**SUMMARY**

**Context:** The long-lived thyroid cell generates, for the synthesis of thyroid hormones, important amounts of H$_2$O$_2$ that are toxic in other cell types. This review analyzes the protection mechanisms of the cell and the pathological consequences of disorders of this system.

**Evidence acquisition:** The literature on H$_2$O$_2$ generation and disposal, thyroid hormone synthesis, and their control in the human thyroid is analyzed.

**Evidence synthesis:** In humans, H$_2$O$_2$ production by dual-oxidases and consequently thyroid hormone synthesis by thyroperoxidase are controlled by the phospholipase C-Ca$^{2+}$-diacylglycerol arm of TSH receptor action. H$_2$O$_2$ in various cell types, and presumably in thyroid cells, is a signal, a mitogen, a mutagen, a carcinogen, and a killer. The various protection mechanisms of the thyroid cell against H$_2$O$_2$ are analyzed. They include the separation of the generating enzymes (dual-oxidases), their coupling to thyroperoxidase in a proposed complex, the thyroxisome, and H$_2$O$_2$ degradation systems.

**Conclusions:** It is proposed that various pathologies can be explained, at least in part, by overproduction and lack of degradation of H$_2$O$_2$ (tumorigenesis, myxedematous cretinism, and thyroiditis) and by failure of the H$_2$O$_2$ generation or its positive control system (congenital hypothyroidism).

**COMMENT**

It is not customary for us to write commentaries on review articles. The present review, however, constitutes an exception worthy of a comment and we encourage our regular BTC readers to have a good look at this remarkable article which, in addition, has been written by our Belgian colleagues from IRIBHM (ULB). The authors review first the general role of H$_2$O$_2$ in cells. At physiological levels, H$_2$O$_2$ enhances proliferation in a variety of vertebrate cells. H$_2$O$_2$ also has several roles in intracellular signalling pathways. Finally, there is an important cellular H$_2$O$_2$-generating system that belongs to the family of the NOX enzymes. At higher concentrations than those that have a signalling role in cells, H$_2$O$_2$ production induces oxidative stress leading to DNA oxidation and potential damage, as well as oxidation of various cellular components. Therefore, H$_2$O$_2$ generation must be tightly controlled and regulated for cells to avoid the consequences of H$_2$O$_2$ poisoning.

Concerning the thyroid gland, the authors review the role of the H$_2$O$_2$-generating system for the production of thyroid hormones. Fundamentally at the apical membrane, iodide is oxidized by TPO in the presence of H$_2$O$_2$ as the other substrate. This serves to covalently link oxidized iodide to the tyrosine residues in the large hormone-forming thyroglobulin matrix. Because of the risk that thyrocytes might be exposed to the toxicity of high doses of H$_2$O$_2$, thyroid cells need to adapt to it.
Thyrocyte protection is ensured by a strict separation of the iodination processes (acting at the apical membrane of the cell in the follicular lumen) from the cell interior. This concept – and the evidence supporting it is reviewed in detail in the present article – has led the authors to postulate the notion of a ‘thyroxisome’, i.e. an assembly of molecules and specific biochemical pathways at the apical membrane in a restricted space, involving TPO, DUOXs (two recently cloned enzymes serving to generate H$_2$O$_2$), TG, and ‘excess’ H$_2$O$_2$ detoxification.

Finally, the authors review thyroid diseases related to H$_2$O$_2$, namely the association with congenital hypothyroidism, tumorogenesis, thyroiditis, myxedematous endemic cretinism.

To end their excellent review, the authors raise the many unresolved questions that remain presently pending for future research.

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See Figure below

![Image](image.png)

**Fig. 4.** The postulated thyroxisome. The producer-consumer unit is composed of the associated DUOX and TPO at the membrane. Generation of H$_2$O$_2$ is in a restricted space where it is consumed by the oxidation of iodide and its binding to thyroglobulin (TG) and plasmalogens (P), generating iodotyrosines and iodothyronines in thyroglobulin (TGI and TGT4) and iodohexadecanals (IHDA) in the membrane. A possible catalase effect of TPO is represented. The participation of other proteins X in H$_2$O$_2$ disposal, such as EFP1, is represented. NADPH$_2$, Nicotinamide adenine dinucleotide phosphate.