

NEWS AND VIEWS

The excessive response: a preparation for harder conditions

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Reactive oxygen species (ROS) are kinds of reactive chemicals mainly formed in mitochondria as byproduct of normal metabolism of oxygen (Balaban et al., 2005). Because of the high reactivity they usually react with proteins, lipid, and nuclear acids (Labuschagne and Brenkman, 2013; Landolfo et al., 2008), and in theory may participate in every aspects of cellular metabolism. The effects of ROS can either be good or bad for organisms. For example, they participate in cell respiration as intermediate products (Devasagayam et al., 2004), act as signals in glucose stimulated insulin secretion (Pi et al., 2007), and be used to attack pathogens in plants (Allan and Fluhr, 1997; Zeng et al., 2015) and microbes in mammals (Kim et al., 2013). However, they will cause damages including protein carbonylation, lipid peroxidation, and DNA mutations at high levels, which contribute to disruptions of cellular homeostasis (Dan Dunn et al., 2015). ROS are believed to have correlations with aging, degenerative disorders, and cancer (Devasagayam et al., 2004). There is complicated antioxidant system composed of enzymes and metabolites in organisms. In response to oxidative stresses antioxidant enzymes such as superoxide dismutases, catalases, and peroxiredoxins are activated to help clearing up ROS (Devasagayam et al., 2004). The FOXO/DAF-16 and Nrf2/SKN-1 mediated redox pathways are also reported to be involved in those processes in mammals and the nematode *C. elegans* (Pi et al., 2007; Putker et al., 2013; Staab et al., 2013). How does the antioxidant system in organisms respond to high level of prooxidant stresses? Recent study shown in *C. elegans* that the response was not only sufficient but also excessive (Ren et al., 2017). When prooxidant stress goes high the antioxidant capacity goes higher and lower levels of reactive oxygen species (ROS) will be observed (Ren et al., 2017). Just like throwing a ball onto the ground: the stronger the force the higher the height will be.

Paraquat (PQ, methyl viologen) is known as the herbicide and is often used as ROS inducer in biomedical studies (Castello et al., 2007; Kiehar et al., 2012). We found that ROS increased in worms treated with 0.1 mmol/L or higher concentrations of paraquat for only thirty minutes and there seemed to be a positive correlation between ROS and prooxidant stresses (Ren et al., 2017). However, the correlation between the two changed from positive to negative under prolonged treatments when paraquat concentration was at the range of 0.1 to 0.5 mmol/L. At these levels worms' growth was retarded and reproduction was reduced although survival was not obviously affected, suggesting sub-lethal effects on worms (Ren et al., 2017). But how could elevated prooxidant stresses lead to lower ROS levels? We believe that although the result is counter intuitive but can be reasonably explained by the "excessive response" of the antioxidant system. In organisms ROS levels should be determined by both the prooxidant and antioxidant capacities. However, when prooxidant capacity elevates to the level beyond some threshold antioxidant mechanisms are excessively activated and lower ROS levels will be observed. That is why ROS increased in worms treated with paraquat for only thirty minutes, because more time should be required for the transcription, translation, and maturation of antioxidant enzymes. This model is also supported by the fact that worms grown on plates containing higher concentrations of paraquat generally showed stronger resistance to adverse conditions (e.g., high salts, heat shock, and extreme oxidative stress) (Ren et al., 2017), and transcription of antioxidants and chaperones were increased under oxidative stresses (Ren et al., 2017; Shin et al., 2011; Zarse et al., 2012). In addition, mutations of *sod2/3* or the redox regulator *daf-16* abolished the negative correlation between ROS and paraquat levels, suggesting major effects of the excessive response was contributed by the antioxidant system (Ren

et al., 2017). Besides FOXO/DAF-16, the Nrf-2/SKN-1 factor was also reported to participate in the antioxidant response (Staab et al., 2013). Our findings are consistent with previous study which showed that increased mitochondrial metabolism and ROS levels due to increased respiration activated antioxidant enzymes and led to further decrease of ROS in the long term (Zarse et al., 2012). Based on the combined results we here proposed the “excessive response” concept illustrated in Fig. 1. It should be noted that persistent prooxidant stresses may exhaust worms by keeping the prooxidant and antioxidant capacities both at high levels and are thus detrimental. However, we do not exclude the possibility that discontinuous prooxidant treatments may still be beneficial and further efforts are required to investigate into this topic.

