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HYPOTHESIS

Thyroid Hormone Pathways in Respiratory Diseases: Mechanism and Therapeutic Potential

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Abstract: Thyroid hormones (THs) influence a wide range of processes, from gene expression to complex signaling pathways, in almost every tissue. Over the past few years, there has been renewed interest in the TH synthesis, metabolism, secretion, and action; and the therapeutic potential of TH-related pathways and factors; as well as the mechanisms involved, including endocrine-immune /inflammatory relation. We hypothesize that TH-related factors and processes (ie, iodothyronine deiodinase, thyroid hormone transporters, etc) might influence the pathomechanism, disease course of respiratory pathology. TH-related molecules and processes may have the potential for use as indicators that may explain biological heterogeneity and/or be biomarkers of respiratory diseases. Furthermore, we postulate to explore whether the immune-inflammatory and/or other pathway components involved in lung diseases represent potential therapeutic agents. Exploration and validation of the distinctive utility of the abovementioned factors in respiratory disease should be planned and performed, paying attention to novel therapies and a panel of biomarkers, especially as the number of studies is limited and lacking, which makes it difficult to come to significant conclusions and find potential applications regarding respiratory diseases.

Keywords: hypothalamic-pituitary-thyroid axis, thyroid hormone, thyroid hormone transporter, iodothyronine deiodinase, thyroid hormone receptor, biomarker, therapeutic potential

Introduction

Thyroid hormones (THs) orchestrate a different kind of mechanism, from gene expression to complex signaling pathways, in almost every tissue. Metabolism of main macromolecules, and controlling of many processes, including membrane-bound enzyme pathways,[1] immune-inflammation reactions, oxidative stress processes,[2] cell proliferation, and cellular homeostasis,[3] is an important role for THs.

Synthesis, Secretion, Transport, and Action of THs

The secretion and metabolism of THs as well as the processes controlled by THs are conducted via many pathways and regulated by numerous determinants: hypothalamus-pituitary-thyroid (HPT) axis, TH transporters that regulate TH inflow into the cells, and iodothyronine deiodinases (DIOs) – enzymes controlling TH synthesis – and metabolism, classical signaling pathways via nuclear receptor and non-genomic pathways via, for example, the plasma-membrane integrin.[4]

The Hypothalamic–Pituitary–Thyroid Axis Related Regulation of Thyroid Hormones

The HPT axis plays a crucial role in determining proper peripheral concentrations of THs – the euthyroid state. Secreted by hypothalamus thyrotropin-releasing hormone (TRH) induces the pituitary cells to secrete thyrotropin (TSH) that is followed by thyroid secretion of TH. On the negative principal of feedback, TH regulate the levels of TRH and TSH. The signaling pathways and metabolism of THs is governed and transduced in the thyroid and other organs, including the lungs.[5]

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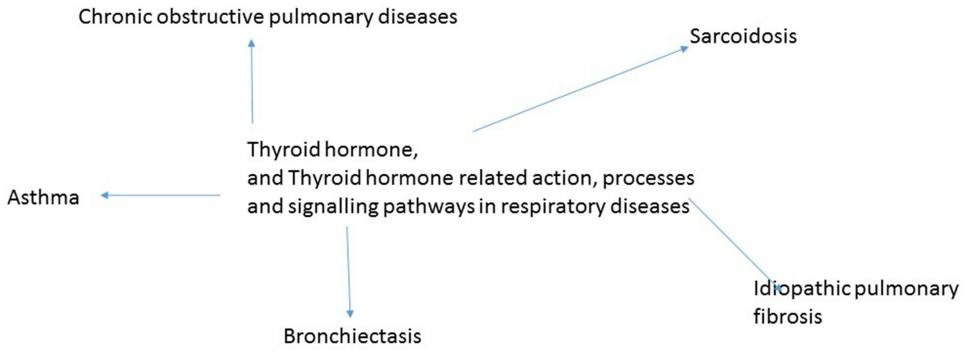
Graphical Abstract



