REVIEW

Role of iodide metabolism in physiology and cancer

Antonio De la Vieja[1,2] and **Pilar Santisteban**[2,3]

[1]Tumor Endocrine Unit, Chronic Disease Program (UFIEC), Instituto de Salud Carlos III, Madrid, Spain
[2]CiberOnc, Instituto de Salud Carlos III, Madrid, Spain
[3]Department of Physiopathology of Endocrine a Nervous System, Instituto de Investigaciones Biomédicas 'Alberto Sols', Consejo Superior de Investigaciones Científicas and Universidad Autónoma de Madrid (CSIC-UAM), Madrid, Spain

Correspondence should be addressed to A De la Vieja: adelavieja@isciii.es

Abstract

Iodide (I^-) metabolism is crucial for the synthesis of thyroid hormones (THs) in the thyroid and the subsequent action of these hormones in the organism. I^- is principally transported by the sodium iodide symporter (NIS) and by the anion exchanger PENDRIN, and recent studies have demonstrated the direct participation of new transporters including anoctamin 1 (ANO1), cystic fibrosis transmembrane conductance regulator (CFTR) and sodium multivitamin transporter (SMVT). Several of these transporters have been found expressed in various tissues, implicating them in I^- recycling. New research supports the exciting idea that I^- participates as a protective antioxidant and can be oxidized to hypoiodite, a potent oxidant involved in the host defense against microorganisms. This was possibly the original role of I^- in biological systems, before the appearance of TH in evolution. I^- per se participates in its own regulation, and new evidence indicates that it may be antineoplastic, anti-proliferative and cytotoxic in human cancer. Alterations in the expression of I^- transporters are associated with tumor development in a cancer-type-dependent manner and, accordingly, NIS, CFTR and ANO1 have been proposed as tumor markers. Radioactive iodide has been the mainstay adjuvant treatment for thyroid cancer for the last seven decades by virtue of its active transport by NIS. The rapid advancement of techniques that detect radioisotopes, in particular I^-, has made NIS a preferred target-specific theranostic agent.

Key Words

- iodine
- cancer
- sodium iodide symporter (NIS)
- iodide transporters
- iodine metabolism

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Introduction

The iodide atom (I^-) is an essential micronutrient for life and plays a crucial role in Earth's biology. As an electron donor, I^- functions as a reducing agent and is oxidized by specialized peroxidase enzymes to generate iodine-containing products such as thyroid hormones (THs). In turn, these hormones are critical for life in all vertebrates and have essential roles in development, growth, metamorphosis and metabolism. The reducing properties of I^- also make it an important scavenger of reactive oxygen species (ROS) (Venturi & Venturi 1999). In addition, recent evidence indicates that the oxidation of I^- to hypoiodite (IO^-) makes it a potent oxidant with strong bactericidal activity (Bosch *et al.* 2000, Huang *et al.* 2016). I^- is an environmentally scarce element. In the human body, it exist as I^-, iodine (I_2), triiodide (I_3), IO^- hypoiodous acid (HIO), iodine anion (HI_2O^-), and iodine-binding molecules, such as THs and iodolipids (Gottardi 1999).

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I^- has been predicted to be one of the oldest terrestrial antioxidants (Venturi & Venturi 1999). Algae were the first organisms to produce oxygen, a poisonous element in the primitive atmosphere and used I^- as a protective antioxidant (Kupper *et al*. 1998). I^- also has antibacterial properties in algae, which helps to safeguard against pathogens. The I^-/peroxidase partner system is preserved through evolution, securing its role as an antioxidant system, but in parallel favoring the production and synthesis of iodotyrosines (monoiodotyrosine (MIT) and diiodotyrosine (DIT)) and iodothyronines (3,3′-5-triiodothryonine (T3), 3,3′-5′-triiodothryonine (rT3) and thyroxine (T4)). Collectively, these hormones play critical roles both in invertebrate metamorphosis, during the early stages of evolution and in vertebrate development and homeostasis.

