Redox Signalling in Physiology, Ageing and Disease

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Ageing is a natural phenomenon associated with deterioration in function of multiple tissues. Whilst lifespan increased in the recent years, this has not been concomitant with an increase in healthspan – the average number of years spent in good health. While scientists continue to study the mechanisms of ageing and potential new therapeutic avenues, progress has been made in recognising ageing-associated condition as diseases, e.g. sarcopenia, age-related loss of muscle mass and function, has recently gained an IC code (ICD-10-CM Diagnosis Code M62.84) and efforts have been made to classify ageing and/or organismal senescence as a disorder (Calimport et al., 2019). It becomes increasingly clear that dysregulation of the redox balance in our cells and tissues is an important contributor to the age-related decline. Last year, two leading UK learned societies, the BSRA and Biochemical Society joined forces to run a scientific meeting on “Redox Signalling in Physiology, Ageing and Disease”. It took place on the banks of the River Tyne in Newcastle, UK, in July 2019 and brought together experts in biochemistry of redox signalling and ageing to discuss the relationship between the two processes.

The three-day conference featured scientific talks by such leading figures in the field as Christine Winterbourn (University of Otago, New Zealand) and Mike Murphy (University of Cambridge, UK) who gave keynote addresses focussing on the mechanisms of redox signalling in health and disease. The meeting was organised into four inter-related sessions. In the first session entitled “Studying redox changes in vivo; in health, ageing and disease” Tobias Dick (DKFZ, Germany) and Cristina Furdui (Wake Forest School of Medicine, USA) highlighted the new tools for measuring reactive oxygen species (ROS) and their application to the development of diagnosis and therapeutic strategies to prevent and treat diseases prevalent in ageing populations such as cancer. A novel mechanism by which redox controls a tumour suppressor p16INK4A was reported by Tobias Dansen (University Medical Center Utrecht, Netherlands) whilst redox regulation of skeletal muscle function in health and ageing has been discussed by Malcolm Jackson (University of Liverpool, UK). Finally, Laura Greaves (Newcastle University, UK) highlighted the role of mitochondrial DNA mutations which accumulate with age in accelerating intestinal tumorigenesis(Whitehall & Greaves, 2019).

The session “Redox signalling in physiology and disease” saw the talks discussing redox regulation of phosphatases (Nicholas K. Tonks, CSHL, USA), kinases (Philip Eaton, King’s College London, UK), peroxiredoxins (Leslie Poole, Wake Forest School of Medicine, USA) and transcriptional factors (Joris Messens, VIB-VUB Center for Structural Biology, Belgium). The third session, “ROS responses in ageing and disease”, continued to discuss the role of redox control of cellular processes whilst looking further into its contribution to age-related diseases. For example, Chris Grant (University of Manchester, UK) explained how peroxiredoxins can protect against protein aggregation, a prominent feature of age-related neurodegenerative diseases, whilst Myra Conway (UWE, Bristol, UK) focussed on targeting redox and metabolic imbalance in Alzheimer’s disease (Conway, 2020). The other topics included the role of senescence in anxiety and the impairment of neurogenesis (Diana Jurk, Mayo Clinic, USA) and the control of mitochondrial function (Alexandra Trifunovic, University of Cologne, Germany). One of the highlights of the meeting was the talk by Suresh Rattan (Aarhus University, Denmark) who reflected on the need for a new, holistic approach to the scientific studies in biogerontology field (Rattan, 2019).

Contribution of cellular ROS to ageing and disease were further discussed in the fourth and final session of the meeting. Here, James Mitchell (Harvard T. H. Chan School of Public Health, USA) described the role of endogenous hydrogen sulphide production in the DNA damage response and ageing whilst Michael Ristow (ETH Zurich, Switzerland) explained how ROS may promote metabolic health and lifespan. The role of ROS in processes such as ferroptosis and autophagy was presented by Marcus Conrad (Helmholtz Zentrum Muenchen, Germany) and Helena Cocheme (LMS London, UK), respectively. Together with exciting elevated talks, busy poster presentation sessions and a public session which attracted over 100 lay audience, the meeting has made it crystal clear that redox biology and biogerontology are the two fields which are currently on the rise. Further integration and cross-pollination in these fields promises not only new understanding of how and why we age but also new approaches to combat age-related diseases and extend human healthy lifespan.

In this special issue spanning from the meeting, the article by Rattan discusses the complexity of the ageing process and approaches to find anti-ageing therapies emphasising that the highly dynamic nature of the living systems, including interaction, interdependence, tolerance, adaptation and constant remodelling, requires a holistic approach to understand and maintain health throughout life (Rattan, 2019). Rattan suggests in his article that ageing interventions which already show health-promoting effects: food, physical activity and social and mental engagement, cannot be simply reduced into the format of a pill targeting limited number of molecular targets. Nevertheless, the majority of research into ageing continues to be focused on investigating how targeting specific molecules can ameliorate ageing-associated disorders. One such disorder is Alzheimer’s disease (AD), a debilitating neurodegenerative disease associated with progressive decline in memory, language and problem solving.  In the second review article of this issue, Conway discusses mechanism-based therapies primarily focused on amyloid β (Aβ) processing and pathways that govern neurofibrillary tangle generation (Conway, 2020). This review highlights alternative therapeutic approaches through discussing the importance of the branched chain aminotransferase proteins in regulating brain glutamate and the potential consequence of dysregulated metabolism in the context of BCAA or glutamate accumulation. Moreover, the article explores how the benefits of BCAA supplementation or restriction may improve cognitive function in AD and other neurological diseases.

