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COMMENTARY

Effects of anti-aging redox medicine on health span and lifespan

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Anti-aging redox medicine is a field focused on addressing the effects of aging by targeting cellular redox (reduction–oxidation) processes, which play crucial roles in various biological functions. Redox processes involve the transfer of electrons between molecules, and maintaining their balance is essential for cellular health and function. With age, these processes tend to become dysregulated, leading to increased oxidative stress and damage, which are associated with age-related diseases and a decline in physiological functions.

Some research suggests that interventions targeting redox signaling pathways could slow down the aging process at a molecular level. By promoting cellular repair mechanisms and reducing the accumulation of damage, these interventions may help delay age-related decline of physiological functions and extend lifespan. Indeed, many age-related diseases are associated with oxidative stress and dysregulated redox signaling. By addressing these underlying mechanisms, anti-aging redox medicine may help prevent or delay the onset of conditions such as cardiovascular disease, Alzheimer's disease, and cancer, thereby extending health span.

However, while anti-aging redox medicine holds significant potential, as supported by encouraging results in experimental models, more study is needed to fully understand its mechanisms of action and long-term effects in humans. Additionally, individual responses to such interventions may vary based on factors such as genetics, lifestyle, and environmental influences.

The complex but fascinating and promising issue of anti-aging redox medicine has been addressed in the 2023 Oxygen Club of California (OCC) Workshop held in November 2023 in Alba, Italy, a meeting invited to be part of the biannual Healthy Aging Week organized by the Fondazione Piera Pietro and Giovanni Ferrero. Taking inspiration from that successful OCC Workshop, the journal Redox Experimental Medicine created a collection of research articles and reviews contributed by presenters at that workshop. A significant bulk of thus collected reports are focused on vitamins and natural compounds proven to be useful in prevention protocols protecting against or counteracting age-related chronic disease, skin aging, and in particular the muscle dysfunction so frequent in the elderly.

The emerging use of natural phenolic compounds as a promising approach to extending lifespan by modulating metabolic pathways involved in aging has been reviewed (Spagnuolo *et al.* 2023). Indeed, selected phenolic compounds, namely quercetin, resveratrol, and curcumin, could contribute, by targeting different mechanisms associated with aging, in particular oxidative stress and inflammation, to extend lifespan and improve overall health in aging individuals. In summary, the review highlights the potential of phenolic compounds as a natural approach to combat aging by targeting various metabolic pathways. Their abundance in the diet, diverse biological activities, and ability to modulate aging-related processes position them as promising candidates for anti-aging nutraceutical support.

The significance of vitamin D in skeletal muscle function, particularly its antioxidant action in counteracting muscle dysfunction has been highlighted (Russo *et al.* 2023). Vitamin D deficiency is prevalent globally, which can lead to mitochondrial dysfunction, reduced ATP production, oxidative damage, and impaired muscle function. Despite widespread vitamin D deficiency, it has been identified as a key compound

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for improving muscle weakness and conditions related to sarcopenia. Overall, the paper. provides a comprehensive overview of the complex interplay between inflammation, oxidative stress, and muscle dysfunction, highlighting the critical role of vitamin D in maintaining muscle health and suggesting avenues for further study and intervention.

While clinical trial evidence regarding the health benefits of vitamin E supplements is limited and equivocal, epidemiological data suggest long-term benefits of increased α-tocopherol intake through 'healthy' diets rich in vegetables, fruits, fish, nuts, seeds, and fiber. Overall, an updated narrative review (Traber 2023) emphasizes the critical role of α-tocopherol in maintaining metabolic health and protecting tissues from oxidative damage, while also highlighting the importance of dietary sources of vitamin E in promoting overall wellbeing. The elaborate regulation of α-tocopherol concentrations by the human body suggests that the consistent consumption of the recommended amounts of dietary α-tocopherol (15 mg daily) over a lifetime is protective of the at-risk tissues, as well as providing protection from chronic diseases.