Primitive prokaryotes have active transport systems selective for halides, which may be the ancestral progenitors of the modern chloride Cl^-/I^- channels and transporters in mammals. In the last few years, several transporters/channels have been demonstrated to transport I^- with different anion selectivity and affinity, including Cl^- channels (Accardi & Picollo 2010), cystic fibrosis transmembrane conductance regulator (CFTR) (Linsdell 2016), calcium-dependent anoctamin 1 (ANO1 or TMEM16A) (Ferrera *et al*. 2011) and the electroneutral exchanger PENDRIN (PDS protein and *SLC26A4* gene) (Alper & Sharma 2013). Until recently, the role of PENDRIN in I^- metabolism was unclear; however, emerging evidence clearly indicates its involvement in human disease associated with iodide (Dossena *et al*. 2006).

The most effective and specific I^- transport system is undoubtedly the sodium/iodide symporter (NIS protein and *SLC5A5* gene), an integral basolateral (BL) plasma membrane glycoprotein that actively accumulates I^- driven by the electrochemical gradient of Na+ across the membrane (Levy *et al*. 1998). NIS can transport I^- with high affinity (10–30 µM), which is at least two orders of magnitude greater that the affinities of the aforementioned transporters/channels (De la Vieja *et al*. 2000). Anion selectivity for NIS has been reported as $ClO_4^- > ReO_4^- > I^- \geq SeCN^- \geq SCN^- > ClO_3^- > NO_3^- >> Br^- > BF_4^- > IO_4^-$ (Paroder-Belenitsky *et al*. 2011). Interestingly, all these transporters/channels have the ability to transport the thiocyanate ion (SCN^-) that, after conversion to the sulfhydryl-reactive hypothiocyanite ($OSCN^-$), also has potent antimicrobial activity (Rada & Leto 2008). Moreover, the sodium-dependent multivitamin transporter (SMVT protein or *SLC5A6* gene) can accumulate I^- with a relatively high affinity (K_m ~150 µM) (de Carvalho & Quick 2011) and may participate in some physiological processes of I^- metabolism.

At some point in the early stages of evolution, the products obtained from ROS detoxification by I^- oxidation (mainly iodotyrosine and iodothyronines) began to be used in different biological processes, creating an evolutionary advantage. Correspondingly, the role of some iodinated compounds became more critical, and new biological elements were developed to synthesize, use or incorporate these products, for example, peroxidases, transporters, regulatory elements and iodo-compound targets, among others, ultimately leading to the development of a very specialized system–viz., the thyroid gland.

The metabolism of iodine in humans retains those characteristics acquired through evolution: defensive and signaling functions. The latter is undoubtedly the better-known process, which proceeds through TH; however, the former is becoming more biologically relevant because systems involved in I^- transport are being discovered in organs where they were not previously suspected. New evidence indicates that I^-, along with SCN^-, with which it shares transporters and oxidative mechanisms, may participate as an antibacterial, antiviral and antifungal agent (Ihalin *et al*. 2006, Fischer *et al*. 2011). An adequate level of I^- in the body is essential for human biology; I^- deficiency can lead to goiter and hypothyroidism at all ages, and mental retardation and cretinism in newborns of mothers who are I^- deficient (Morreale de Escobar *et al*. 2008). I^- excess is also associated with hypothyroidism in susceptible patients, including those with autoimmune thyroid disease, subacute thyroiditis, postpartum thyroiditis, type 2 amiodarone-induced thyrotoxicosis, hemithyroidectomy, in addition to patients on antithyroid drug therapy and the concomitant use of potential goitrogens, such as lithium. Further, I^- excess is associated with hyperthyroidism in susceptible patients with risk factors including nontoxic or diffuse nodular goiter, latent Graves' disease and long-standing iodine deficiency (Leung & Braverman 2014). It is well recognized that radioiodide isotopes resulting from nuclear accidents can cause thyroid dysfunction and thyroid cancer (Pfinder *et al*. 2016). On the other hand, radioactive iodine (RAI) therapy with ^{131}I has been the cornerstone adjuvant therapy for the treatment of thyroid cancer for decades (Seidlin *et al*. 1946), with considerable success and relatively minor side effects. The exploitation of NIS to accumulate ^{131}I forms the basis of this therapy and is the preferred molecular choice in target-specific theragnosis (Chung & Cheon 2014). Finally, recent studies have

