Ageing in Chronic Kidney Disease

Author: Robin Stannard, Editorial Assistant

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DAY 4 of the 59th ERA Congress 2022 included an expert session on cellular ageing. In a symposium session featuring specialist insight from researchers in the field, discussions focused on the cellular processes that contribute to aging, environmental influences that correlate with ageing phenotype, and chronic kidney disease (CKD) as a model for dysregulated ageing. Exploring treatments and lifestyle changes that slow ageing and increase health span, experts also shared research underlining the importance of the microbiome and the role dysbiosis plays in triggering age-related pathways.

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Ageing Markers in Chronic Kidney Disease: Is It Time for Rejuvenation?

The first speaker, Katrien De Vusser, Nephrology and Renal Transplantation Research Group, Katholieke Universiteit (KU) Leuven, Belgium, opened her talk by describing ageing as a disease, stating that it was a disease that she hoped, in some years, could be curable. Age in mammals is marked by the decline of multiple separate organ systems, causing an overall deterioration that leads to dysfunction. De Vusser underlined the value of CKD as a model for studying and deepening scientific understanding of common cellular and molecular patterns associated with ageing.

Articulating cellular processes associated with ageing, De Vusser focused on cellular senescence and the causes, consequences, and role it plays in both ageing and disease. Senescence is a cellular response that limits the proliferation of aged and damaged cells. It is required for tissue homeostasis and is often triggered as a stress response to insults. Senescence is a directed cellular programme that prevents stable growth, whereby cells stop dividing yet remain metabolically active. This growth rest is accompanied by chromatin remodelling, metabolic reprogramming, increased autophagy, and, pivotally, the implementation of proinflammatory mechanisms. Two pathways play essential roles in driving a cell into senescence: P53 and P16. Both are triggered in response to DNA damage, stress, or inflammation. Upregulation of P16 leads to irreversible growth arrest. This permanent arrest works to prevent the perpetuation of DNA damaged cells and their genome. Senescence is a powerful method of tumour suppression; however, this protection comes at a cost. Aged senescent cells are not destroyed by apoptosis and accumulate over time and this accumulation drives ageing in tissues.

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De Vusser analysed major disease, and age-inducing mechanisms. Firstly, increasing allosteric load, which she described as adaptation to unfavourable conditions leading to chronic activation of allosteric mechanisms, is likely to cause oxidative responses, innate immune cell activation, and chronic low-grade inflammation. Secondly, De Vusser used the interstitial sodium accumulation seen in CKD as an example of the activation of age-promoting mechanisms. Finally, the activation of 'stress resistance pathways' and impairment of anti-ageing pathways. Listing 'stress resistance pathways' such as insulin-like growth factor 1, target of rapamycin-S6K1, and forkhead box O3 for their role in cell growth, stress resistance, and energy deprivation, De Vusser emphasised the damaging effects of their activation.

Placing age-related damage in the context of disease, De Vusser used the example lupus nephritis (LN). The pathophysiology of LN presents as active immune-driven flares that are paired with interstitial fibrotic damage, which is key to determining long-term outcomes. Analysis of 40 active flare lupus kidney biopsies found no association between levels of P16 and active disease; however, chronic damage and disease were associated with increased levels of P16. Notably, 5 years after biopsy, P16 was significantly associated with poor renal function.

Furthermore, meta-analysis examination has demonstrated that patients with LN have a shorter telomere length than healthy patients, regardless of age, ethnicity, and gender. These are both clear indications of prevalent cellular senescence in LN; however, it remains unclear why this senescence occurs. De Vusser shared theories that centred on the inflammatory and oxidative environment caused within the LN kidney that are exerted through the profibrotic and proinflammatory secretome typical of senescent cells.

De Vusser closed her presentation by emphasising how little is still known about ageing as a process, highlighting the value of CKD as a model for ageing cells for further study, and reiterating that more knowledge brings us closer to a cure for ageing as a disease.

The Road to Healthy Ageing

Paul Shiels, Institute of Cancer Sciences, University of Glasgow, UK, led the second presentation, using his time to place cellular ageing within the context of the aging population. There are now more people aged over 60 than at any other time in history and this demographic is growing. However, years of healthy living have not kept pace with increasing lifespan. Shiels highlighted the huge inequities in global ageing, which relate to social deprivation, by using the example of his home city of Glasgow, which has, in certain areas, both the highest and the lowest life expectancy in Europe. Summarising, he stated that in areas of deprivation, the process of ageing happens over a shorter period.

