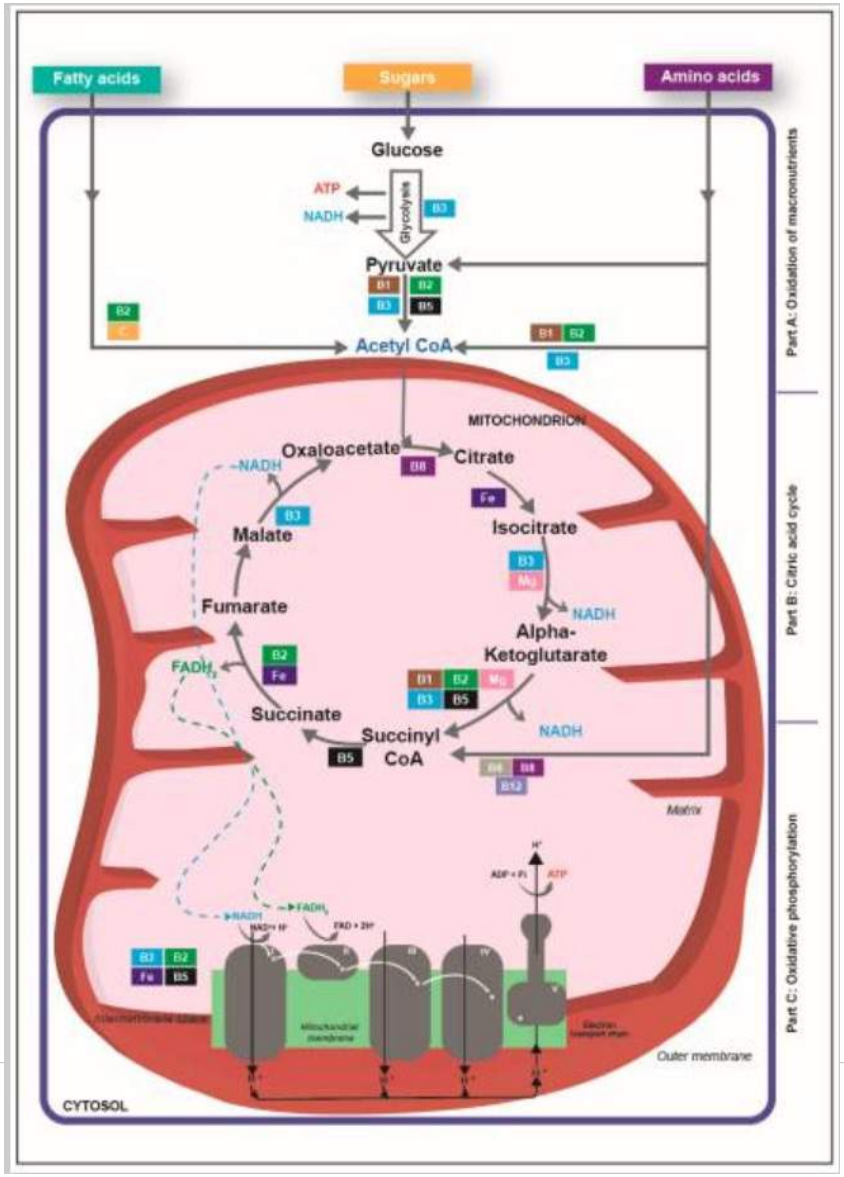
Nrf2 protects against M1 microglia activation

NF-κB participates in the development of fatigue by regulating excitatory and inhibitory neurotransmitters



Rojo, A.I., McBean, G., Cindric, M., Egea, J., López, M.G., Rada, P., Zarkovic, N. and Cuadrado, A., 2014. Redox control of microglial function: molecular mechanisms and functional significance. *Antioxidants & redox signaling*, *21*(12), pp.1766-1801.