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demonstrated the antineoplastic effects of I^- in mammary cancer (Soriano *et al*. 2011) and also antiproliferative and cytotoxic effects in human carcinoma cell lines (Rosner *et al*. 2016). In this review, we describe recent findings on the role of different transporter systems (NIS, PENDRIN, ANO1, CFTR and SMVT) in I^- metabolism, including TH biosynthesis. We also discuss the participation of these transporters in redox homeostasis and their contribution to host defense against microorganisms. Finally, we focus on the critical role of those transporters in cancer as tumor markers and therapy candidates; in particular, the dual role of NIS as a reporter and therapeutic tool for targeted therapies using biological vectors in anticancer strategies with I^- as antiproliferative and cytotoxic agent.

Iodide highway

Diet

The World Health Organization (WHO) recommends a daily dose of 150 µg I^- for a healthy adult individual. Given its importance in metabolism, however, the body recycles dietary I^-, iodine or iodo-compounds by dehalogenation. This recycling process is very effective and begins in the salivary glands (Fig. 1).

Salivary gland

It has been known for decades that saliva accumulates I^- and SCN^- (Burgen & Seeman 1957). Bloodstream I^- that is not incorporated into the thyroid or that arises from the deiodination of iodo-compounds in peripheral tissues is transported and accumulated by NIS across the BL surface of ductal epithelial salivary cells (Spitzweg *et al*. 1999, La Perle *et al*. 2013). From here, it can diffuse by osmosis to the opposite apical (Ap) surface, where other transporters with less affinity to I^-, such as CFTR, ANO1 and/or PENDRIN, mediate its passage through to the cell interstice. Whereas the role of CFTR in Cl^- or HCO_3^- transport in salivary glands is well established (Dorwart *et al*. 2008), much less is known for the other two transporters. All three have been identified at the Ap surface of ductal salivary cells, where they are able to transport I^- (Shcheynikov *et al*. 2008, Perez-Cornejo *et al*. 2012). I^- that is recycled can be added back to the diet pool via the gastric juice, and thus, the salivary gland contributes as a recycler of I^- in the body. In addition, I^- can be oxidized by a peroxidase/H_2O_2 system to generate IO^-, which may act in host defense. The dual oxidase, DUOX2, which produces H_2O_2, is also expressed at the Ap surface of salivary glands (Geiszt *et al*. 2003). Moreover, both salivary peroxidase and myeloperoxidase from leukocytes (Ihalin *et al*. 2006) are abundantly secreted into saliva to convert I^- to IO^- using H_2O_2. The bactericidal role of I^- in saliva may be similar to the well-established role of SCN^-, which is converted to $OSCN^-$ and is also accumulated by NIS at the BL surface, and by CFTR, ANO1 and PENDRIN at the Ap surface. Indeed, some reports have demonstrated synergistic antimicrobial actions between $OSCN^-$ and IO^- (Bosch *et al*. 2000), reinforcing the idea of a defensive role for I^- (Fig. 1, salivary panel).

