

## Commentary

# The sodium iodide symporter and thyroid disease

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The movement of a variety of species from the iodine-rich environment of the sea to the relatively iodine-deficient land has necessitated the development of mechanisms which will trap more efficiently inorganic iodide ( $I^-$ ) necessary for the formation of thyroid hormones (Venturi *et al.*, 2000). In man as in other mammals iodide uptake by the thyroid is mediated via a TSH-dependent transmembrane protein, the sodium iodide symporter (NIS), so-called because it co-transporters  $Na^+$  with  $I^-$  into the thyroid against the concentration gradient (De La Vieja *et al.*, 2000). The NIS is located in the basolateral membrane of thyroid follicular cells, and accumulated  $I^-$  is organified to molecular iodine ( $I_2$ ) through the action of the enzyme thyroid peroxidase (TPO) in the presence of  $H_2O_2$ , which takes place mainly at the apical membrane of the follicular cell. Organified iodine iodates the thyroid protein thyroglobulin, which when stored in the lumen of thyroid follicles represents a storage site for the hormones thyroxine (T4) and triiodothyronine (T3) (Taurog, 1996). Possession of NIS enables the thyroid to concentrate  $I^-$  20–40-fold. Although the thyroid is the most efficient organ concentrating iodide, it is not the only one to have this ability as NIS expression and the ability to concentrate  $I^-$  has been demonstrated in the salivary and lacrimal glands, breast, gastric mucosa, placenta and kidney (Spitzweg *et al.*, 1998, 2001; Bidart *et al.*, 2000; Lacroix *et al.*, 2001). The NIS gene was first cloned in 1996 (Dai *et al.*, 1996); it is located on chromosome 19 and spans more than 20 Kb of the genome (De La Vieja *et al.*, 2000). The cloning of NIS has resulted in multiple studies on its role in thyroid physiology and disease (Shen *et al.*, 2001).

NIS is expressed sporadically and at different levels in resting thyrocytes. Greater levels of expression affecting most if not all thyrocytes are observed following TSH stimulation or in pathological states of thyroidal stimulation, such as Graves' disease or autoimmune thyroiditis (Caillou *et al.*, 1998). Mutations in the NIS gene have been implicated in some patients with congenital hypothyroidism, which is consistent with the observed failure of

such patients to accumulate  $I^-$  in their thyroids (Levy *et al.*, 1998; Pohlenz & Refetoff, 1999).

The area of study with the greatest potential and clinical importance lies in the upregulation of functionally active NIS to achieve greater  $I^-$  accumulation. This can be applied diagnostically to locate more effectively iodide concentrating metastatic tumours, or therapeutically to promote radioiodide uptake used in ablation of thyroid cancers or their metastases. One of the features of tumour dedifferentiation in thyroid cancer is the loss of  $I^-$  accumulating ability (Filetti *et al.*, 1999). Between 20 and 25% of metastatic thyroid cancers do not take up administered radioiodide, while anaplastic cancers rarely take up iodide (Arturi *et al.*, 1998). These findings fostered the belief of a failed iodide accumulating mechanism in thyroid cancer (Caillou *et al.*, 1998). Although some studies have shown decreased NIS expression in thyroid cancer (Arturi *et al.*, 1998; Ringel *et al.*, 2001) many reports show variable findings, with some recent studies suggesting increased NIS expression (Saito *et al.*, 1998; Dohan *et al.*, 2001). Despite these divergent reports a high positive predictive value was reported for therapeutic outcome between NIS expression by immunohistochemistry and tumour  $^{131}I$  uptake in both primary and recurrent thyroid carcinoma (Minutes *et al.*, 2001).

