The impact of DNA damage, transcription stress and nutrition on aging

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Aging appears remarkably plastic: e.g. suppressing insulin signalling extends lifespan in numerous species. However, virtually all premature aging syndromes link with genome instability. We have generated mouse models which strikingly mimic human DNA repair deficiency syndromes and display wide-spread accelerated aging. For instance, *Ercc1*$^{\Delta/-}$ mice defective in four repair pathways show multi-morbidity in both proliferative and post-mitotic tissues, limiting lifespan to 4-6 month. Simultaneously, they exhibit an anti-aging 'survival response', which suppresses growth and enhances maintenance, resembling the longevity response induced by dietary restriction (DR) and providing a link with insulin signalling. Interestingly, subjecting these progeroid mutants to actual (30%) DR tripled lifespan, and drastically retarded accelerated aging, e.g. DR animals retained 50% more neurons and maintained full motoric function. The DR response in these mice resembled DR in wild type animals including reduced insulin signaling and reduced DNA damage load, explaining why DNA repair mutants overrespond to DR. Interestingly, *Ercc1*$^{\Delta/-}$ liver expression profiles showed gradual decline of expression preferentially of long genes, consistent with genome-wide accumulation of stochastic, transcription-blocking lesions, which affect long genes more than short ones. This phenomenon was also discovered in normal aging of post-mitotic tissues. DR largely prevented transcription stress, indicating that DR prolongs genome function. We will present phenotypes of conditional DNA repair models targeting aging to selected organs, and striking parallels with Alzheimer's disease. Our findings support the link between DNA damage and aging, establish *Ercc1*$^{\Delta/-}$ mice as powerful model for identifying interventions to promote healthy aging, reveal untapped potential for reducing endogenous damage and transcription stress, provide new venues for understanding the molecular mechanism of DR, explain the aging component of all proteinopathies based on transcription stress and promote a counterintuitive DR-like therapy for human progeroid genome instability syndromes and DR-like interventions for preventing neurodegenerative diseases and ischemia reperfusion damage.