The excessive response may be a preparation for unpredictable and harder conditions forthcoming. If the extent of the response is only appropriate but not excessive, the organism will be killed immediately by worse environmental factors before it has time to motivate stronger protective mechanisms. Such kind of response may also exist in other cellular processes besides ROS metabolism. It is well known that physical activity is beneficial for health in terms of prevention of heart disease and cancer, fat control, and maintenance of mental function (Berra et al., 1977; Douchi et al., 2000; Hotting and Roder, 2013). However, toxic lactate and ROS are generated during exercise. The paradox can be reconciled by the excessive response which implicates that lactate or ROS will activate stronger protective mechanisms and may protect against potential diseases inducing factors in the long term.

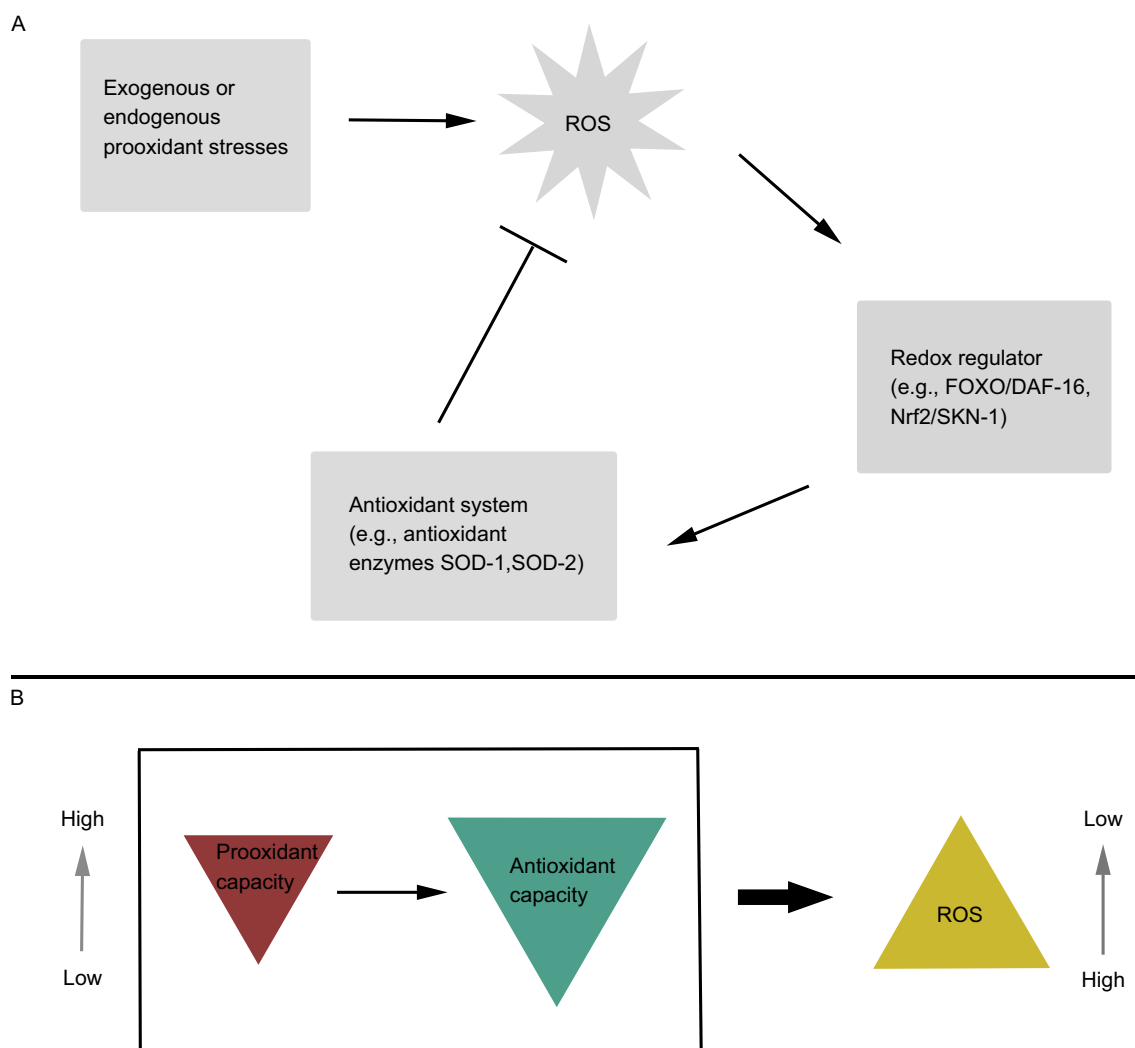


Figure 1. Description of the excessive response of the antioxidant system under prooxidant stresses. (A) Exogenous or endogenous prooxidant stresses promote the generation of ROS. The antioxidant system is persistently and excessively activated by the redox regulators and ROS generation is inhibited in the long term. (B) At the level beyond some threshold, when the prooxidant capacity goes high the antioxidant capacity will go higher and lower ROS levels will be observed.