Transport of Thyroid Hormones

The cellular transport of THs is facilitated by transmembrane protein transporters, namely thyroid hormone transporters (THTs). Detailed information for the THTs is presented and reviewed by Penna et al.[6] Among these transporters, monocarboxylate transporter (MCT) 8 and 10 and organic anion transporter polypeptide including (OATP) 1C1, are very specific for the transport of THs and some of their derivatives.[7] Large neutral amino acid transporter (LAT) 1 and 2 also govern the transport of THs.[8] Recently, human SLC17A4 was characterized as a novel transporter that mainly govern the influx of T3 and T4, but reverse (r)T3 and 3,3′-diiodothyronine (T2) also are transported by SLC17A4.[9] MCT 8 and 10, OATP1C1, large neutral amino acid transporter LAT 1 and 2, and SLC17A4 display the highest specificity toward THs.[10] MCT8 is expressed in the area of thyroid, lung, skeletal muscle, heart, kidney skin, and brain. Meanwhile, transporter MCT10 is more strongly expressed in the skeletal muscle, kidney, intestine, liver, heart, and placenta.[6] OATP1C1 is characteristically present in the lung, heart, liver, and kidney,[11] while SLC17A4 is widely observed in the gastrointestinal tract.[9]

Synthesis and Metabolism of Thyroid Hormones

The type 1–3 iodothyronine deiodinases (DIOs) mediate the metabolism and synthesis of THs and influence THs levels. The expression of DIO1 has been found in the liver, kidney and thyroid. The presence of DIO1 is also observed in lymphocytes.[12] DIO2 type expression is varied and tissue-dependent. The presence of DIO2 has been found in the pituitary, lung, skeletal muscle and brain cells. DIO2 mainly determines intracellular synthesis of T3.[13] According to preclinical studies, DIO2 is also a sensitive marker of peripheral thyroid status.[14] DIO3 is a type of selenoenzyme that is mainly responsible for the determination of reverse (r) T3 from thyroxine (T4) and synthesis of diiodothyronine (T2) from T3.[15] Physiologically, DIO3 covers most of the human organs. Recent findings have confirmed the presence of mRNA for DIO3 in human neutrophils.[16]

Genomic and Non-Genomic Action of Thyroid Hormones

The effect of THs is generated through different pathways influencing or not gene expression. The genomic action of THs is dependent upon its receptor (TR) isoforms – TRβ1, TRβ2, and TRβ3 – and TRα and the action is tissue dependent.[3]

The non-genomic intracellular effect of THs is present in, for example, the cytoplasm and mitochondria, and involves PI3K-dependent activation. The non-genomic effect of THs occurs at the plasma membrane and involves different proteins such as integrin αvβ, interacting with mostly T4, and their derivatives, resulting in the activation of AMPK, PI3K/Akt, and MAPK pathways.[17]

Thyroid Hormone Secretion-, Metabolism-, and Signaling Pathway-Related Molecules in Respiratory Diseases

The presence of interaction and dependence exist between respiratory system physiology/pathology and thyroid function and related molecules. Thyroid hormones play a role in forming the respiratory system, its volume, and its flow. The

respiratory center in the brain is also governed by THs. Generally, normal respiratory function is dependent on proper thyroid work and related molecules.[18]

Disturbances in the overall function of the HPT axis as well as disrupted synthesis, metabolism, and transport influence both THs function and THs levels.

Respiratory-related disorders, having immune-inflammation based pathology, are common illnesses, with HPT axis- and TH-related disturbances often described.[19] A link is suggested to exist between the THs-related pathways and respiratory drive and disturbances in the link may be related to immune-inflammation pathways disturbances as they are important targets for THs, their transport, metabolism and effect processed by transporters, receptors, and deiodinases, respectively.[20] In addition, crosstalk between TH-related pathways and immune-inflammatory processes (immune/inflammatory-endocrine relation) have been documented.[21]

Asthma

Thyroid hormones importantly affect development of asthma. A study examining how THs influence the mechanism of the inflammatory process with airway in rats revealed that deficiency of THs affects the development of inflammatory components of asthma.[22] Hyperthyroidism in patients with asthma can cause asthma exacerbation, while hypothyroidism is associated with milder asthma symptoms due to reduced concentrations of T4 and T3, resulting in lower oxygen consumption.[23] In asthmatic patients, there is a correlation between the sum of peripheral activity of deiodinases and ratio between value of forced expiratory volume in 1 second (FEV1) and value of forced volume capacity (FVC).[24] Another study indicates that the bronchodilatory effect of fenoterol in patients with asthma is impaired when TH concentration is higher than normal ranges and improves after the achievement of euthyroid state.[25] An in vitro study by Nishizawa et al[26] revealed that thyroxine directly influences the production of superoxide anion – a marker of inflammation-related oxidative stress – by human neutrophils and alveolar macrophages and the level of asthma exacerbation correlates with hyperthyroidism.

