DNA Damage: Impact on Aging and the Effect of Nutritional Interventions on Neurodegeneration

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The molecular basis underlying ageing and ageing-related diseases is one of the main unsolved questions in biology. Ageing appears remarkably plastic: e.g. suppressing insulin signalling extends lifespan in worms, flies and mice. However, virtually all premature ageing syndromes in man provide links with genome instability. We have generated mouse models which strikingly mimic human DNA repair deficiency disorders and display wide-spread accelerated ageing, e.g. Ercc1Δ/- mice defective in ≥3 repair pathways show accelerated ageing in post-mitotic and proliferative tissues limiting lifespan to 4-6 month. Simultaneously these mice exhibit anti-ageing 'survival response', which suppresses growth and enhances maintenance, resembling the longevity response induced by dietary restriction (DR). Interestingly, subjecting these progeroid, dwarf mutants to actual DR resulted in the largest lifespan increase recorded in mammals. 30% DR tripled remaining lifespan, and drastically retarded numerous aspects of accelerated ageing, e.g. DR animals retained 50% more neurons and maintained full motoric function, delaying motor decline ~30(!)-fold. Repair-deficient Xpg-/- mice also showing many premature ageing symptoms responded similarly. The DR response in Ercc1Δ/- mice resembled wt DR including (further) reduced insulin signaling. Interestingly, ad libitum Ercc1Δ/- liver expression profiles showed declining expression of long genes, consistent with genome-wide accumulation of stochastic, transcription-blocking lesions, which affect long genes more than short ones. Similar findings were made in human brain profiles upon aging, demonstrating relevance for normal aging in humans. DR in repair-deficient mice alleviated this decline, indicating that DR prolongs genome function. We will present phenotypes of conditional DNA repair models targeting ageing to selected organs and links with the unfolded protein response and protein aggregation disorders (Alzheimer's and Parkinson diseases). Our findings strengthen the link between DNA damage and ageing, establish Ercc1Δ/- mice as powerful model for identifying interventions to promote healthy ageing, reveal untapped potential for reducing endogenous damage, provide new venues for understanding the molecular mechanism of DR, and suggest a counterintuitive DR-like therapy for human progeroid genome instability syndromes and DR-like interventions for preventing neurodegenerative diseases.