Stomach

The likely importance of the stomach in I^- recycling (Fig. 1, stomach panel) is supported by the finding that I^- from the bloodstream is accumulated by NIS expressed at the BL surface of mucin-secreting and parietal cells (Altorjay *et al*. 2007). I^- is then secreted into the lumen of the stomach in the gastric juice, probably by CFTR and ANO1 (Mazzone *et al*. 2011) that are present on the Ap/luminal site of those cells. Accordingly, gastric epithelial cells participate in I^- recycling, but not I^- absorption to the bloodstream. The protective role of $OSCN^-$ and IO^- may also be apparent in the stomach lumen given the presence of DUOX2 and gastric peroxidase in this region.

Intestine

Iodate and other iodine forms are reduced to I^- for absorption in the intestine by NIS (Fig. 1, intestine panel). Around one-half of the ingested iodo-compounds are reduced and absorbed, with the remainder excreted in feces (Albert & Keating 1949). Interestingly, the I^- pool from the diet, plus that recycled in the saliva and the stomach, is absorbed by NIS localized at the Ap/laminal surface of the brush border or microvilli in all three regions of the small intestine (duodenum, jejunum and ileum) (Mitsuma *et al*. 1997, Nicola *et al*. 2009). Intestinal I^- absorption is thus remarkably efficient, as demonstrated by the finding that less than 1% of administered I^- can be detected in feces (Fisher *et al*. 1965). SMVT is also expressed at the Ap brush border of enterocytes (Prasad *et al*. 1999) and may contribute to I^- absorption. CFTR maintains an Ap expression gradient in the gastrointestinal tract, with low expression in the stomach, highest expression in the duodenum and lowest expression in the large intestine (Strong *et al*. 1994). Its recognized function is to regulate the secretion of Cl^- and HCO_3^- as a driving force for water flow and to use HCO_3^- to neutralize acid from the stomach.

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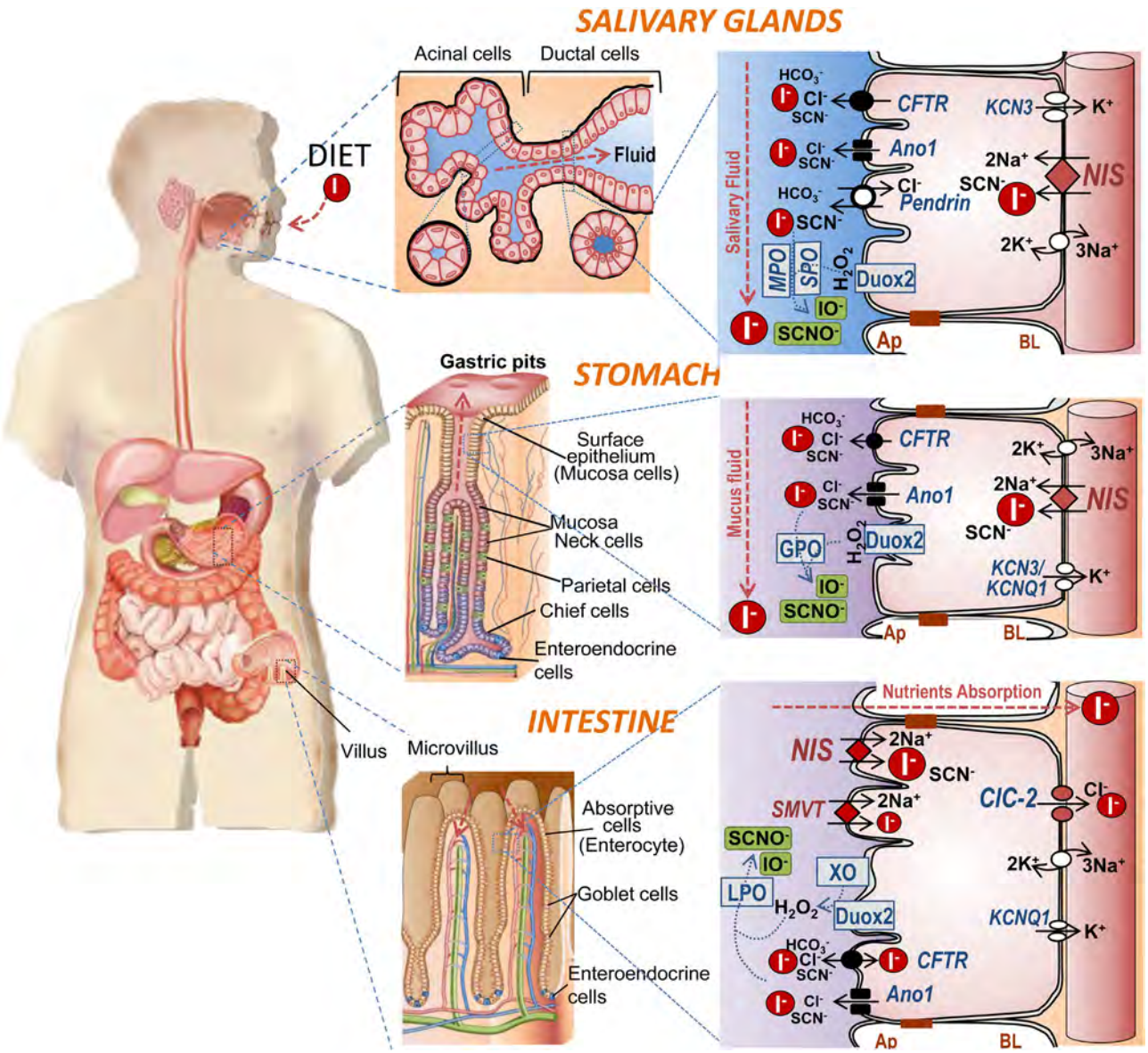