COPD

Regarding COPD, patients with COPD show no thyrotropin responses to TRH.[27] The number of exacerbation in COPD related to lung function indicators value was associated with TSH concentration.[28] Low peripheral switch of T4 to T3 is not rarely observed in patients with COPD.[29] Results of pulmonary function tests, blood gases analyses are associated with fT3 concentrations[30] and a negative relation exists between low fT3,4 levels, invasive mechanical ventilation, and death of patients diagnosed with COPD.[31] The presence of hypothyroidism has been found to be positively correlated with COPD stage and respiratory muscle dysfunction.[29] Patients with COPD and coexisting hypothyroidism are characterized by drop in pO2 value, maximal inspiratory and expiratory pressure, and a tendency towards a pCO2 levels increase.[19] Immune-inflammatory reaction oxidative stress is linked with low T3 levels in COPD patients.[32]

Lung Fibrosis

An association has been found between a decrease in thyroid work and the presence of liver, heart, and lung fibrosis.[33] Wang et al[34] observed that TH by affecting/controlling cell to cell interaction (ie, alveolar epithelial cells, macrophages, and fibroblasts) influence proper cell physiology, determine alveolar recovery, and terminate fibrosis. The mechanism of TH-related inhibition of fibrosis include determination of mitochondrial functionality by regulation of energy processes and inhibition of apoptosis of alveolar epithelial cells.[35] Administration of T3 to a mice model of pulmonary fibrosis reduces bleomycin-induced lung fibrosis and stimulates microbiome recovery of the lung.[36] Triiodothyronine has been observed to ameliorate lung inflammation and fibrosis in mice caused by silica.[37] Hypothyroidism has recently been observed as a common and predictive factor of mortality in IPF patients.[38] Lungs of IPF patients are characterized by high expressions of DIO2.[35] The hypothalamic–pituitary–adrenal axis as well as THs and their signaling pathways related factors are of interest in IPF, and the application of these hormones and other molecules in novel therapies for IPF is under discussion.[39,40]

Varia

An association exists between hyperthyroidism and cancer occurrence. Zhenchao Ma et al[41] showed that serum TSH, pulled concentration of T4, T3, and free (F)T3 were importantly lower, while FT4 concentrations were higher in a group of patients diagnosed with lung cancer. Low levels of TSH, T3, and T4 have been observed to cause pulmonary and systemic inflammation in patients with COVID-19.[42] Low T3 syndrome is related to the appearance of pneumonia during stroke.[43] THs were found to determine alveolar fluid purification and alleviation of lung damage caused by hypoxia. Proper thyroid function and TH concentration control and determine lung extravascular fluid, aquaporin 5 expression and alveolar viscoelasticity when mechanical ventilation is present.[44]

Hypothesis

Little is known from the existing studies (translational and or clinical) about the therapeutic or biomarkers potential of TH-related molecules in respiratory diseases.

Clinical study by Khalek et al[45] observed that T3 administration to clinically euthyroid children with chronic asthma reduced the dosage of bronchodilators used.

A need exists for further research as the role of THs and THs pathway-related molecules regarding respiratory diseases is underexplored, results are not confirmed and not enlarged. The need exists to develop studies regarding the roles of THs and THs pathway-related molecules, especially, but not only in the context of immune–inflammation–endocrine interaction in lung diseases with inflammation background.

We hypothesize that TH-related factors (ie, iodothyronine deiodinase, thyroid hormone transporters) and signaling pathways, and their potential modulation, might influence the pathomechanism, disease course, and treatment of respiratory pathology and might be explored as possible indicators that may explain biological heterogeneity (ie, immune–endocrine interaction) of lung disease and/or potential biomarkers of respiratory diseases as well as potential therapeutic targets, what should be explored and confirmed in further studies.

Methods

The PubMed data were chosen to select the article used in this manuscript.

Original article, meta-analyses, reviews, and systematic reviews were searched. As the issue is not deeply explored, no start year was defined while choosing the articles. We have focused on all published article linking TH related factors and pathways in immunity and inflammation and those including immune-endocrine interaction in lung/respiratory diseases. Here, we aim to answer the question about of whether TH secretion-, metabolism-, and action-related factors and signals have the potential for use as indicators that may explain biological heterogeneity and/or biomarkers of respiratory diseases or have potential therapeutic value.

