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Review

Hormesis and epigenetics: Is there a link?

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ABSTRACT

Epigenetic regulation of gene expression is a key molecular mechanism linking environmental factors with the genome with consequences for health status throughout the life course. According to the modern view, epigenetic changes are far more likely than genetic changes to be directed, and many of these changes are manifestly adaptive. Recent experimental studies clearly indicate that environmental fluctuations can induce specific and predictable epigenetic-related molecular changes, and support the possibility of adaptive epigenetic phenomenon. The epigenetic adaptation processes implying alterations of gene expression to buffer the organism against environmental changes support adaptability to the expected life-course conditions. It appears likely that adaptive epigenetic rearrangements can occur not only during early developmental stages but also through the adulthood, and they can cause hormesis, a phenomenon in which adaptive responses to low doses of otherwise harmful conditions improve the functional ability of cells and organisms. In this review, several lines of evidence are presented that epigenetic mechanisms can be involved in hormesis-like responses.

1. Introduction

Hormesis is a phenomenon in which adaptive responses to low doses of otherwise harmful conditions improve the functional ability of cells and organisms (Rattan, 2008; Le Bourg and Rattan, 2010; Kendig et al., 2010; Calabrese, 2010). The hormetic dose-response can occur (1) as a direct stimulatory response, (2) after an initial disruption in homeostasis followed by the modest over-compensation response, and (3) as a response to an 'adapting' or 'pre-conditioning' dose followed by a more massive challenging dose (Calabrese et al., 2009). Over the past decade, there has been a remarkable growth of interest throughout the world in the phenomenon of hormesis (Calabrese, 2008). The molecular mechanisms that bring about the hormetic effects comprise a cascade of stress response and other pathways of maintenance and repair (Rattan, 2008). Additionally, it seems that a number of therapeutic agents are based on the hormetic dose response and its low dose stimulatory characteristics (Vaiserman, 2008a; Calabrese, 2010). A broad spectrum of applications of the hormesis concept for clinical medicine includes anxiety, seizure, memory, stroke, cancer chemotherapy, dermatological processes such as hair growth, osteoporosis, ocular diseases, including retinal detachment, statin effects on cardiovascular function and tumor development, benign prostate enlargement, male sexual behaviors/dysfunctions, and prion diseases (Calabrese, 2008). For gerontologists, most important are the survival-enhancing aspects of hormesis. Increasingly more data are accumulating from studies on experimental animals showing that mild stresses at a young age can protect from severe stresses at old age as well as delay ageing and increase longevity. Single or multiple exposures to low doses of otherwise harmful agents, such as irradiation, food limitation, heat stress, hypergravity, reactive oxygen species and other free radicals can cause a variety of anti-ageing and longevity-extending hormetic effects (Neafsey, 1990; Rattan, 2008; Le Bourg and Rattan, 2010).

Acceptance of hormesis as a viable dose-response theory and practical use of the mild stresses as a means to modulate ageing and to extend health span in human beings, however, have been limited until now due to the poor conceptual understanding and lack of clearly defined mechanisms by which hormesis works. Recently, the hormetic effect was proposed to be attributed to induction of the adaptive-response genes due to a long-lasting epigenetic memory (Scott et al., 2009). The epigenetic alterations affect the gene expression by influencing DNA methylation, chromatin remodelling and microRNA-regulated transcriptional silencing without changes in DNA sequence. The epigenetic status of the genome changes very dynamically compared with the static DNA sequence and is influenced by the environment (Jaenisch and Bird, 2003). Most of the environmentally stress-induced epigenetic modifications are return to the basal level once the stress is relieved, while some of the modifications may be stable. The idea that epigenetic modifications could be adaptive is very controversial. Nevertheless, convincing data were obtained showing that environmental stress can induce specific and predictable epigenetic changes that even-

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