Figure 1
Schematic overview of tissues that participate in I⁻ metabolism: salivary glands, stomach and intestine. Dietary I⁻ passes through the oral cavity; additional unused I⁻ or I⁻ resulting from deiodination in peripheral tissues is recycled in the salivary gland (top panels). I⁻ from bloodstream is translocated across the basolateral (BL) membrane of the ductal salivary cells by NIS (red diamond). This translocation uses the Na+ electrochemical gradient of the Na+/K+-ATPase and by the K+ current of KCNQn/KCNEn K+ channels. Next, I⁻ exits the apical (Ap) side via a group of transporter/channels (CFTR, ANO1 and PENDRIN) to the salivary fluid. The I⁻ pool may then continue to the gastrointestinal tract or can be oxidized to the potent oxidant IO⁻ by myeloperoxidase (MPO) and salivary peroxidase (SPO) (blue squares), which use the H_2O_2 produced by DUOX2. Using the same transporters, SCN⁻ passes to the salivary fluid where it is converted into OSCN⁻ by the same enzymes. Both, OSCN⁻ and IO⁻, individually or synergistically, play a defensive role given their antimicrobial, antiviral and antifungal properties. I⁻ recycling continues in the gastric juice by the participation of the mucin and parietal cells of the stomach (middle panels). Gastric peroxidase (GPO) is responsible for converting I⁻ and SCN⁻ to IO⁻ and OSCN⁻, respectively, in the gastric mucus of the surface epithelium so they can participate in pathogen protection. Finally, the pool of I⁻ is absorbed in the small intestine (bottom panels), where NIS is localized in the Ap side. Other transporters such as SMVT or CFTR may participate in I⁻ translocation. It is not known how I⁻ exits the BL side of the epithelial cells to the bloodstream, but ClC-2 channels could participate. DUOX2, XO and LPO also participate in the production of IO⁻ and OSCN⁻ in the intestinal mucosa.