- HPT axis TRH, TSH, and inflammation/HPT axis, TRH, TSH, and immune cells,
- Thyroid hormone transporters and inflammation/thyroid hormone transporters and immune cells,
- Iodothyronine deiodinase and inflammation/iodothyronine deiodinase and immune cells,
- Thyroid hormones genomic and non-genomic effect and inflammation/thyroid hormone genomic and non-genomic effect and immune cells,
- HPT axis, TRH, TSH and mutation, single nucleotide polymorphism, gene expression protein, levels in lung-respiratory diseases including: asthma/COPD/lung fibrosis – IPF/bronchiectasis (BQ),
- Thyroid hormones transporter and mutation, single nucleotide polymorphism, gene expression, protein levels in lung-respiratory diseases including: asthma/COPD/lung fibrosis – IPF/BQ,
- Iodothyronine deiodinase and mutation, single nucleotide polymorphism, gene expression, protein levels, enzymatic activities in lung-respiratory diseases including: asthma/COPD/lung fibrosis – IPF/BQ,
- Thyroid hormone receptors and mutation, single nucleotide polymorphism, gene expression protein levels in lung-respiratory diseases including: asthma/COPD/lung fibrosis – IPF/BQ.

We have tried to choose studies of good quality, performed with well-designed methods and/or proper statistical analyses and reviews written by experts in the field.

The relevant articles were analyzed and when the results indicated involvement and the role of TH related factors in lung/respiratory disease and immunity and inflammation, the data was described in the context of potential biomarkers of respiratory diseases as well as potential therapeutic targets.

Results and Discussion

Thyroid Hormone Secretion-, Metabolism-, and Signaling Pathway-Related Molecules in the Immune-Inflammation Processes

The Hypothalamic–Pituitary–Thyroid (HPT) Axis in Immune-Inflammation Processes

Over the past few years, there has been a renewed interest in TH secretion, synthesis, metabolism, and action and the therapeutic potential of TH-related pathways and factors. Pre-clinical, in vitro, in vivo, animal model studies, cell line studies, and cross-sectional, observational studies have revealed the presence of interactions between TH metabolism, transport, and signaling pathway-related molecules and immune-inflammatory processes, as well as the involvement of the above molecules in immunity and inflammation, physiological, and pathological processes. Results from animal model studies have revealed that, in some conditions, local inflammation results in a decrease in TRH levels.[46] A study in mice confirmed the interaction between inflammation and TRH, as ReIA, that is a components of nuclear factor (NF) kB, a key regulator in immune-inflammation response – is related to the lipopolysaccharide (LPS)-induced decrease in TRH levels.[47] Administration of TRH to cancer patients was found to decrease C-reactive protein levels, a biomarker of inflammation.[48] Interactions between TSH and the immune system have also been found. Studies using cell lines have found TSH affects macrophage inflammation[49] through activation of MAPs, ERK ½, p38, JNK, and IkB/p65 signaling within macrophages, which results in higher levels of cytokine secretion and subsequently an increase in the recruitment of monocytes; meanwhile, in patients with thyroid carcinoma, TSH suppression aggravates inflammation.[50]

Thyroid Hormones Transporters in Immune-Inflammation Processes

TH transporters and their immune-inflammation interaction have been examined and observed. LPS-induced inflammation influences the expression of THTs transporters such as OATP1c1 and MCT8. Gene and protein expression assessment by in situ hybridization, quantitative polymerase chain reaction (PCR), methods in the rat and mouse forebrain, observed time-dependent regulation in gene expression of *OATP1c1* and *MCT852*. Reduction in protein expression levels has been confirmed during the period of the first 9 hours after injection with LPS, while *OATP1c1* mRNA and *MCT8* mRNA levels did not change. *OATP1c1* and *MCT8* mRNA levels were higher after a longer period (24H/and 48H) from LPS-injection. OATP1c1 protein concentration decreased within 24 hours, whereas important lowering of MCT8 amount was not observed. Similarly, but kinetically slower gene expression *LAT1* is also LPS determined.[51]