The review 'Carotenoid basics: from food to skin' (Weber & Grune 2023) provides a comprehensive and very clear graphical overview of carotenoids, detailing their journey from food to skin. Factors that affect carotenoid absorption are first summarized, outlining the seasonal variations in plasma concentrations of the six most prominent carotenoids, namely α-carotene, β-carotene, lutein, zeaxanthin, lycopene, and β-cryptoxanthin. The paper also focuses on the process of transport across the enterocyte and the receptors involved in carotenoid uptake by peripheral cells and it illustrates how carotenoids are delivered to various tissues in the body, including the skin. Finally, the main factors that affect the accumulation of carotenoids in the skin, such as sun exposure, dietary habits, and metabolic processes are considered.

The pilot study 'Intake of palmitic acid and its association with metabolic flexibility in middle-aged individuals: a preliminary study' (Murru *et al.* 2023) emphasizes the potential nutritional importance of palmitic acid intake in promoting metabolic flexibility and regulating body fat percentage in middle-aged individuals. Palmitic acid, a very common saturated fatty acid, appears to enhance substrate oxidation capacity, which contributes to improved metabolic flexibility. By promoting metabolic flexibility, palmitic acid intake may help mitigate excessive body fat deposition in middle-aged adults. The study underscores the significance of dietary composition, particularly the intake of specific fat classes like palmitic acid, in influencing metabolic health outcomes. It suggests that within physiological limits, saturated fatty acids, including palmitic acid, may play a beneficial role in metabolic function. The special collection is completed by three reviews that feature redox mechanisms contributing to the development

