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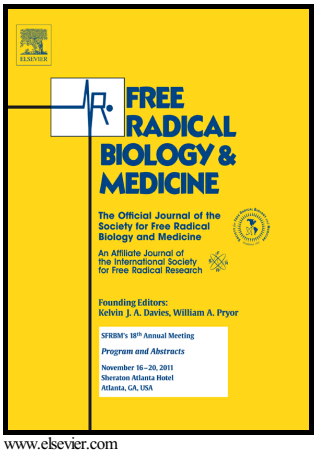

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ADAPTIVE HOMEOSTASIS AND THE FREE RADICAL THEORY OF AGEING

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ABSTRACT

The Free Radical Theory of Ageing, was first proposed by Denham Harman in the mid-1950's, based largely on work conducted by Rebeca Gerschman and Daniel Gilbert. At its core, the Free Radical Theory of Ageing posits that free radical and related oxidants, from the environment and internal metabolism, cause damage to cellular constituents that, over time, result in an accumulation of structural and functional problems. Several variations on the original concept have been advanced over the past six decades, including the suggestion of a central role for mitochondria-derived reactive species, and the proposal of an age-related decline in the effectiveness of protein, lipid, and DNA repair systems. Such innovations have helped the Free Radical Theory of Aging to achieve widespread popularity. Nevertheless, an ever-growing number of apparent 'exceptions' to the Theory have seriously undermined its acceptance. In part, we suggest, this has resulted from a rather simplistic experimental approach of knocking-out, knocking-down, knocking-in, or overexpressing antioxidant-related genes to determine effects on lifespan. In some cases such experiments have yielded results that appear to support the Free Radical Theory of Aging, but there are just as many published papers that appear to contradict the Theory. We suggest that free radicals and related oxidants are but one subset of stressors with which all life forms must cope over their lifespans. Adaptive Homeostasis is the mechanism by which organisms dynamically expand or contract the homeostatic range of stress defense and repair systems, employing a veritable armory of signal transduction pathways (such as the Keap1-Nrf2 system) to generate a complex profile of inducible and enzymatic protection that best fits the particular need. Viewed as a component of Adaptive Homeostasis, the Free Radical Theory of Aging appears both viable and robust.