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The sodium iodide symporter (NIS): Regulation and approaches to targeting for cancer therapeutics

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ABSTRACT

Expression of the sodium iodide symporter (NIS) is required for efficient iodide uptake in thyroid and lactating breast. Since most differentiated thyroid cancer expresses NIS, β-emitting radioactive iodide is routinely utilized to target remnant thyroid cancer and metastasis after total thyroidectomy. Stimulation of NIS expression by high levels of thyroid-stimulating hormone is necessary to achieve radioiodide uptake into thyroid cancer that is sufficient for therapy. The majority of breast cancer also expresses NIS, but at a low level insufficient for radioiodine therapy. Retinoic acid is a potent *NIS* inducer in some breast cancer cells. NIS is also modestly expressed in some non-thyroidal tissues, including salivary glands, lacrimal glands and stomach. Selective induction of iodide uptake is required to target tumors with radioiodide. Iodide uptake in mammalian cells is dependent on the level of NIS gene expression, but also successful translocation of NIS to the cell membrane and correct insertion. The regulatory mechanisms of NIS expression and membrane insertion are regulated by signal transduction pathways that differ by tissue. Differential regulation of NIS confers selective induction of functional NIS in thyroid cancer cells, as well as some breast cancer cells, leading to more efficient radioiodide therapy for thyroid cancer and a new strategy for breast cancer therapy. The potential for systemic radioiodide treatment of a range of other cancers, that do not express endogenous NIS, has been demonstrated in models with tumor-selective introduction of exogenous *NIS*.

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Abbreviations: APL, acute promyelocytic leukemia; B-ZIP, basic-leucine zipper; cAMP, cyclic AMP; CBZ, carbamazepine; CRE, cAMP-response element; CREM, CRE-modulator; Dex, dexamethasone; DR, direct repeat; DUOX, dual oxidase; EC_{50}, 50% effective concentration; ER, estrogen receptor; ERK, extracellular signal-regulated kinase; GR, glucocorticoid receptor; Gy, gray; HDAC, histone deacetylase; IGF, insulin-like growth factor; MAPK, mitogen-activated protein kinase; MEK, MAP/ERK kinase; MKK, MAPK kinase; MMI, methimazole; MMTV-PyVT, murine mammary tumor virus-polyoma virus middle T antigen; NIS, sodium iodide symporter; NUE, *NIS* upstream enhancer; PBF, PTTG1-binding factor; %ID/g, % of injected dose per gram of tumor; PI3K, phosphatidylinositol 3-kinase; PKA, protein kinase-A; PPAR, peroxisome proliferator-activated receptor; PTTG1, pituitary tumor-transforming gene-1; RA, retinoic acid; RAR, retinoic acid receptor; RTK, receptor tyrosine kinase; RXR, retinoid-X receptor; Tg, thyroglobulin; TGF, transforming growth factor; TLR, Toll-like receptor; TPO, thyroid peroxidase; tRA, All-*trans* RA; TSH, thyroid-stimulating hormone; TSHR, TSH Receptor.

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1. Introduction

Sodium iodide symporter (NIS, or SLC5A5, solute carrier family 5, member 5) (Dai et al., 1996; Smanik et al., 1997) is expressed at the highest level in the thyroid and lactating breast (Dohan et al., 2003). Since NIS confers highly efficient iodide accumulation in cells, its expression in cancer cells allows for the diagnostic and therapeutic application of radioactive substrates of NIS, such as iodide (^{123}I, ^{124}I, and ^{131}I) and pertechnetate ($^{99m}TcO_4^-$). A majority (68–86%) of thyroid cancer retains functional NIS expression (Castro et al., 2001; Wapnir et al., 2003). β-emitting radioiodide-131 (^{131}I) is, therefore, routinely used for ablation of remnant tumors after total thyroidectomy. In thyroid cancer, the native NIS expression and radioiodide uptake are reduced. Stimulation of NIS expression by increasing the serum levels of thyroid-stimulating hormone (TSH), is required, prior to ^{131}I administration. Most differentiated thyroid cancer responds to these high levels of serum TSH with an increase in NIS expression and iodide uptake (Schlumberger, 1998). The elevation of serum TSH can be achieved either by withdrawal of thyroid hormone supplement after thyroidectomy or administration of recombinant TSH (thyrogen) (Ladenson et al., 1997).

The majority of breast cancer (70–80%) also expresses NIS (Tazebay et al., 2000; Wapnir et al., 2003), although iodide uptake is usually reduced or absent (Moon et al., 2001; Wapnir et al., 2004). Enhancement of the endogenous NIS expression in breast cancer has been proposed as an approach that would allow ^{131}I therapy (Boelaert & Franklyn, 2003). NIS, however, is expressed in the thyroid gland and other sites, such as stomach and salivary glands (Dohan et al., 2003), so selective induction of NIS in the target cancer is required.

The efficacy of ^{131}I to destroy target tumors is dependent on the tissue-selective *NIS* gene induction, but also the effective translocation of NIS protein to the cell membrane and correct membrane insertion. ^{131}I retention in the target tumors, and the biological half-life of ^{131}I in the body, also influence treatment efficacy. Normal thyroid tissue incorporates the trapped iodide into thyroglobulin (Tg), referred to as organification, resulting in longer iodide retention. Iodide in most thyroid cancer, as well as breast cancer, however, is not efficiently incorporated into proteins and hence more easily discharged from cancer tissues (Schlumberger et al., 2007).