Describing ageing as the accumulation of deficits over time, Shiels introduced the concept of the exposome. An individual's exposome being the sum total of biotic and abiotic exposures starting before conception, with epigenetic modifications, until death. The exposome's importance is underlined by three simple factors, which account for approximately 50% of global mortality: air pollution, tobacco smoke, and diet. The accumulation of allostatic load over the course of life leads to an eventual tipping point at which point you reach the 'diseasome of ageing'. Kidney disease, cancer, osteoporosis, non-alcoholic fatty liver disease are all distinct diseases with the common underpinning component of dysregulated ageing. All are associated with the hallmarks of ageing; low level chronic inflammation; diminished cytoprotective responses from nmuclear factor erythroid 2-related factor 2 (NrF2); activation of ancestral retroviral elements; changes to the microbiome; calcipotriene particle toxicity; and the accumulation of non-somatic mutations.

Returning to his example of the Glasgow exposome, Shiels highlighted the relationship between diet, the microbiome, and ageing, stating that diet is "possibly the single strongest lever to optimise human health." Drawing comparisons with carnivorous big cats, he highlighted health problems associated with diets high in red meat. Big cats are hyperphosphatemic; 87% have renal pathology, 50% have colonic tumours, and they suffer from elevated inflammatory burden. In humans, those with diets high in red meat tend to die earlier, have poorer renal function, higher incidence of colon cancer, and a strong association with a range of neurodegenerative diseases. The carnitine compound, which is found in red meat, is a substrate in the gut for microbes that produce trimethadione. In the liver, trimethadione is converted to trimethylamine-N-oxide, a metabolite highly associated with inflammation, atherosclerosis, rheumatoid arthritis, and CKD. In the deprived regions of Glasgow, an imbalanced diet is associated with phosphataemia, genomic hypomethylation, telomere shortening, and inflammation. Analysis of bacterial fragments from the microbiome in the blood stream has demonstrated a significant increase in 'unfriendly' bacteria in the guts of socially deprived groups.

Salutogenic bacteria in the gut break down phenolic acids from plant proteins creating alkyl catechols, which in turn activate NrF2, an activator of cytoprotective processes. Poor NrF2 expression is naturally associated with ageing but also with poor diet and smoking. Increased levels of pathobionts are associated with CKD; however, dietary intervention can ameliorate this situation. For example, resistant starch type 2, a prebiotic, has been demonstrated to mitigate oxidative stress in patients with CKD on haemodialysis. This simple intervention increases salutogenic gut bacteria and can induce NrF2 agonism.

Closing his presentation, Shiels emphasised that manipulating the exposome can have dramatic effects on both ageing and health span. He

further looked to the future, criticising current standards that see diseases of age treated separately, organ by organ, theorising the increased overall improvements to health span that could be made by looking at the holistic, underlying components of the aging process.

Is Food as Medicine an Option?

The third and final presentation, given by Denise Mafra, Federal Fluminense University, Niterói , Brazil, provided further depth to the relationship between diet and the ageing phenotype. Discussing inflammation as a key cause of ageing, Mafra, detailed the molecular pathways involved. The activation of nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) and high production of reactive oxygen species (ROS) causes NF-κB translocation to the nucleus, where the molecule promotes increased production of inflammatory cytokines. NrF2 is a master regulator of cytoprotective responses. In a healthy situation there should be some production ROS, balanced with antioxidant responses that is controlled by NrF2.

A 2014 study demonstrated that patients with CKD on haemodialysis had a significantly increased expression of NF-κB compared with healthy individuals, with reduced NrF2 expression. Furthermore, gut inflammation contributed to an increased production of uraemic toxins and decreased short chain fatty acids, further activating NF-κB. These factors all link to the premature ageing phenotype of increased ROS, telomere shortening, DNA damage, cell cycle arrest, and senescent cells.

Mafra highlighted that food can reduce NF-κB and improve NrF2 production, with a good diet correlated with positive bioactive compounds, producing a balanced gut microbiome with increased short chain fatty acids and decreased uremic toxin. Listing positive foods and compounds such as suffurophane, beetroot, brazil nuts, fermented food, ginger, and garlic, she emphasised the need for further studies. Many of the positive cellular anti-ageing effects of these foods have only been demonstrated *in vitro* in mouse or in small-scale human studies. Large-scale clinical trials are needed to fully comprehend and act upon the possible benefits that these foods might provide.

Conclusion

Focusing on the cellular process of ageing, the experts were able to highlight the association between environmental influences and human health over time. Using CKD as a model for ageing allowed the researchers to explain the influence of individual molecules and explore possibilities of future treatments or mitigating diet choices. However, all experts highlighted how little is still understood about the processes behind ageing and the lack of evidence in the form of clinical studies to support potential mitigating dietary and medical therapies.