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Selenium and thyroid

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Inadequate supply of the essential trace element selenium (Se) has been associated with predisposition for, or manifestation of, various human diseases such as Keshan and Kashin–Beck disease, cancer, impaired immune function, neurodegenerative and age-related disorders and disturbances of the thyroid hormone axis. Se deficiency in combination with inadequate iodine contributes to the pathogenesis of myxedematous cretinism. The recent identification of various distinct selenocysteine-containing proteins, encoded by 25 human genes, provides information on the molecular and biochemical basis of beneficial and possible adverse effects of this trace element. The thyroid gland is among the human tissues with the highest Se content per mass unit similar to other endocrine organs and the brain. Selenoproteins involved in cellular antioxidative defence systems and redox control, such as the glutathione peroxidase (GPx) and the thioredoxin reductase (TxnRd) family, are involved in protection of the thyroid gland from excess hydrogen peroxide and reactive oxygen species produced by the follicles for biosynthesis of thyroid hormones. In addition, the three key enzymes involved in activation and inactivation of thyroid hormones, the iodothyronine deiodinases (DIO1,2,3), are selenoproteins with development, cell- and pathology-related expression patterns. While nutritional Se supply is normally sufficient for adequate expression of functional Dio enzymes with exception of long-term parenteral nutrition and certain diseases impairing gastrointestinal absorption of Se compounds, the nutritional Se supply for the protection of the thyroid gland and synthesis of some more abundant selenoproteins of the GPx and the TrxR family might be limiting their proper expression under (patho-)physiological conditions.

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Introduction

The understanding of the essential role of selenium (Se) in thyroid hormone synthesis, metabolism and action, as well as for normal thyroid function, increased substantially during the past decades.[1–3] It has long been known that the thyroid belongs to the organs with the highest Se content due to the expression of several Se-dependent enzymes that are important in maintaining thyroid hormone metabolism such as the deiodinases (DIOs) and in preventing the thyroid cells from oxidative damage such as cytosolic and plasma glutathione peroxidases (cGPx and pGPx) as well as phospholipid-hydroperoxide glutathione peroxidase (PHGPx)[2–5] (Fig. 1). The classical diseases linked to severe Se deficiency, the destructive osteoarthritis (Kashin–Beck disease) and the lethal myocarditis (Keshan disease), are not associated with a thyroid dysfunction.[3,6–8] The first clinical evidence that severe Se deficiency in combination with other environmental factors is deleterious for the thyroid was found in Central Africa. Here, the supplementation of iodide alone was ineffective in restoring the thyroid function, and children developed myxedematous cretinism in a region with endemic iodine and/or Se deficiency.[9–11] This form of cretinism is characterised by persistent postnatal hypothyroidism, despite iodine supplementation. The thyroid gland of these children is atrophic and firm, suggesting cell damage and fibrotic degeneration (for histology see Köhrle et al.[3]). Further examinations revealed that in severe Se deficiency, the activity of thyroid glutathione peroxidases (GPx) is markedly decreased. This results in oxidative cell damage followed by necrosis and invasion of the thyroid tissue by macrophages and T lymphocytes. Chronic inflammation destroys the thyroid via TGF-dependent processes, resulting in an atrophy of the gland.[12] It is now hypothesised that even mild–to-moderate nutritional Se deficiency might be responsible for the initiation or progression of autoimmune thyroid disorders in patients with the background of genetic susceptibility to develop autoimmune diseases.[13]

Furthermore, Se has been shown to be important in the regulation of immune function (for review see refs. [14–16]). Se deficiency is accompanied by loss of immune competence. Both cell-mediated immunity and B-cell function can be impaired. This might be related to the fact that the Se-dependent

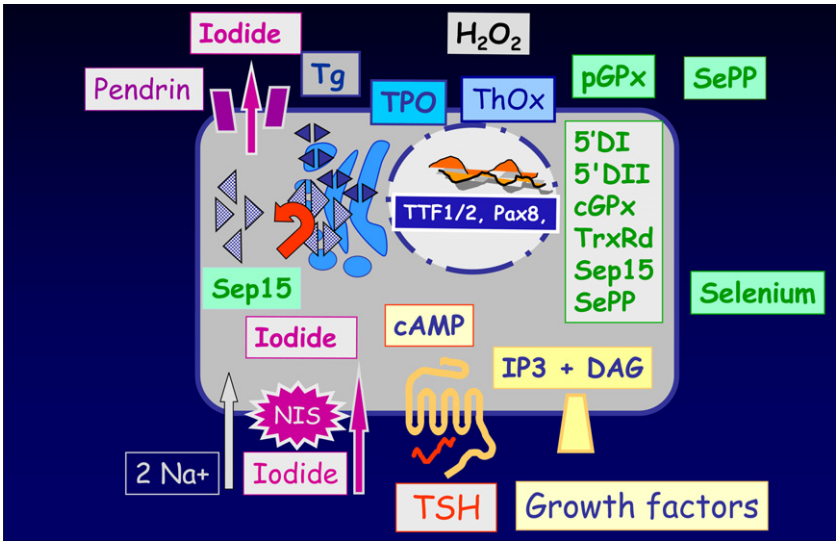

Fig. 1. Relevant Proteins and Factors involved in Thyroid Hormones Biosynthesis in Thyrocytes. Abbreviations: DAG, diacylglycerol; 5′DI, type I 5′-deiodinase; 5′DII, type II 5′-deiodinase; cGPx, cytosolic glutathione peroxidase, GPx1; pGPx, plasma glutathione peroxidase, GPx3; IP3, inositol trisphophate; Sep15, selenoprotein 15; SePP, selenoprotein P; Tg, thyroglobulin; ThOx, thyrooxidase, dual oxidase (DuOx); TSH, thyroid stimulating hormone, thyrotropin.