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MOLECULAR MECHANISMS OF AGING IN THYROID CELLS

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Abstract

This paper presents the molecular mechanisms of aging in thyroid cells of elderly people and the causes of disturbances in the regulation of thyroglobulin gene expression. It was found that during aging, there is a disturbance in the regulation of thyroglobulin gene expression at the transcription level. A direct correlation was found between the degree of thyroglobulin gene expression in thyroid cells during cellular aging and DNase I – nuclear chromatin hypersensitivity.
Keywords: *molecular mechanisms, thyroid gland, aging, gene expression, thyroid pathology*

Introduction

Aging is a basic biological property of all living organisms; it is a process that is evolutionarily genetically programmed and predetermined. The problem of aging has been and remains one of the most pressing in modern science. It can be said that the problem of aging is equal to the problem of deciphering the genetic program of organism development. The solution to this problem is associated with the clarification of the molecular mechanisms of aging, the development of means to increase human life expectancy. In age-related changes, shifts at two levels are of particular importance: 1 – changes in the functioning of genes that encode protein synthesis;

2 – changes in nervous and hormonal regulation. The first system acts from the inside and leads to a change in the amount of hormones secreted by the endocrine glands and cells of other tissues into the blood. Acting together, they achieve their disappointing results for the organism: on the one hand, DNA damage accumulates in the cell, functionally inactive abnormal proteins are synthesized. The structure of genes and the direction of their functioning change (Anisimov V. N., 1999). Regulation of gene expression fundamentally affects the aging process and age-related changes. Dysfunction of gene expression at various levels is the cause of aging. Formation of insufficient amount of protein or its synthesis in an inactive form is inevitably accompanied by the development of disease and aging. There are various molecular factors in the pathogenesis of thyroid diseases: mutational changes in DNA sequences, dysregulation of thyroglobulin (TG) gene expression, dysregulation of methylation sites in TG. In a number of thyroid diseases, the TG content in thyroid tissue changes significantly, and changes in the TG structure are also noted (De Vijlder J. J.M. Carber B., 1999). TG is the main protein synthesized by thyroid cells, playing a key role in the metabolism of thyroid hormones. The molecular weight of native TG is 660,000 Da. Normally, the TG content is 50–60% of the total mass of thyroid tissue proteins. With age, the secretory function of the thyroid gland decreases. This is due to dysregulation of TG gene expression in elderly people. During aging, small quantitative and qualitative changes in TG also occur. Low TG levels in various thyroid diseases and cellular aging can be a priori explained by disturbances occurring at the stages of protein biosynthesis regulation.

Objective: to study the molecular mechanisms of cellular aging in thyroid cells of elderly people and the causes of disturbances in the regulation of TG gene expression during cellular aging in thyroid cells of elderly people with some forms of thyroid pathology.

Material and methods of research

Blood and thyroid glands of elderly people with some forms of thyroid pathology were taken as the object of research. Three age groups of elderly people were created: 45–55 years (9 people); 55–65 years (8 people); 75–85 years (6 people). Five people aged 19–24 years served as controls.

High-molecular DNA was isolated from blood leukocytes of elderly people by phenol extraction (Dashkevich V. S., Arshinova T. V., 1963). Nuclei from thyroid cells were isolated by precipitation in 0.25 M sucrose containing 5 mM MgCl2, 1 mM dithiothreitol (DTT), 10 mM Tris-HCI pH7.5, and nuclei were purified by layering on a solution of 2 M sucrose in buffer B (24,000 rpm for 1 hour, SW 27 rotor). To determine DNase sensitivity, nuclei were treated with DNase I (2000 U/mg Serva) and incubated at 4 °C for 5 min with different concentrations of DNAase I (0.1 to 100 U/ml) or with a fixed enzyme concentration (20 U/ml) at 37 °C for 15 min. Complementary DNA for the TG gene was synthesized by polymerase chain reaction (PCR) on 0.5 μg of total RNA in the presence of reverse transcriptase using primers specific for the TG gene: 51-AGGCTAGGAAAATGGCCCTGGTCC-31 and 51-TTGGATCCTTATGTGGGGGAATCTGCC-31. PCR was performed in an incubation medium: 50 μl contained 60 mM Tris-HCl (pH 8.6), 6 mM EDTA, 10 mM b-mercaptoethanol, 10 μg/ml BCA, 1 mM of each of the 4 nucleotides, 2 units of reverse transcriptase. PCR had a total of 55 cycles. Synthesis was carried out at 72 °C for 4 min. Subsequent cycles included denaturation (1 min, 49 °C), primer annealing (1 min, 55 °C), cDNA synthesis (2 min, 72 °C). After 55 amplification cycles, the samples were kept at 72 °C for 10 min and then cooled, aliquots were taken, and cDNA electrophoresis for the TG gene was performed in 1% agarose with ethidium bromide.