Mitochondrial energy production relies on many vitamins and minerals



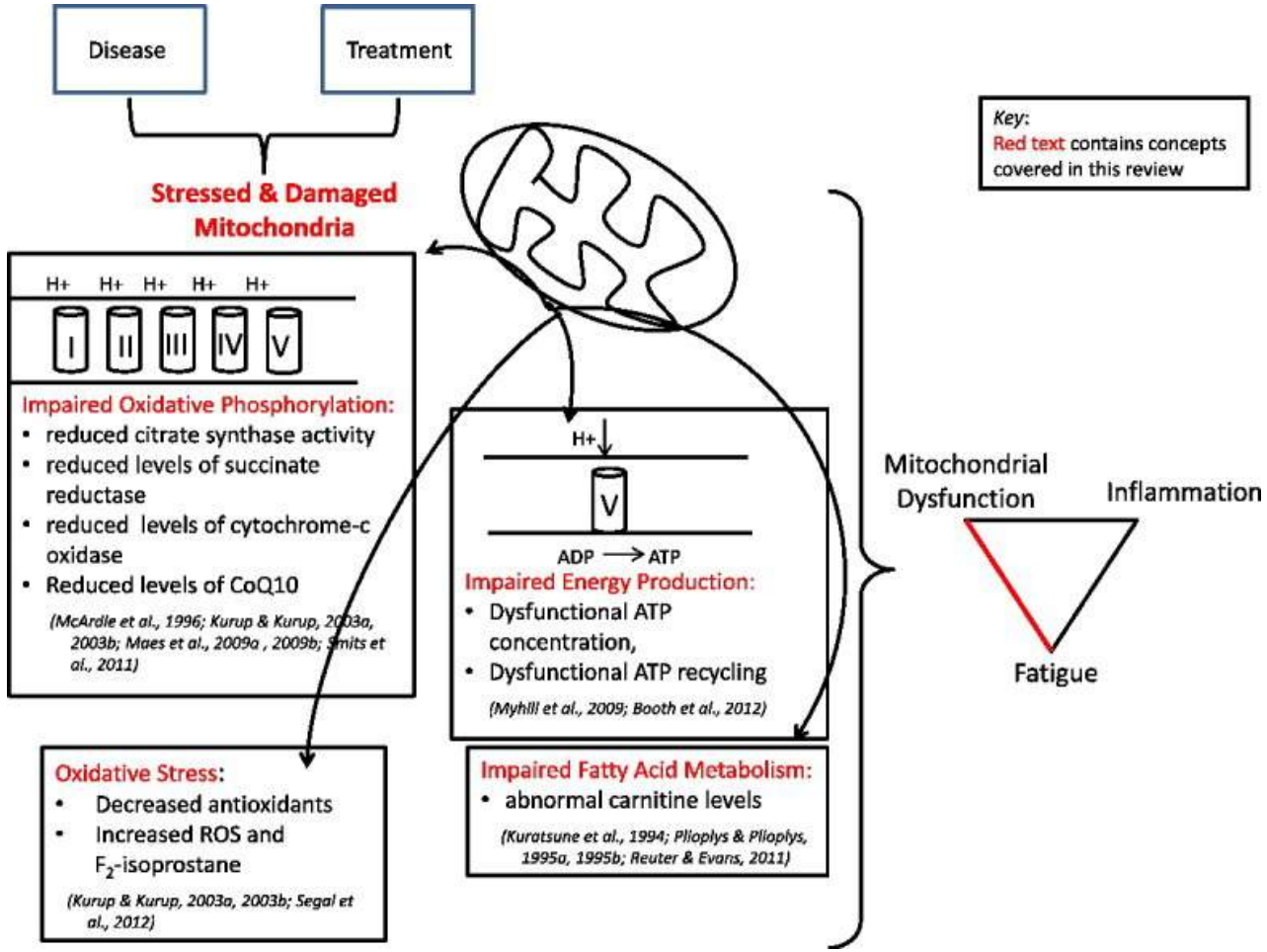
Vitamins:
B1, B2, B3, B5, B6, B12, biotin, C

Minerals:
Mg, Fe

Tardy, A.L., Pouteau, E., Marquez, D., Yilmaz, C. and Scholey, A., 2020. Vitamins and minerals for energy, fatigue and cognition: a narrative review of the biochemical and clinical evidence. *Nutrients*, *12*(1), p.228.

In addition to B vitamins, low levels of Coenzyme Q10 are consistently associated with fatigue

Acetyl-L-Carnitine helps reduce physical and mental fatigue



Castro-Marrero, J., Sáez-Francàs, N., Santillo, D. and Alegre, J., 2017. Treatment and management of chronic fatigue syndrome/myalgic encephalomyelitis: all roads lead to Rome. *British journal of pharmacology*, *174*(5), pp.345-369.

Filler, K., Lyon, D., Bennett, J., McCain, N., Elswick, R., Lukkahatai, N. and Saligan, L.N., 2014. Association of mitochondrial dysfunction and fatigue: a review of the literature. *BBA clinical*, *1*, pp.12-23.

Test Options

Raised GGT is a predictive biomarker of cellular antioxidant inadequacy

Glutathione and vitamin C – Organic Acid test

Plasma or serum vitamin C

8-hydroxy-2'-deoxyguanosine (8-OHdG) – Urinary Oxidative stress marker

Viral tests from Armin Labs –
Including: EBV, CMV, HSV, HHV6, HHV8, Coxsackie

Koenig, G. and Seneff, S., 2015. Gamma-glutamyltransferase: a predictive biomarker of cellular antioxidant inadequacy and disease risk. *Disease markers*, *2015*.

Dietary Compound Summary

Curcumin – turmeric

Quercetin - apples, berries, cruciferous vegetables, capers, grapes, onions, shallots, tea, tomatoes, as well as many nuts and seeds

Sulforaphane/glucoraphanin – broccoli

Resveratrol - grapes

Treatment Options

Intervention	Function	Typical Dosing
CoQ10	Mitochondrial support	120 mg 2-3 times daily
O.N.E.™ Multivitamin B Complex Plus	Mitochondrial support	1 capsule a day
Vitamin C	Redox support/antiviral	>500 mg twice a day Can be up to 6000 mg or bowel tolerance
NAC	Redox support/antiviral	600 mg 1-3 times daily
Reduced Glutathione	Redox support/antiviral	100 mg 1-2 times daily
Vitamin D_3	Antiviral/anti-inflammatory	1000 IU 1-4 times daily

Thank You

Learn more at

www.pure-encapsulations.co.uk/education