Ionizing radiation and ROS inducing strategies are widely used for cancer treatments (Gupta et al., 2012; Kong et al., 2000; Schumacker, 2006). According to the excessive response model survived tumor cells may obtain higher capability to deal with additional ROS-generating insults and higher dose of irradiation, which makes them harder to be killed by the immune system. Thus, “super” tumor cell is born out of adverse environment, which to some extent explains why people with cancer usually die sooner after radiotherapy. Consistently, adaptation to hydrogen peroxide enhances PC12 cell tolerance against oxidative damage (Chen et al., 2005), and worms grown on plates containing higher level of the prooxidant paraquat show stronger resistance to multiple kinds of stresses (Ren et al., 2017). Similar kinds of excessive responses may also exist in lipid metabolism, inflammation, and other cellular processes, which deserve further investigations.

FOOTNOTES

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REFERENCES

- Allan AC, Fluhr R (1997) Two distinct sources of elicited reactive oxygen species in tobacco epidermal cells. *Plant Cell* 9(9):1559–1572
- Balaban RS, Nemoto S, Finkel T (2005) Mitochondria, oxidants, and aging. *Cell* 120(4):483–495
- Berra KA, Fair JM, Houston N (1977) The role of physical exercise in the prevention and treatment of coronary heart disease. *Heart Lung* 6(2):288–292
- Castello PR, Drechsel DA, Patel M (2007) Mitochondria are a major source of paraquat-induced reactive oxygen species production in the brain. *J Biol Chem* 282(19):14186–14193