It is also possible that CFTR contributes to I⁻ absorption, resulting in the accumulation of I⁻ inside of the cell as a result of reverse transport. This would probably depend on the Cl⁻ gradient. A similar mechanism has been proposed in colon surface epithelial cells (Kunzelmann & Mall 2002). Once absorbed by the intestine, I⁻ needs

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to be subsequently absorbed into the bloodstream. Unfortunately, little is known about the mechanisms implicated in I^- transport to the BL surface of intestinal cells. However, due to the high I^- concentration within the cells, other transporters involved in Cl^- transport and with affinity for I^- may perform this transport. One such transporter, the Cl^- channel ClC-2, is expressed on the BL surface of intestinal villi and colon surface epithelium and is implicated in Cl^- absorption (Pena-Munzenmayer *et al.* 2005), but also may participate in I^- absorption (Fahlke 2001). Lactoperoxidase (LPO) is present in the intestinal mucus and, along with DUOX2 and xanthine oxidase (XO) in the Ap surface of the upper villi, provides the oxidation system for the bactericidal activity of several anions, similar to that found in saliva (van der Vliet *et al.* 1989), and contributes to the innate immune defense of the gastrointestinal tract chiefly through the production of $OSCN^-$. A defensive role has also been described for CFTR in cystic fibrosis as shown in mice lacking CFTR function (Norkina *et al.* 2004).

Kidney

The last chance to recover I^- before its elimination is by reabsorption in the kidney (Fig. 2, kidney panel). It is unclear, however, whether NIS is located in the BL or Ap site in kidney cells. An initial study using immunohistochemistry showed BL and cytoplasmic NIS localization in the distal tubular system in all nephron segments, suggesting that NIS participates in I^- elimination (Spitzweg *et al.* 2001). However, other results (Wapnir *et al.* 2003) and our unpublished observations indicate that NIS is localized at the Ap surface of the proximal and cortical collecting tubes and therefore likely participates in I^- reabsorption. It will be essential to clarify this to better understand I^- metabolism in kidney. CFTR expression has also been found in the Ap surface of most of the tubular system. Moreover, PENDRIN expression is located in the Ap surface of B-intercalated cells in the kidney cortical-collecting ducts and connecting tubules, where it mediates the secretion of HCO_3^- and the reabsorption of Cl^- (Xu *et al.* 2011). ANO1 is expressed in the principal and proximal tubular cells of the kidney-collecting duct (Svenningsen *et al.* 2014), and SMVT is also found in the Ap surface of the renal epithelia cells, where it participates in biotin reabsorption (Subramanian *et al.* 2011). Expression and localization of these transporters to these regions points to a role in I^- reabsorption, similar to that found in the intestine. Nevertheless, for the most part, all of these transporters are localized in the lumen/urine site. ClC-K1 and ClC-Kb/2 expressed on the BL surface may participate in I^- reabsorption because they have permeability for I^- (Zaika *et al.* 2016). Despite this preliminary evidence, I^- metabolism has not been sufficiently explored in this organ, and more investigation is needed to be able to correctly interpret the results of urine I^- concentrations in medical practice.

