

Anti-inflammatory Action of Calorie Restriction for Life-Prolongation: A Possible Mechanism

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Oxidative modification of cellular structures and functions by redox imbalance is the basis of the current oxidative stress hypothesis of aging. The experimental support for this hypothesis has been generated from recent molecular probing on the interrelation between the age-related functional impairments and the pathogenesis. One major revelation of the molecular insights is the altered redox-sensitive signal transduction pathways, providing plausible mechanistic links between the functional deterioration and disease occurrence. Considering the pro-inflammatory nature of the aging process as evidenced by the many activated inflammatory mediators, "Molecular Inflammation Hypothesis of Aging" has recently been proposed. Evidences are the up-regulation and production of pro-inflammatory cytokines, prostaglandins, inducible NO synthase, and cyclooxygenase-2 during aging. The significance of the proposal highlights the oxidatively activated inflammatory-related signal pathways, thereby predisposing the aged organism's vulnerability to disease insults. Chronic diseases such as atherosclerosis, vascular degeneration, diabetes, senile dementia, arthritis, and tumorigenesis are all implicated with inflammatory processes. The life-prolonging action by the well-established antioxidative calorie restriction (CR) plays a central role in modulation of redox-sensitive, divergent transcription factor, NF- κ B. The molecular process leading to the activation of NF- κ B involves in NIK/IKK and mitogen-activated protein (MAP) kinase pathways that are down-regulated by CR. Recent our study utilizing a subtraction method (RDA), DNA chip and 2D/Maldi-top mass spectrometer generated further evidence, supporting the tenet of the proposed molecular inflammatory hypothesis. Another recent endeavor, which will be described during the presentation, is the documentation of computerized database, "Aging DB", collected from existing publications in the literature on the age-related alterations and their modulation on

oxidative stress and gene expressions by CR.

In conclusion, it became clear that the aging process and its related pathogenesis are profoundly influenced by oxidative stress-induced redox imbalance, altering redox-sensitive intracellular signaling pathways. As a consequence, cellular and tissue responses to such molecular alterations are converted into the pro-inflammatory state, which may well bridging between normal aging and age-related diseases. The validity of this premise can further be strengthened by recent data generated from molecular analyses on the age-related changes in genomic and proteomic profiles.