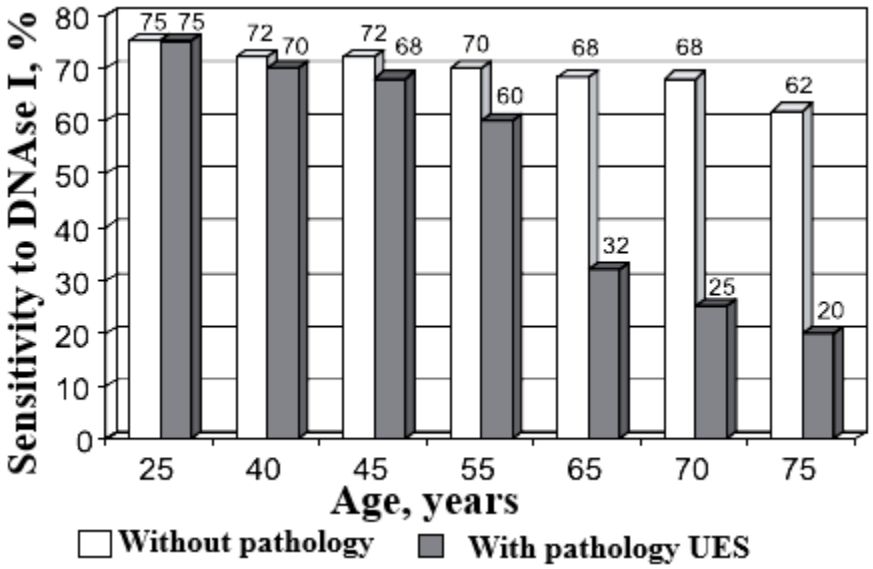
Results of the research and their discussion

Most thyroid diseases are caused by defects in the expression of the TG gene, i.e. disorders of complex processes regulating the synthesis of the corresponding protein. In thyroid diseases, there is a violation of the regulation of gene expression at all levels, namely: at the level of translation, transcription, processing (maturation of the mRNA molecule), at the level of mRNA exit from the nucleus and entry of mRNA into polyribosomes, at the level of DNA methylation.

We studied the structure of chromatin using the enzyme DNase I. It is known that there are hypersensitive regions localized in the 51 or 31 regions of an actively transcribed gene; these regions contain DNA sequences that are necessary for transcription. Identification of hypersensitive regions can clarify their regulatory function. The appearance of chromatin regions hypersensitive to DNAse I is associated with transcriptional activity and precedes the onset of transcription. Based on the above, it was of interest to study the effect of differences in the degree of TG gene expression during cellular aging on the chromatin structure.

A study of DNAse I – hypersensitivity of chromatin of thyroid cells in elderly people with various thyroid pathologies was conducted. Elderly people without thyroid disorders were observed as a control. In this case, the nuclei were isolated from the epithelial cells of the patients' saliva. Figure 1 shows data on DNAse I – hypersensitivity of chromatin of nuclei in elderly people without thyroid pathology and with nodular euthyroid goiter. It was shown that DNAse I – hypersensitivity of chromatin of nuclei in elderly people with nodular euthyroid goiter decreases by 2 times, compared with elderly patients without pathology.

Figure 1. *DNAase I – hypersensitivity of nuclear chromatin*



The obtained data show that there is a direct correlation between the degree of TG gene expressivity and DNase I – hypersensitivity of chromatin of thyroid nuclei of elderly people with nodular euthyroid goiter, expressed genes are more sensitive to DNase than inactive genes. DNAse I – hypersensitivity of chromatin in isolated nuclei by the release of hydrolyzed DNA from nuclei of old people aged 85 years was 45%, which is 35% lower than DNAse I – hypersensitivity of young people. The obtained results indicate that there is a direct correlation between the degree of TG gene expression DNAse I – hypersensitivity of chromatin of nuclei, i.e. violation of regulation of TG gene expression occurs at the transcription level. To understand the expression of the TG gene, it is important to clarify the structural organization of the functional properties of transcriptionally active regions of the genome. Identification of the factors determining the potentially active state of the TG gene is extremely important for understanding the molecular mechanisms regulating the expression of this gene during cellular aging (Wei J. Y., 2005).

Conclusions:

1. It has been shown that during aging, there is a violation of the regulation of TG gene expression at the transcription level.

2. A direct correlation has been established between the degree of TG gene expression in thyroid cells during cellular aging and DNAse I – nuclear chromatin hypersensitivity.

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