Thyroid

The final and main destination for I^- is the thyroid (Fig. 2, thyroid panel). The thyroid gland is the most sophisticated system designed to accumulate I^- and synthesizes TH. BL NIS in follicular thyroid cells actively accumulates I^- against its concentration gradient using a Na+-driven force generated by the Na+/K+-ATPase (De la Vieja *et al.* 2000, Riesco-Eizaguirre & Santisteban 2007). Subsequently, I^- is transported through the Ap membrane to the colloid, the thyroid lumen, by a group of transporters including PENDRIN (Scott *et al.* 1999), CFTR (Devuyst *et al.* 1997) and ANO1 (Twyffels *et al.* 2014); however, the level of participation of each in I^- transport in thyrocytes is still unclear. Some mutations in PENDRIN (but not others) (Dossena *et al.* 2006), and in CFTR (Li *et al.* 2010), are observed in hypothyroidism, suggesting that both may participate in apical I^- transport, but not exclusively. Synthesis of T3 and T4 begins with thyroid peroxidase (TPO) (Dunn & Dunn 2001), which uses H_2O_2 provided by DUOX2 and perhaps also by DUOX1 (Dupuy *et al.* 1999, De Deken *et al.* 2000), to oxidize specific tyrosine amino acids within thyroglobulin (Di Jeso & Arvan 2016). MIT and DIT are then synthesized, and the coupling of the two iodo-compounds yields the complete TH. The iodinated thyroglobulin is stored in the colloid and is internalized in follicular cells by micropinocytosis or endocytosis. It then undergoes proteolysis in lysosomes to release free T3 and T4 and other iodo-compounds (MIT, DIT) (Di Jeso & Arvan 2016). I^- from MIT and DIT is recycled by iodotyrosine deiodinase (IYD or DEHAL) (Moreno & Visser 2010). This enzyme is also expressed in other tissues such as duodenum, rectum, stomach, small intestine, colon and kidney and may contribute to I^- recycling (Sun *et al.* 2015). Finally, TH is transported to the bloodstream mainly by monocarboxylate transporter 8 (MCT8) (Visser *et al.* 2011), which is also expressed in several target tissues such us brain, heart, liver, kidney and adrenal and additionally could contribute to the general I^- recycling.

Thyroid-stimulating hormone (TSH), through its receptor TSH-R, is the master regulator of thyroid cell

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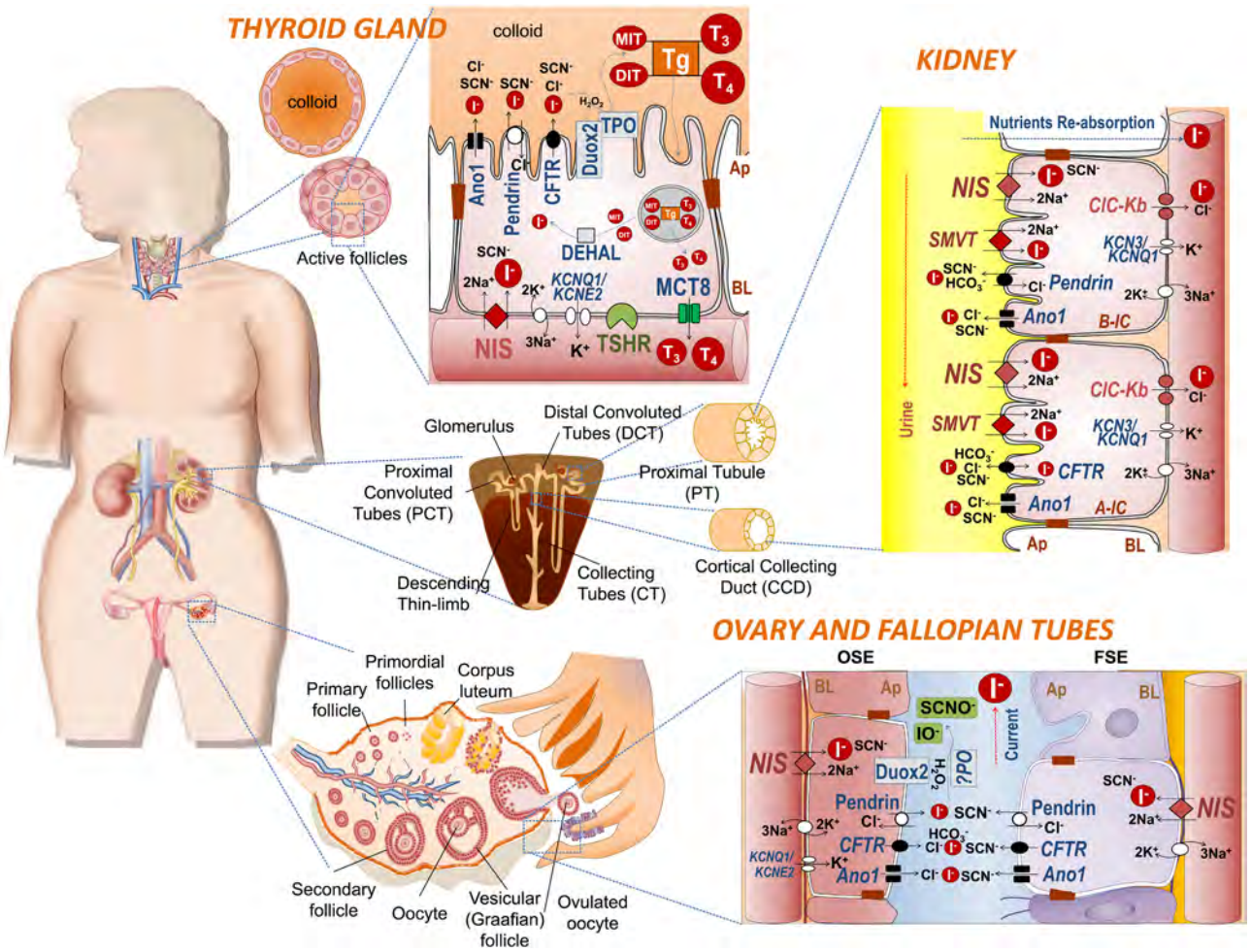

