HDAC inhibitors: a new promise for anti-aging

Epigenetic modifications provide a mechanism of heritable but reversible changes in gene function that occur without the change in the primary DNA sequence due to alterations in chromatin structure. The global changes in chromatin structure and certain local epigenetic modifications in the promoter regions of several specific genes are among the key age-associated epigenetic processes. Epigenetic dysregulation has been shown to be implicated in a wide variety of age-related chronic diseases such as decline of immune function, atherosclerosis, type 2 diabetes, cancer, and neurodegenerative diseases. An important point is that, unlike genetic mutations that cannot be restored, epigenetic aberrations (epimutations) are reversible and can be relatively easily corrected through nutritional and pharmacological interventions. The potential reversibility of epigenetic aberrations makes them attractive targets for therapeutic drug development.

A new class of drugs specifically targeting epigenetic pathways (“epigenetic drugs”) has been recently proposed. Among others, histone deacetylase (HDAC) inhibitors are regarded as most promising potential therapeutics in treatment of age-associated chronic disorders. Since transcriptional levels of numerous genes, primarily the biosynthetic and metabolic ones, are shown to significantly decrease with aging, a recovery of their transcriptional activity through HDAC inhibitors might likely delay age-associated functional declines. Furthermore, inhibition of HDACs may lead to an up-regulation of genes implicated in inflammation and responses to stress – pathways known to be substantially involved in the control of aging and longevity. Moreover, great life-extending potential of these agents was evident in a number of animal studies. Despite some contradictions in the details concerning the optimum age of exposure to the inhibitor, its concentration and other conditions, in general, animal models undoubtedly point to the positive effects of HDAC inhibitors on expression of several aging-related genes and lifespan.

In recent years, HDAC inhibitors have undergone a phase of clinical development in different cancer types, either as monotherapy or combined with other anticancer treatment strategies. By now, several HDAC inhibitors were approved by FDA for the treatment of various cancers. The therapeutic potential of HDAC inhibition in treatment of various types of non-malignant pathological conditions, such as neurodegenerative, inflammatory and cardiovascular disorders, has been evident in some preclinical studies. HDAC inhibitors have emerged as a promising therapeutic modality for the treatment of vascular calcification, hypertension, atherosclerosis, myocardial infarction, supraventricular arrhythmia, cardiac remodeling, fibrosis, and neointima formation. These substances also demonstrated a great promise to combat neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. However, despite high therapeutic potential of HDAC inhibiton in the therapy of aging-associated pathological conditions, the future clinical application of these substances will require thorough safety. A major concern impeding widespread use of HDAC inhibitors in clinical practice is related to their relatively low specificity. Therefore, serious efforts are currently aimed at the development of tissue-, stage-, and HDAC-specific inhibitors. In recent years, some research groups are making increasing efforts to improve this pharmaceutical class, designing more selective substances. If this issue will be resolved, then

HDAC inhibitors would apparently be among the most promising drugs in anti-aging medicine.

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