Seminar

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«Chemistry of aging and age-related diseases»

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11:30 am

Aging is an accelerating degradation of biological activities causing progressive malfunction, morbidity and death. Maintenance of fit organisms requires constant renewal of proteins to maintain cellular life, renewal of cells to maintain functional organs, and functional organs make-up healthy organism. This hierarchy, short lifetime of most proteins and the dependence of DNA destiny on dedicated proteins, means that maintenance of protein activities underlies maintenance of life.

Similarity among mortality and disease rates suggests a common biological clock for aging and age-related diseases. Exploring the chemistry and biology of such clock, called intrinsic aging, reveals that accumulation of dysfunctional proteins damaged by oxidation correlates with increased morbidity and mortality caused by radiation and aging[1,4]. When protection and defence against oxidative protein damage become insufficient, or when protein susceptibility to oxidation increases, the inadequacy of protein turnover leads to accumulation of damaged proteins[1-4] displaying variable deleterious phenotypic effects[1-3]. Protein damage determines mutation rates to the extent of being more mutagenic than the incurred DNA damage[1].

Our studies support a familiar concept[5] that oxidative damage underlies aging and age-related diseases[6]. Specifically, we posit that aging and its countless manifestations, including degenerative diseases, can be viewed as snowballing consequences of age-related accumulation of damage to the proteome. Age-related diseases appear as emerging phenotypes of progressive damage to specific oxidation-sensitive proteins. The deterministic predisposition to particular age-related disease can be identified as "silent" mutational polymorphism sensitizing the affected protein to age-related oxidative damage. I promote a concept that aging and age-related diseases are progressive phenotypes of the patterns of accumulating proteome damage. Such concept predicts the reversibility of aging and offers strategies for prognosis, prevention and even cure of degenerative diseases by acting pharmacologically upon their root cause.

Readings:

(1) A. Krisko, M. Radman, *Phenotypic and genetic consequences of protein damage.* PLOS Genetics, 9, e1003810 (2013).
(2) A. Krisko, M. Radman, *Protein damage and death by radiation in Escherichia coli and Deinococcus radiodurans*. Proc. Natl. Acad. Sci. USA, 107, 14373-14377 (2010).
(3) A. Krisko et al., *Extreme anti-oxidant protection against ionizing radiation in bdelloid rotifers.* Proc. Natl. Acad. Sci. USA 109, 2354-2357 (2012).
(4) C. N. Oliver et al*., Age-related changes in oxidized proteins*. J. Biol. Chem. 262, 5488-5491 (1987).
(5) D. Harman, *Aging: a theory based on free radical and radiation chemistry,* J. Gerontol. 11(3), 298-300 (1956)
(6) I. Dalle-Donne et al., *Protein carbonylation in human diseases*. Trends Mol. Med. 9, 169-176 (2003).

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