Several other molecular targets have been researched in the ageing field, such as metformin or rapamycin and rapalogues which suppress mTOR signalling and show promising results as anti-ageing interventions (Glossmann & Lutz, 2019; Kucheryavenko, Nelson, von Zglinicki, Korolchuk, & Carroll, 2019; Schreiber et al., 2019). mTOR is one of the key signalling pathways regulating adult skeletal muscle homeostasis. Loss of muscle mass and function (sarcopenia) is one of the hallmarks of ageing. Whilst progress has been made in understanding the processes underlying muscle ageing, this has yet to be translated into therapeutic approaches. So far, diet and exercise remain the only interventions aimed at improving muscle mass and function during ageing, however these do not restore muscle mass and some elderly people are not able to adhere to these regimes (Sannicandro, Soriano-Arroquia, & Goljanek-Whysall, 2019). Moreover, blunted response to exercise has also been described during ageing (Cuthbertson et al., 2005). In this special issue, Shally and McDonagh discuss the contribution of the myofibrillar redox environment in relation to mitochondrial dynamics in skeletal muscle (Shally & McDonagh, 2020). The authors discuss how an altered redox environment with age contributes to the disruption of the regulatory mechanisms controlling mitochondrial biogenesis and degradation. Finally, the authors discuss the link between contractile-induced ROS generation and mitochondrial turnover, how redox relays may provide specificity in redox signalling and an altered redox environment can contribute to the blunted response of old muscle to exercise.

Changes in mitochondrial metabolism are also discussed by Whitehall and Greaves in the context of both ageing and cancer (Whitehall & Greaves, 2019). As age is one of the biggest risk factors for the development cancer, the authors discuss an emerging link between age-related mitochondrial dysfunction and the changes in mitochondrial metabolism prevalent in cancer cells focusing on somatic mutations of the mitochondrial genome which may drive compensatory alterations in mitochondrial metabolism advantageous for tumour growth.  In a related article, Guo *et al.* discuss mitochondrial dysfunction in the context of cochlear ageing associated with age-related hearing loss, which can reduce the signal transmission capacity (Guo et al., 2020). The article by Thoma *et al*. further discusses the association of disrupted mitochondrial dynamics with modified ROS generation and oxidative stress during ageing (Thoma et al., 2020). The authors review research on the potential of ROS-targeted therapies such as nutritional-based interventions, e.g. vitamin E/C, polyphenols (resveratrol), as well as targeted pharmacological compounds such as SS-31 and MitoQ. It has to be noted however that high doses of antioxidant molecules can blunt the response to exercise (Ristow et al., 2009) and therefore we need to exercise caution when moving these interventions into the clinic.

Interestingly, epigenetic regulators, such as non-coding RNAs could be considered as a way of regulating mitochondrial dynamics and ROS generation during ageing (Goljanek-Whysall, Soriano-Arroquia, McCormick, Chinda, & McDonagh, 2020; Lang et al., 2016). In this special issue, Braga *et al.* discuss epigenetics as a critical component of the ageing process, both as a bona-fide marker of biological age and a potentially targetable mechanism underlying ageing (Braga, Mousovich-Neto, Tonon-da-Silva, Salgueiro, & Mori, 2020). The authors discuss multiple data demonstrating the relationship between epigenetic changes, such as DNA methylation, histone modifications, chromatin remodelling, small non-coding RNAs and ageing-related phenotypes. The theme of redox regulation and its interplay with cellular metabolism continues in the article by Sedlackova and Korolchuk exploring the link between cellular adaptation to metabolic and oxidative stresses by activation of autophagy, which is a crucial cellular catabolic pathway previously shown to be an important regulator of age-associated tissue degeneration (Sedlackova & Korolchuk, 2020). The article discusses the latest findings and outstanding questions on the association of autophagy with metabolic and oxidative stress. Furthermore, here the authors extend their recent review of the topic ((Sedlackova, Kelly, & Korolchuk, 2020; Sedlackova & Korolchuk, 2020) by focussing on autophagy proteins that are regulated by post-translational modifications in the context of healthy human ageing.

Taken together, it becomes apparent that ageing is a complex process and the increase in longevity is not necessarily associated with the extension of healthspan. In order to develop effective treatments or preventative strategies for ageing-associated tissue dysfunction and resulting disorders, a comprehensive approach aiming at understanding the complex processes of the whole body ageing is needed. Such approach would need to integrate physical, mental and sociological changes. This comprehensive approach may result in the future in new effective anti-ageing therapies, aiming at improving the health of elderly people which would benefit not only the elderly individuals but the society as a whole.

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