The dissociation between  $I^-$  uptake and NIS expression seen in some thyroid cancers may reflect different assay methodologies or incorrect intracellular localization of NIS, perhaps as a result of tumour dedifferentiation. It has been demonstrated that for optimal  $I^-$  uptake to occur thyroid follicular cells must be polarized around the follicular lumen (Kohn *et al.*, 2001) with their basal and apical surfaces facing the bloodstream and lumen, respectively, and also that NIS must be properly targeted to the plasma membrane (Dohan *et al.*, 2001). Defects in thyroidal uptake of radioiodide have led to attempts to promote such uptake with a view to providing the potential for restoring tissue responsiveness to therapeutically administered radioiodide (Smit *et al.*, 2000; Spitzweg *et al.*, 2001). These studies have included demethylation of NIS DNA in human thyroid cancer cell lines (Venkataraman *et al.*, 1999), stimulation of NIS expression using TSH (Kogai *et al.*, 1997; Ajjan *et al.*, 1998a) or retinoic acid (Schmutzler & Kohrle, 2001). Radioiodine therapy after NIS gene transfection has also been studied in non-thyroidal cancers such as melanoma, ovarian carcinoma, colon carcinoma and prostate cancer cell lines (Mandel *et al.*, 1999; Spitzweg *et al.*, 2000).

The primary thyroid cellular regulator TSH induces the three crucial genes involved in thyroid hormone formation NIS, Tg and TPO. Regulation of NIS expression is under the control of both TSH and Tg. Upregulation of NIS is achieved through the TSH-cAMP system, which regulates not only NIS expression and function but also the thyroid restricted transcription factors,

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TTF1, TTF2 and PAX8 (Kohn *et al.*, 1992). In contrast, down-regulation of NIS and its function can be brought about by Tg or  $\Gamma$  acting as feedback counter regulators of TSH-cAMP increased thyroid function (Uyttersprot *et al.*, 1997; Eng *et al.*, 2001; Kohn *et al.*, 2001) and by antithyroid agents such as thionamide drugs methimazole (MMI) or propylthiouracil (PTU) (Spitzweg *et al.*, 1999), cytokines (Ajjan *et al.*, 1998b) or oestradiol (Furlanetto *et al.*, 1999).

NIS, together with Tg, TPO and the TSH receptor (TSH-R), have been implicated as autoantigens involved in autoimmune thyroid disease (Morris *et al.*, 1997; Spitzweg & Morris, 2000). Antibodies against NIS have been reported in a proportion of patients with Graves disease (Endo *et al.*, 1996; Ajjan *et al.*, 1998a; Kilbane *et al.*, 2000), although this was not a consistent finding (Chin *et al.*, 2000). The mechanism through which antibodies might affect NIS function remains unknown (Ajjan *et al.*, 2000; Spitzweg & Morris, 2000).

NIS exerts its effect as an iodide symporter at the basolateral membrane of the thyroid follicular cell while another transporter, pendrin, acts at its apical end. Like NIS, pendrin is also a transmembrane protein which transports both chloride and iodide (Everett *et al.*, 1997). Pendrin is believed to act in the thyroid, perhaps in conjunction with other transporters, in facilitating efflux of iodide from the thyroid follicular cell into the lumen of the thyroid follicle (Kohn *et al.*, 2001). In contrast to NIS pendrin, encoded by the Pendred syndrome (characterized by deafness and goitre) gene (PDS), is not under TSH control and is upregulated by Tg (Royaux *et al.*, 2000). In addition to the thyroid follicular cells, pendrin is also found in placenta and kidney (Lacroix *et al.*, 2001; Spitzweg *et al.*, 2001). As the main role of pendrin is in promoting  $\Gamma$  transport from the thyroid follicular cell into the follicular lumen, its functional activity is necessary for thyroid hormonogenesis and in this role it functions in concert with NIS. It remains to be elucidated whether the same or distinct subsets of thyrocytes express both pendrin and NIS (Royaux *et al.*, 2000). The interaction between NIS and pendrin will also determine the amount of uptake and retention within the thyroid of  $^{131}\text{I}$  administered diagnostically, therapeutically or taken up as a result of radioactive iodine emissions following a nuclear accident. This has special relevance for the fetus, whose thyroid is more susceptible to radiation damage (Johnson, 1982), particularly as placenta is known to express both NIS and pendrin (Bidart *et al.*, 2000).

The discovery of the NIS gene has dramatically increased the potential for understanding pathways involved in iodide transport both in the thyroid and extrathyroidally. Greater understanding of these pathways offers the possibility not only for studying iodide transport but also the previously unknown potential extrathyroidal roles for iodine. It also offers the exciting prospect of applying the findings to the effective use of radioiodines as diagnostic or systemic therapeutic agents in a variety of cancers.

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