Iodothyronine Deiodinases in Immune-Inflammation Processes

Deiodinases metabolizing THs regulate cell accessibility in physiology but also with the presence of inflammation. All three types of DIOs are involved in immune-inflammatory signaling. Pro-inflammatory cytokines affect the expression levels of DIO1. Reduction in the mRNA levels of DIO1 is induced by IL-1, IL-6, and TNF-α in that order, as measured by RT-PCR using a functioning rat thyroid cell line.[52–54] Meanwhile, human recombinant IL-1β, interferon (IFN)-ɣ has been shown to reduce DIO1 enzyme activity in human hepatocarcinoma cells.[55] Similarly, local DIO2 expression in pituitary cell culture rises after incubation with pro-inflammatory cytokines.[56] Suppression of the DIO2 mRNA and protein expression levels in human chondrocytes is parallel with high release of IL-1β, cyclooxygenase 2.[57] Aberrant DIO3 expression is observed in activated monocytes, macrophages, and granulocytes during sterile and/or bacterial inflammation.[58,59]

Thyroid Hormones Signaling Pathways in Immune-Inflammation Processes

THs/THs receptors signaling pathways affecting gene expression and non-gene expression related processes are involved in immune cell function, including leucocyte activity and inflammatory response, as described in a detailed review by

Montesinos and Pelizas,[17] Wenzek et al,[60] Lasa and Contreras-Jurado.[21] In brief, in macrophages, the physiological TH levels, through a genomic mechanism, promote the anti-inflammatory response by downregulating several factors such as NF-κB, the inflammasome, and pro-IL1β. Disturbances in THs levels activate pro-inflammatory pathways. Higher TH levels induce acute and chronic inflammation through integrin αvβ pathways linked to increased pro-inflammatory cytokine secretion. Physiological levels of T3 in dendritic cells expressing TRβ1 drive the Th1 profile of inflammation.[21] By the mechanism involving integrin, TH stimulate ROS secretion by neutrophils, while THR expression and the genomic mechanism have not been widely explored regarding neutrophils. In human NK cells, the expression of both types of THRs has been observed. The role of TH signaling and affection on natural killers functionality need further examination.[60]

Respiratory Disease and Putative TH-Related Immune-Inflammatory Pathways

A relationship between respiratory disease and TH-related pathways has been observed, although the exact mechanism remains obscure. Asthma, COPD, sarcoidosis, IPF, and bronchiectasis (BQ) are characterized by pathomechanisms related to immune-inflammation processes, immune cells, and the reaction between the respiratory tract and periphery. Briefly, asthma and COPD result from distinct pathogeneses, but have several inflammatory pathways in common. Eosinophilic airway and peripheral inflammation is present in both diseases. Similarly, type-2 inflammation related to neutrophil counts is involved in the outcome of both diseases.[61] Immune cells, including: macrophages, natural killer cells, and dendritic cells also participate in asthma and COPD development and course.[62] The presence of granulomas including layers of immune cells is typical for lung sarcoidosis with important roles for macrophages and DCs. The latter and NK cells also have been found highly present in bronchoalveolar lavage fluid (BALF) of sarcoidosis patients.[63] Amount of neutrophils measured in BALF indicates the intensity and score of the disease.[64] Innate immunity cells have been recognized as key players in the path-mechanism and etiology of IPF. Specific subsets of macrophages participate in equilibrium between pro-, anti-fibrotic pathways, with the main role being regulation of fibrosis by the M2 type.[65] Similarly, neutrophils, products of their activity such as neutrophil extracellular traps (NETs) and macrophages are involved in the path-mechanism and inflammation of bronchiectasis (BQ).[66]

Regarding adaptive immunity cells, lymphocytes levels are a prominent feature of asthma and COPD.[67] Evidence for the contribution of lymphocytes to sarcoidosis pathobiology is increasing.[68] In IPF, the immune response is also driven by lymphocytes and adaptive immunity participants importantly.[69] Infiltration with lymphocytes has been confirmed in small airways and lungs of patients with BQ.[70]

All abovementioned immune-inflammatory cell express THTs, DIOs, and TR and are under the influence of THs. Neutrophils, macrophages, NKs, and DCs are also potential targets for THs and THs-related factors and pathways, and can in turn affect TH metabolism and mechanism of action.

THs Related Factors and Innate Immunity Cells

Human neutrophils express MCT10, DIO1, DIO3, and TRα, while NKs express both MCT8 and MCT10, TRα and β, and, similarly, T and B cells. Preclinical studies on mice confirmed macrophage expression of MCT8, MCT10, LAT 2, DIO2, and TRα, resulting in complex crosstalk between TH and immunity. In addition, T4 interact with immune cell-surface integrin αVβ3, influencing different pathways.[60]

The circulating levels of THs are determined by the HPT axis, while the local action of THs is determined by transport into the cells, including immune cells, metabolism to active and/or inactive form, and receptor and/or non-receptor mediated signal. What is important in the above steps may change and be different when comparing health and disturbances and disease.

