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Perspective

Epigenetic Regulation of Thyroid Hormone Receptor Expression

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DESCRIPTION

The primary Thyroid Hormones (THs) that regulate metabolism, development and differentiation are triiodothyronine (T3) and Thyroxine (T4). Thyroid Hormone Receptors (TRs), nuclear receptors that control the expression of target genes, mediate the activities of these hormones. Numerous mechanisms, including epigenetic changes, closely control the production and function of TRs. Heritable variations in gene expression that do not result from changes in the DNA sequence are referred to as epigenetics. The thyroid hormone receptor's expression is examined in this article along with the therapeutic implications of these regulatory processes.

Epigenetic mechanisms and thyroid hormone receptors

Changes including DNA methylation, histone modifications and non-coding RNAs are all part of epigenetic control. These alterations may affect how easily accessible TR genes are to the transcriptional machinery, which may change how expressed they are. A methyl group is added to the cytosine residues of CpG dinucleotides in DNA methylation. Usually, this change results in the suppression of genes. Hypo methylation can result in enhanced expression of thyroid hormone receptors, whilst hyper methylation of TR gene promoters can cause decreased expression. For instance, research has demonstrated that reduced TRβ expression in some malignancies can result from hyper methylation of the TRβ gene promoter. Tumor growth may be aided by this down regulation, which may interfere with regular TH signaling. On the other hand, hypo methylation of TR promoters in certain tissues might impact metabolic processes and increase TH sensitivity.

Proteins called histones wrap DNA and post-translational changes to these proteins, including acetylation, methylation, phosphorylation, and ubiquitination, can have a big impact on how genes are expressed. While deacetylation and methylation of histones can result in chromatin compaction and gene suppression, acetylation of histones typically causes an open chromatin shape and active transcription. The promotion of TH activity can be achieved by up regulating TR expression through histone acetylation at TR gene loci. On the other hand, TR expression can be suppressed by histone methylation or deacetylation. Histone deacetylase inhibitors, for instance, have been demonstrated to raise TR expression in certain mice, indicating a possible treatment approach for illnesses linked to decreased TR levels. Long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) are two types of non-coding RNAs that are essential for post-transcriptional regulation of gene expression. Translational repression or mRNA degradation can occur when miRNAs bind to the 3' Untranslated Regions (3' UTRs) of TR mRNAs. It has been discovered that a number of miRNAs selectively target TR mRNAs, changing the degree of their expression. TH signaling disruption and altered TR expression can result from these miRNAs' dysregulation. In order to affect TR gene expression, lncRNAs can also interact with chromatin-modifying enzymes.

Therapeutic implications

New therapeutic approaches for treating illnesses such as cancer, metabolic disorders, and thyroid dysfunction can be made possible by comprehending the epigenetic control of thyroid hormone receptor expression. The advancement of several malignancies, such as hepatocellular carcinoma, thyroid cancer, and breast cancer, has been linked to aberrant TR expression. By correcting abnormal epigenetic alterations, epigenetic medications like DNA methyltransferase inhibitors (like 5-azacytidine) and histone deacetylase inhibitors (like vorinostat) can regulate the expression of TR. For example, DNA methyltransferase inhibitor therapy can restore TRβ expression in thyroid cancer, where TRβ is frequently down regulated due to promoter hyper methylation. This re-sensitizes cancer cells to TH and inhibits tumor development. In a similar vein, in malignancies exhibiting aberrant histone modification, histone deacetylase inhibitors can stimulate the production of TR again.

The regulation of metabolic rate, lipid metabolism, and glucose homeostasis is significantly influenced by thyroid hormones.

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Obesity, diabetes and dyslipidemia are metabolic diseases that may be exacerbated by dysregulation of TR expression. Histone modifications or miRNAs that are the focus of epigenetic therapy may be able to normalize TR expression and restore metabolic equilibrium. To improve metabolic outcomes, it may be possible to boost TH signaling in areas where it is low by modifying the expression of miRNAs targeting TRα or TRβ. Changes in TR expression might worsen the illness phenotype in thyroid dysfunctional diseases including hypothyroidism and hyperthyroidism. Traditional hormone replacement or antithyroid medications may be used in conjunction with epigenetic therapies that alter TR expression. Enhancing the expression of the TR gene by epigenetics may increase the effects of exogenous thyroxine treatment in hypothyroid individuals, when TR expression may be inadequate. On the other hand, in individuals with hyperthyroidism, lowering TR expression *via* certain epigenetic alterations may be able to lessen excessive TH activity.

CONCLUSION

One important component of thyroid hormone signaling that has important consequences for both health and disease is the epigenetic control of thyroid hormone receptor expression. Novel treatment approaches for illnesses such as thyroid dysfunction, cancer, and metabolic disorders can be developed by modifying the expression of TR through epigenetic pathways. Even if there are still obstacles, continued study and technology developments might lead to the creation of efficient and focused epigenetic treatments. New avenues for enhancing metabolic health and treating thyroid-related disorders will keep arising as our comprehension of the complex interactions between epigenetics and thyroid hormone signaling expands.