

Modulation of Thyroid DuOx Promoters by NKX2.5 and the Co Activator TAZ: Potential Role in Thyroid Malignancy

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Thyroid cancer represents 90% of the endocrine malignancy with a prevalence ratio of 3:1 in female sex [1]. By 2019, the estimation is that, thyroid cancer will be the third most frequent type of women's cancer [2]. Thyroid carcinoma are derived from the follicular epithelium and is divided into three main categories: differentiated thyroid carcinoma, comprising papillary, follicular and hürthle cell cancers (90 - 95%), medullary thyroid carcinoma (6%) and anaplastic thyroid carcinoma (less than 1% of thyroid malignancies) [3]. Oxidative damage due to high levels of reactive oxygen species (ROS) are frequently associated to cancer and the thyroid is an organ particularly sensitive to ROS accumulation. Indeed, oxidative stress due to accumulation of H₂O₂ is responsible for RET/PTC1 chromosomal rearrangements in human thyroid cells which accounts for 70% of papillary thyroid carcinoma (PTC) [4].

Thyroid follicular cells produce regular amounts of ROS through activation and/or induction of NADPH oxidases, which in turn generate nanomolar ratios of H₂O₂, essential for thyroid hormones biosynthesis [5-8]. Thyroid H₂O₂ generation is set up in the apical pole of thyrocytes by two NADPH oxidases called dual oxidases 1 and 2 (DuOx 1 e 2) [5,6]. It was showed that DuOx1 expression, but not DuOx2 was stimulated in thyroid tumors induced by Ionizing radiation (IR) which lead to an increase in intraglandular levels of H₂O₂ [9]. Thus, suggesting that DuOx1 might be involved in the oxidative stress related to the genomic instability, causing thyroid tumorigenesis. Increased levels of ROS generated by DuOx2 is implicated in the development of thyroid autoimmune disease [10], but its questioning if the H₂O₂ produced by DuOx2 is involved in thyroid malignancy.

Transcriptional factors (TF) able to positively modulate both DuOx 1 and 2 expressions can be involved in thyroid malignancy, as both enzymes generate H₂O₂ within thyroid follicular cells. In this way, our group showed that DuOx2 transcription can be positively modulated by hormones and TF, assessing DuOx2 promoter regulation [11]. We showed the functional activation of DuOx2 promoter by thyroid hormone stimulation (TSH) and insulin like growth factor 1 (IGF-1), and by TTF-1/NKX 2.1 and PAX 8. Moreover, we also investigated the role of NKX 2.5 which is expressed during thyroid organogenesis [12] and the transcriptional coactivator with PDZ-binding motif (TAZ) on DuOx2 transcriptional regulation [13,14]. We found a 15-fold increase in DuOx2 promoter activity in the presence of that Nkx2.5 and TAZ, suggesting that TAZ could be a relevant partner to Nkx2.5 on DuOx2 regulation [11]. The positive modulation of DuOx2 promoter in the thyroid by TAZ and Nkx2.5 raised the possibility that both factors are involved in thyroid tumorigenesis. Indeed, TAZ is overexpressed in thyroid papillary carcinoma and is involved in epithelial-mesenchymal transition, suggesting an important role in papillary thyroid carcinomas development [14].

In conclusion, the functional study with DuOx2 promoter indicated that DuOx2 expression is modulated by hormones and transcription factors, involved in thyroid organogenesis and carcinogenesis, reinforcing the importance of the control of H₂O₂ generation in the thyroid. Moreover, the fact that DuOx1 expression is stimulated in thyroid cell lines irradiated with RI (radiant ionization) and in the presence of H₂O₂ [4], reinforce the importance of the investigation of DuOx1 expression at the transcriptional level, by hormones

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and TF. Regarding the modulation of DuOx1 promoter activity by TF, potential candidates are Nkx2.5 and TAZ, as both are expressed in thyroid cancer cell lines (unpublished data), suggesting that they could also play a role in regulating DuOx1 expression in pathological conditions, such as cancer.

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