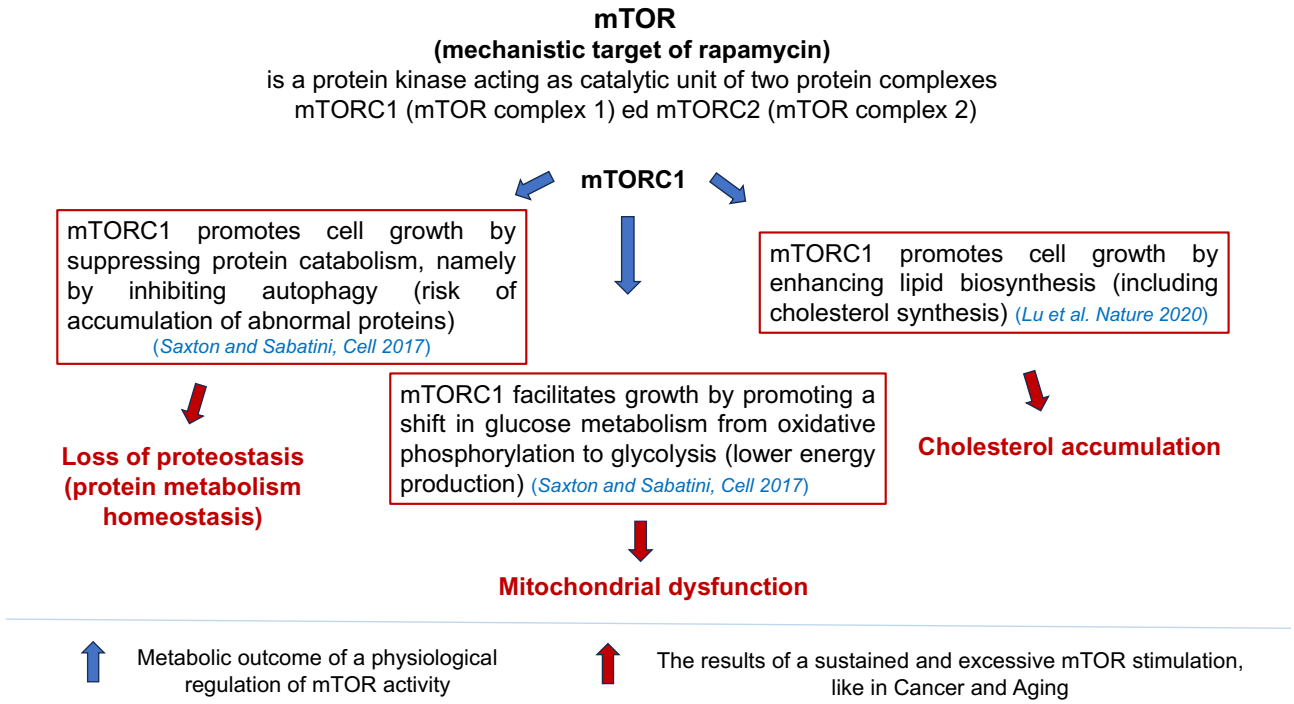

Figure 1

mTOR pathophysiology: a schematic representation of its metabolic effects in physiological and pathological conditions. mTOR, mammalian target of rapamycin.

of major chronic diseases or reduced skeletal muscle contractility or the therapeutic effect of metformin, a specific drug in the front line against type 2 diabetes.

Oxidative damage, particularly from reactive oxygen species (ROS), is identified as a major factor associated with aging. Indeed, oxidative stress is suggested to play a significant role in the decline of muscle function with age (Jackson 2023). In the young adult, 'redox-regulated' pathways are efficiently able to respond to oxidative stress. These pathways are beneficial for muscle adaptation to exercise, indicating that some level of ROS generation during muscle contraction is normal and even helpful for signaling adaptations. However, the beneficial adaptations mediated by redox-regulated pathways are diminished or attenuated during aging, contributing to age-related muscle decline. In summary, this work highlights the detrimental impact of aging on muscle mass and function, the role of oxidative stress in this process, the importance of redox-regulated pathways in muscle adaptation to exercise, and how these pathways are impaired with aging.

An informative analysis of the impact of dysregulation of a key redox-regulated signaling pathway in age-related diseases has been performed (Martín-Bocanegra *et al.* 2024). The mammalian target of rapamycin (mTOR) is described as a crucial regulator of cell metabolism (Fig. 1), influencing various signaling pathways involved in cell proliferation, cell death, and the recycling of cellular components to adapt to different physiological or pathological conditions (Saxton & Sabatini 2017, Lu *et al.* 2020). The mTOR is composed of two distinct complexes, mTORC1 and mTORC2, each with different structural and functional characteristics. These complexes can be independently regulated, which affects the effectiveness of therapeutic interventions in different clinical and experimental contexts. mTORC1 interacts with specific chaperones or immunophilins, which are intracellular receptors for immunosuppressive drugs. Different molecular weights of immunophilins have varied intracellular functions, suggesting a complex regulatory role in mTOR signaling. The review aims to provide updates on the molecular structure and signaling pathways associated with mTOR, as well as its regulation by immunophilins and upstream and downstream signaling events. It also highlights the potential therapeutic interventions targeting mTOR in conditions such as cancer, metabolic disturbances, and aging.

A strong association exists between hyperglycemia, oxidative stress, and the development and progression of type 2 diabetes (T2D) (Vezza *et al.* 2023). Hyperglycemia is said to reduce the activity of antioxidant enzymes and increase the production of lipid peroxidation, protein oxidation products, and DNA damage. Metformin is identified as the recommended first-line glucose-lowering agent for T2D. Despite its extensive clinical use, some mechanisms of action remain unclear. This review paper aims to explore the molecular mechanisms underlying metformin's actions related to redox processes. These mechanisms include interactions with AMP-activated protein kinase (AMPK) pathways, both dependent and independent, inhibition of gluconeogenesis, and effects on leukocyte-endothelium interactions.

In conclusion, the here reported collection of updated findings and concepts stemming from the 2023 OCC Workshop in Alba might help understand the great potential that anti-aging redox medicine holds for improving health span and possibly extending lifespan by targeting fundamental mechanisms of aging and age-related diseases.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this commentary.

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