Detailed information on the action of THs on immune cells, mainly neutrophils and macrophages, have been presented by Montesinos and Pellizas,[17] Wenzek et al,[60] Lasa and Contreras-Jurado,[21] and de Luca et al,[71] for example. As is widely known, neutrophils are firstly recruited to the area of inflammation and participate in this process via complex mechanisms. Processes within the intracellular space of neutrophils include TH metabolism as the cells express THs and action-related elements such as THTs, DIOs, and TRs. Beside the metabolic processes of the THs in the neutrophils, circulating THs, during transport into the cells, determine oxidative stress by increasing NADPH oxidase

activity, inducing bacterial killing. A correlation has been observed between hypothyroidism and markers of oxidative stress and restoration of ROS production at normal TH levels.[20] An important role is also dedicated to the DIO3 enzyme, as higher expression is observed during bacterial and sterile inflammation. DIO3 is a source of iodine ion (I^-) released during a deiodination reaction (T4 to rT3, and T3 to T2). In reaction with hydrogen peroxide catalyzed by myeloperoxidase (MPO), I^- generates toxic bacteria killing molecules. Lack of DIO3 impairs bacterial killing and increases inflammation. In macrophages, at physiological levels, T3 promotes bactericidal and phagocytic activity as well as anti-inflammatory effects via binding TR. During hypothyroidism, higher T4 via plasma membrane integrin activates oxidative stress and the pro-inflammatory pathway by releasing pro-inflammatory cytokines and inducing cyclooxygenase 2 expression. Lack of TH results in exacerbation of inflammation. The important role is played by THs in macrophages by affection their polarization. Lack of DIO2 activity, which results in low T3 levels, reduces proper macrophage function. The action of thyroid hormones on NK is controversial, with increasing NK activity with high levels of T4 and impairment in NK function with high levels of T3. In DCs, T3 is involved in the maturation process and regulation of functional activity.[17,21,71]

THs Related Factors and Adaptive Immunity Cells

Interaction between TH-related processes/molecules and lymphocytes are not well explored. The TRs are confirmed to be present in T and B cells as well as the deiodination process. TH in T cells act locally which may be mediated indirectly by DCs or directly mediated by depending on TH levels induction of proliferation or apoptosis. Similarly to T cells, TR are expressed in B cells, and THs are involved in induction of proliferation. The role of TSH and its receptor in immune function is under debate with TSH involvement as a regulator of immune function by promoting activation and proliferation of lymphocytes, enhancing phagocytic activity, and increasing pro-inflammatory cytokine secretion.[60]

Mutations, Genetic Variants, Disturbances in mRNA Expression, Protein Expression, Enzyme Activity, THs Levels, and Action-Regulated Factors

Changes in the concentrations of THs and disturbances in signaling pathways observed in respiratory-related diseases may be determined by the changes in the area of HPT axis, THTs, DIOs, and the molecules involved in signal transduction pathways with nuclear and cytoplasmic TRs and/or integrin. A possible mechanism may be related to the presence of mutations; genetic variants; disturbances in mRNA expression; variations in protein expression, hormone levels, enzyme activity; and modifications of underlying processes. THs and related molecules may be associated with not only inflammation, the important path-mechanism in respiratory diseases, but other processes involved in that process.

Thyroid Hormones Transporters

A study examining transporter expression has revealed that the peripheral phenotype of MCT8 deficiency include a drop of body weight, loss of muscle mass, scoliosis, higher sera (F) T3, lower sera (F) T4, and rT3.[72]

Iodothyronine Deiodinase

Iodothyronine deiodinases are of interest in different diseases from the perspective of their polymorphic variants, gene and protein expression, enzymatic activity, and correlation with other factors.[73] The published data have demonstrated that a SNP in the *DIO2* gene may be associated with TH levels, and that there is an association between a SNP and DIO2 protein levels and its activity. ORF–Gly 3A Asp (C/T) variant is related to DIO2 activity. Carriers of the T allele are characteristically found to have higher DIO2 activity/TH levels, while carriers of the C allele low DIO2 activity.[74] The presence of Ala 92–DIO2 phenotype of Thr92Ala variant is characterized by reduced DIO2 activity and failure of L-T4 therapy is observed in Ala carriers.[75] A relationship has been found between the above variant and lower amount of TSH-induced Ft4 secretion.[76] Genotyping, microarrays and immunoblot methods confirmed DIO2 expression on mRNA and protein levels in leucocytes when using animal acute lung injury (ALI) model. Results indicated that the *DIO2* gene is a new gene to explore in ALI. Detailed results revealed that presence of (Ala) was beneficial during severe sepsis and severe sepsis-related ALI.[77] Correlations were also found between DIO2 expression and score of lung injury, with lack of *DIO2* and/or low DIO2 during ventilator-induced lung injury and high levels of lung damage, and increase in chemokine/cytokine amount within the area of