- Chen ZH, Yoshida Y, Saito Y, Niki E (2005) Adaptation to hydrogen peroxide enhances PC12 cell tolerance against oxidative damage. *Neurosci Lett* 383(3):256–259
- Dan Dunn J, Alvarez LA, Zhang X, Soldati T (2015) Reactive oxygen species and mitochondria: a nexus of cellular homeostasis. *Redox Biol* 6:472–485
- Devasagayam TP, Tilak JC, Boloor KK, Sane KS, Ghaskadbi SS, Lele RD (2004) Free radicals and antioxidants in human health: current status and future prospects. *J Assoc Phys India* 52:794–804
- Douchi T, Yamamoto S, Oki T, Maruta K, Kuwahata R, Yamasaki H, Nagata Y (2000) The effects of physical exercise on body fat distribution and bone mineral density in postmenopausal women. *Maturitas* 35(1):25–30
- Gupta SC, Hevia D, Patchva S, Park B, Koh W, Aggarwal BB (2012) Upsides and downsides of reactive oxygen species for cancer: the roles of reactive oxygen species in tumorigenesis, prevention, and therapy. *Antioxid Redox Signal* 16(11):1295–1322
- Hotting K, Roder B (2013) Beneficial effects of physical exercise on neuroplasticity and cognition. *Neurosci Biobehav Rev* 37(9 Pt B):2243–2257
- Kielar F, Hesel ME, Wang Q, Franz KJ (2012) Prochelatase BHAPI protects cells against paraquat-induced damage by ROS-triggered iron chelation. *Metallomics* 4(9):899–909
- Kim HJ, Kim CH, Ryu JH, Kim MJ, Park CY, Lee JM, Holtzman MJ, Yoon JH (2013) Reactive oxygen species induce antiviral innate immune response through IFN- λ regulation in human nasal epithelial cells. *Am J Respir Cell Mol Biol* 49(5):855–865
- Kong Q, Beel JA, Lillehei KO (2000) A threshold concept for cancer therapy. *Med Hypotheses* 55(1):29–35
- Labuschagne CF, Brenkman AB (2013) Current methods in quantifying ROS and oxidative damage in *Caenorhabditis elegans* and other model organism of aging. *Ageing Res Rev* 12(4):918–930
- Landolfo S, Politi H, Angelozzi D, Mannazzu I (2008) ROS accumulation and oxidative damage to cell structures in *Saccharomyces cerevisiae* wine strains during fermentation of high-sugar-containing medium. *Biochim Biophys Acta* 1780(6):892–898
- Pi J, Bai Y, Zhang Q, Wong V, Floering LM, Daniel K, Reece JM, Deeney JT, Andersen ME, Corkey BE et al (2007) Reactive oxygen species as a signal in glucose-stimulated insulin secretion. *Diabetes* 56(7):1783–1791
- Putker M, Madl T, Vos HR, de Ruiter H, Visscher M, van den Berg MC, Kaplan M, Korswagen HC, Boelens R, Vermeulen M et al (2013) Redox-dependent control of FOXO/DAF-16 by transportin-1. *Mol Cell* 49(4):730–742
- Ren Y, Chen S, Ma M, Zhang C, Wang K, Li F, Guo W, Huang J, Zhang C (2017) Do ROS really slow down aging in *C. elegans*? [arXiv:1704.06086v2\[q-bio.CB\]](https://arxiv.org/abs/1704.06086v2[q-bio.CB])
- Schumacker PT (2006) Reactive oxygen species in cancer cells: live by the sword, die by the sword. *Cancer Cell* 10(3):175–176
- Shin H, Lee H, Fejes AP, Baillie DL, Koo HS, Jones SJ (2011) Gene expression profiling of oxidative stress response of *C. elegans* aging defective AMPK mutants using massively parallel transcriptome sequencing. *BMC Res Notes* 4:34
- Staab TA, Griffen TC, Corcoran C, Evgrafov O, Knowles JA, Sieburth D (2013) The conserved SKN-1/Nrf2 stress response

- pathway regulates synaptic function in *Caenorhabditis elegans*. PLoS Genet 9(3):e1003354
- Zarse K, Schmeisser S, Groth M, Priebe S, Beuster G, Kuhlow D, Guthke R, Platzer M, Kahn CR, Ristow M (2012) Impaired insulin/IGF1 signaling extends life span by promoting mitochondrial L-proline catabolism to induce a transient ROS signal. Cell Metab 15(4):451–465
- Zeng L, Zhou J, Li B, Xing D (2015) A high-sensitivity optical device for the early monitoring of plant pathogen attack via the in vivo detection of ROS bursts. Front Plant Sci 6:96