DNA damage and its impact on cancer, aging and longevity

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DNA, the carrier of genetic information, is incessantly damaged by exogenous agents (UV-, gamma-radiation and numerous natural or man-made chemicals), which are in part avoidable and -importantly- also by inevitable (by)products of normal cellular metabolism. The latter include reactive oxygen and nitrogen species and other natural reactive cellular metabolites. DNA damage may have two major, distinct consequences. Some DNA lesions induce permanent changes in the genetic code (mutations) upon replication or chromosomal aberrations after mitosis. Alternatively, DNA injury may trigger permanent cell cycle arrest or cell death. To counteract the negative effects of damage to our genes a complex genome maintenance apparatus has evolved comprised of an intricate network of DNA repair systems and cell cycle checkpoints which acts as a guardian of the genome. Each repair system is designed to eliminate a specific category of DNA damage. For instance, nucleotide excision repair (NER) removes a wide range of helix-distorting lesions of exogenous origin (UV-induced lesions, bulky chemical adducts), but also endogenous damage (e.g. oxidative cyclopurines). The molecular mechanism of NER involves >30 proteins acting in a multi-step reaction: lesion detection, local opening of the DNA helix, lesion verification and stabilization of the open NER intermediate, dual incision of the damaged strand to release the lesion as part of a 22-30 oligonucleotide, gap-filling DNA synthesis and final ligation to the pre-existing strand. Two NER sub-pathways exist. Global genome (GG-)NER covers the entire genome and is particularly important for preventing mutations. Transcription-coupled repair (TCR) removes damage that obstructs ongoing transcription to enable recovery of this vital cellular process and mainly counteracts cytotoxic effects of DNA injury.

Several rare, autosomal recessive inherited NER syndromes are known which are characterized by extreme sun(UV)sensitivity, but otherwise display a striking clinical heterogeneity: very strong (skin)cancer predisposition in xeroderma pigmentosum (XP) as well as dramatic neuro-developmental deficits as in Cockayne syndrome (CS) and the brittle hair disease trichothiodystrophy (TTD). Remarkably, although life expectancy in the latter 2 conditions is frequently limited to childhood, they appear not associated with any cancer susceptibility, in striking contrast to XP. Intriguingly, mutations in core NER helicases XPB and XPD, which are subunits of the repair/transcription factor TFIIH, are associated with all three disorders or combinations.

To assess the medical impact of DNA damage and NER and to get insight into the puzzling clinical heterogeneity we have generated a series of transgenic mouse mutants, several with identical mutations in NER genes as found in NER patients. E.g. XPDTTD mice, mimicking an XPD point mutation of a TTD patient exhibit strikingly similar clinical features as the human syndrome including the characteristic brittle hair. Detailed analysis of these mice revealed that TTD is in fact a segmental premature aging syndrome, like CS, which is indeed less susceptible to spontaneous cancer. XPDXP/CS mutant mice, on the other hand, carrying a XPD point mutation of a patient with combined XP and CS, are highly predisposed to cancer, but also display premature aging, demonstrating that both phenotypes can also co-exist. Different single and double NER mutants exhibit multiple premature aging features, including osteoporosis, neuro-degeneration, early infertility and cessation of growth, liver and kidney aging, deafness, retinal photoreceptor loss, depletion of hematopoietic stem cells, etc. Life span is limited to ~1,5 year for milder mutants to 3-5 weeks for dramatic double mutants. A striking correlation is found between severity and type of compromised repair and rate of onset and severity of the clinical aging manifestations providing strong experimental support for the DNA damage theory of aging. The different defects in DNA repair and their effects on cancer and aging can be rationalized as follows. Generally, compromised GG-NER, which eliminates distorting DNA injury over the entire genome, leads to enhanced damage levels everywhere, which -upon replication- will increase mutagenesis and thereby cancer. TCR only focuses on lesions in the transcribed strand of active genes that arrest transcription. Since this is only a very small proportion of all DNA damage in the genome this repair system has little impact on mutagenesis and cancer, but is vital for resumption of

transcription and thereby for cellular viability. Defects in TCR will thus render cells more sensitive to DNA damage-induced cell death, thereby strongly protecting from cancer, but at the expense of enhanced cell death which in turn accelerates aging. GG-NER mutations in TCR/GG-NER double mutant mice will enhance the overall DNA damage load, which aggravates the TCR problems causing even earlier cell death further reducing life expectancy. Conditional mutants in which specific dramatic aging occurs only in e.g. the brain, display many signs of neurodegeneration whereas the remainder of the body appears normal, revealing organ-specific accelerated aging. We propose that endogenous lesions hamper transcription and replication triggering cellular apoptosis-senescence and in the end (premature) aging.
Microarray, functional and physiological studies have revealed that persisting DNA damage elicits a systemic downregulation of the IGF1 somatotrophic axis and upregulation of anti-oxidant defences, favouring maintenance and defences at the expense of growth and development, explaining the severe growth defect of repair mutants and progeroid NER patients. Persisting DNA damage triggers this 'survival' response in a cell autonomous manner and implicates regulation by a set of ageing-related microRNAs. Caloric restriction and fasting trigger a similar 'survival' response, which maximizes anti-oxidant defence and -when constitutive- promotes longevity at least under laboratory conditions. These data link accumulation of DNA damage and the IGF1 control of life span and open perspectives for the promotion of healthy aging, including reduced risk of cancer.

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