the lung.[78] The type 2 deiodinase and its Thr92Ala-DIo2 variant have been found to be important in pulmonary fibrosis. Measurement of DIO2 expression and activity in lung of IPF patients confirmed that both expression and activity were higher comparing to controls and correlated with the range of disease severity. In addition, bleomycin-induced fibrosis in mice is increasing while lack of DIO2 is present.[35] DIO2 levels have been studied in a group of patients with COPD. The results reveal higher protein levels expression in COPD compared with that in healthy controls.[79] Data regarding the roles of other DIOs, including DIO1 and DIO3, in respiratory disease also include estimation of genetic variants and expression levels. The widely explored polymorphism within *DIO1* genes are DIO1a-C/T and DIO1b-A/G, which are known to correlate with TH levels. Allele T is associated with increase in sera rT3 levels and a decrease in T3/rT3 ratio. The G allele is associated with anincrease in T3/rT3 ratio and results in higher DIO 1 activity in the carriers of this allele.[80] The interesting information is that, the decrease in DIO1 activity resulting from the presence of genetic variant correlates with higher levels of IGF-1 and associated with muscle mass and strength.[81]

Changes in DIO1 and DIO3 concentration have been evaluated in COPD.[82] The important observation from this study is that the concentrations of both DIO1 and DIO3 differ between the examined groups (COPD vs control).[82]

Thyroid Hormone Receptors

Genetic variants in the forms of TRβ resulted in the presence of resistance to TH and disturbances in proper concentrations of TSH under high levels of T4 and T3 caused by disruption in TH feedback.[83] Only one study has evaluated the gene encoding for TR in respiratory diseases. Polymorphisms within THR have been evaluated in patients with asthma, revealing that a new SNP for inter-individual variability in bronchodilator response (BDR) in these patients, as *THRβ* variant is related to BDR in children and two adult populations.[84]

Limitations

Demonstrated in the paper, studies are of good quality with proper and well-designed methods according to standard, including statistical analysis but presents single results that had not been confirmed with larger studies and/or with the use or other models and/or methods. Some publication may bias the results and, if available in the future, the results may differ across the studies. In addition, contradictory findings are lacking. That could add value to further discussion and research.

Future Suggestions, Possible Directions, and Conclusions

From the above presented results, some suggestion may arise for further discussion. Given the above, the possible need exists to examine HPT axis, and THs-related molecules and affected by them processes in respiratory diseases, regarding potential mutations, SNP, gene, protein expression, and enzyme activity in relation to immune–inflammation–endocrine interaction but not only.

It is important to emphasize the expression of the molecule (DIOs) in immune cells and participation in inflammation mechanism reaction.[20] Presence of both DIO1 and DIO3 is characteristically found in neutrophils.[60] The DIO1, and with more evidence presence of DIO3 may reflect the state of immune and pro- and anti-inflammatory balance. The role of DIO3 in neutrophil activity is explored further. DIO3 is involved in neutrophil activation by the mechanism in which, during deiodination process I, is released that in reaction with MPO generates IOH with ability to kill bacteria.[60] DIO3 concentrations may reflect the number and the activity of neutrophils.[85] Considering the relation between neutrophils, immunity, immune-deficiency, low circulating DIO3 may reflect the low neutrophils levels and immunodeficiency – risky factors for the presence of exacerbation and disease progression.[86] Contrary, higher DIO3 reflecting higher neutrophils levels may result in lung tissue damage as fatty acid metabolism in neutrophils promotes lung damage.[87]