In this review, we will describe recent findings of pathways and agents that stimulate endogenous *NIS* gene expression, as well as intracellular NIS translocation, in thyroid cells and breast cancer cells. Dissection of signal transduction pathways for NIS regulation confers novel potential targets to increase the efficacy of radioiodide therapy and expand its application to radioiodide-refractory thyroid cancer, as well as breast cancer and other NIS-expressing tumors.

2. Physiology of iodide metabolism and sodium iodide symporter

The thyroid must trap ~60 μg iodide/day from the bloodstream to produce adequate thyroid hormone. The thyroid contains 70–90% of the iodide in the body (9–10 mg) (Riggs, 1952), and this iodide accumulation is dependent on NIS (Dai et al., 1996), expressed on the basolateral membrane of thyroid follicular cells (Fig. 1). NIS is a glycosylated protein with 13 trans-membrane domains, transporting 2 Na^+ and one I^-, dependent on the Na^+ gradient maintained by Na^+/K^+ ATPase (Dohan et al., 2003). NIS activity produces the iodide concentration gradient from blood to NIS-expressing cells, up to 30-fold. Iodide taken up into the thyroid follicular cell by NIS, is released to the lumen via pendrin, oxidized by thyroid peroxidase (TPO) with hydrogen peroxide (H_2O_2) produced mainly by dual oxidase-2 (DUOX2), and binds to tyrosine residues of Tg accumulated in the lumen (Fig. 1). The process of iodide incorporation into Tg is termed "organification". The iodized tyrosine residues are then used for thyroid hormone synthesis. The transport of iodide into and through the thyroid gland is tightly regulated by TSH from the pituitary gland (Dohan et al., 2003; Kogai et al., 2006; Pesce et al., 2012). TSH stimulates *NIS* transcription (Kogai et al., 1997; Saito et al., 1997; Kogai et al., 2000a), prolongs NIS protein half-life, and stimulates translocation of NIS into the cell membrane (Riedel et al., 2001), maximizing iodide uptake in thyroid cells.

Infants need ~90 μg/day of iodide to produce thyroid hormone, essential for normal brain development. Lactating mammary glands efficiently accumulates iodide so that breast milk contains 150–180 μg/L iodide (Semba & Delange, 2001). NIS is expressed on the basolateral membrane of lactating mammary alveolar cells (Cho et al., 2000), and accumulates iodide from the bloodstream into milk. Expression of breast NIS is induced by oxytocin secreted from the posterior pituitary, and this action is enhanced by the elevated levels of serum prolactin and estrogen present in the postnatal period (Cho et al., 2000; Tazebay et al., 2000).

Several other extra-thyroidal tissues express NIS, including salivary glands, stomach, intestine, and lacrimal glands (Dohan et al., 2003). In the gastrointestinal system, salivary ductal cells, as well as gastric mucosa, express NIS on the basolateral membrane (Josefsson et al., 2002; Altorjay et al., 2007), while epithelium of the small intestine expresses NIS on the brush border membrane (apical side) (Nicola et al., 2009a). The iodide in food and water taken orally is absorbed in the intestines through the apical NIS (Nicola et al., 2009a), and transferred into circulation (Fig. 2). In contrast, the salivary glands (mainly parotid glands) and stomach take iodide from the bloodstream and release it into gastrointestinal tract (Brown-Grant, 1961). The kidneys excrete more than 90% of ingested iodide (Cavalieri, 1997). Renal clearance of iodide is mainly dependent on glomerular filtration rate and not re-absorption by renal tubules (Bricker & Hlad, 1955). The iodide secretion by salivary glands and stomach into the gastrointestinal tract, followed by re-absorption through intestine, is likely a mechanism to conserve iodide (Fig. 2), as demonstrated in the cow (Miller et al., 1975). The factors that regulate

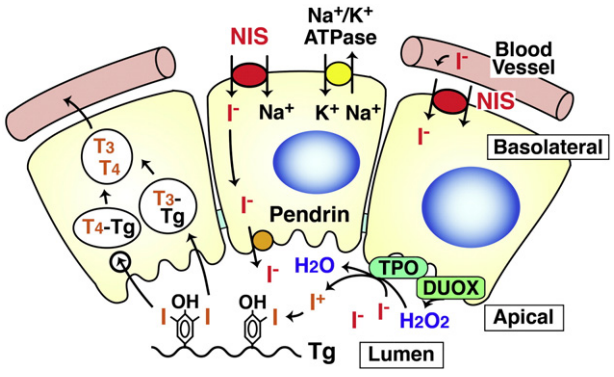

Fig. 1. Schematic representation of iodide transport in the thyroid gland. The thyroid gland consist of follicles with one layer of epithelial cells surrounding the lumen. Iodide (I^-) in circulation is transported into the lumen via basolateral NIS and apical pendrin. The activity of NIS requires the Na^+-gradient maintained by Na^+-K^+ ATPase. Iodide in the lumen is organified with Tg by TPO in the presence of H_2O_2 produced mainly by DUOX2. The iodinated tyrosine residues are used for synthesis of thyroid hormones, triiodothyronine (T_3) or thyroxine (T_4).