Neutrophils influence inflammation by determining processes of phagocytosis and/or the secretion of neutrophil extracellular traps (NETs). Contrary action of neutrophils comprises of modulation of NET production by reducing their amount, followed by lowering NET amount in the area of injured tissue.[88] The main elements of NET include cell-free DNA, histones, and granule proteins including MPO.[89] Location of iodothyronine deiodinase type 3 encompasses cytoplasm of the cells and granules containing MPO.[20] One may suggest the DIO3 as one of the proteins included in NET can be an indicator of the level of NET formation, a marker of neutrophilic inflammation measured in the periphery. The relation to neutrophilic

inflammation presence of NET has importantly participated in processes characteristic for respiratory diseases with neutrophilic components.[90] Recently, DIO2 gene expression has been found to be a diagnostic value in inflammatory diseases.[91] According to Di Zhao et al[91] the upregulated expression of DIO2 gene measured by mRNA levels signified importantly higher levels of immune infiltration. An animal model study has revealed that LPS induces an increase in DIO2 mRNA levels.[92] DIO2 deregulations are characteristically found during bacterial inflammation but also during muscle wasting, both processes of the role in respiratory diseases.[93,94] Similarly to neutrophils, macrophages secrete macrophage extracellular traps (MET) and DIO2 may also be suggested as one of the protein composing MET. Based on this deeper investigation of DIO2 circulating levels regarding MET formation and its composes is needed. DIO2 could be potentially discussed as a marker/indicator of macrophage inflammation. Considering the link between DIO2 and bacterial inflammation increase of the DIO2 may be considered as a marker of potential infection. Link between DIO2 and impaired phagocytosis, levels of DIO2 in some cases may be a prognostic sign for exacerbation while infected by *H. influenzae* or *S. pneumoniae* and can be explore as a therapeutic target.[95] The increase in DIO2 level may be a target for pharmacotherapy as cefalosporine (cefuroxime) acts as a novel DIO2 specific selective inhibitor.[93] DIO2 and DIO3 are proposed to be further examined as markers and differentiating factors for inflammation.

Attention should also be paid to TRH as a new marker of inflammation, blocking theTSH receptor within immune cells may results in decreasing levels of inflammation. Similarly, gene induction for TR may result in inhibition of inflammation. MCT8 deficiency may impact the development of respiratory diseases by the loss of muscle mass and be a risky factor for this process. Regarding correlation between genetic variants in respiratory disease and low skeletal muscle expression and activity of DIO2, the presence of respective variant may reflect a decline in skeletal muscle size and influence the outcome of the disease. Thr92Ala polymorphism may influence the risk of ALI. Expression levels of DIO2 and TH concentrations may be useful as a protector of alveolar epithelial cells and in rebuilding of a proper mitochondrial metabolism.[35] Supplementation with optimal dosage of T3 may reduce the level of inflammation and inflammation related processes. Activity level of DIO2 may be suggested as a risk factor for fibrosis development. While supplementation with T3 may have beneficial effects for process of fibrosis.

The method use for further examination of biomarker and therapeutic potential of TH-related molecules include: examination of genetic variant, tissue and/or peripheral gene/protein expression, enzymatic activity and correlation with the clinical data, course of the disease and pharmacotherapy effectivity. In addition, efforts should be taken on developing of potential receptor agonist and/or antagonist and gene therapy. All the studies should be performed on preclinical models and clinical studies with the different group of patients with different population, adequate sample size, and confirmed results.

Respiratory diseases have an immune-inflammatory background, with THs and TH-related factors and processes playing important roles, given the latter have been found to influence the etiology and course of respiratory disease. Here, we postulate to examine the importance of TH-related factors and pathways in respiratory disease to expand existing knowledge on the subject.

The complex involvement and interaction between TH secretion, metabolism, signaling pathway molecules, and the immune system is not well understood for many diseases, including respiratory diseases where the crosstalk between THs and immunity remains elusive. In addition, results of studies are often in conflict depending on the model, cell line, or tissue, or whether the study is in vitro or in vivo. Further examination is needed to better understand the action and communication among TH pathways, immunity and inflammation in respiratory diseases, with important prospects for clinical application.

Abbreviations

ALI, Acute lung injury; BALF, Bronchoalveolar lavage fluid; BQ, bronchiectasis; BDR, Bronchodilator response; FVC, Forced volume capacity; HPT, Hypothalamus–pituitary–thyroid; NET, Neutrophil extracellular traps; NF, Nuclear factor; PCR, Polymerase chain reaction; TH, Thyroid hormones; THT, Thyroid hormone transporters; TRH, Thyrotropin-releasing hormone; VILI, Ventilator-induced lung injury.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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