Figure 2

Schematic overview of tissues that participate in I^- metabolism: kidney, thyroid gland, ovary and fallopian tubes. Urine I^- is reabsorbed in the collecting tubes of the kidney (middle and top right panels). I^- from the urine is translocated across the apical (Ap) membrane of the nephron collecting tubes by NIS (red diamond). Other transporters localized in the Ap side such as SMVT or CFTR could participate in I^- translocation. ClC-K channels may participate as I^- exits the basolateral (BL) side to the bloodstream. The primary function of I^- metabolism is the synthesis of TH in the thyroid (middle top panels). I^- from the bloodstream is accumulated by NIS in the BL membrane of epithelial thyroid follicular cells (thyrocytes), mainly in small active follicles. PENDRIN, ANO1 and CFTR, localized in the Ap side, participate as I^- exits to the colloid. There, I^- is oxidized by thyroid peroxidase (TPO) (blue square) in the presence of H_2O_2 generated by DUOX2 (blue square) and incorporated into the tyrosine residues of thyroglobulin (Tg) (orange square) to form MIT and DIT. Further oxidation by TPO yields T3 and T4. Iodinated Tg is endocytosed and proteolyzed in the lysosomal vesicles to release iodo-compounds. Dehalogenation of MIT and DIT by DEHAL1 recycles I^- ions. T3 and T4 are translocated to the bloodstream by MCT8 and MCT10 transporters. TSHR localized in the BL side is the master regulator of the majority of processes described. I^- is secreted into the fallopian fluid by ovarian surface epithelial cells and the secretory cells of the fallopian fimbriae (bottom panels). I^- and SCN^- are translocated by NIS localized at the BL surface of both cell types. I^- and SCN^- are secreted into the fluid by PENDRIN, ANO1 and CFTR at the Ap side. An unidentified peroxidase uses the H_2O_2 generated by DUOX2 to generate the antipathogenic IO^- and $OSCN^-$ that participate in maintaining a sterile reproductive tract.

function (Kopp 2001). In addition to this, we and others have identified a group of transcription factors (PAX8, FOXE1, NKX2.1 and HHEX) that are crucial in regulating the expression of NIS, thyroglobulin and TPO in a thyroid-specific manner and are essential for thyroid development and functional differentiation in adults (Fernandez *et al*. 2015). Because thyroid cells have elevated concentrations of H_2O_2 (as a by-product of TH synthesis), to avoid ROS build-up within cells, the thyroid expresses several selenoproteins (Schomburg 2011), among them, we demonstrated that thioredoxin reductase (TXNRD1) is directly involved in the expression and regulation of NIS in the thyroid (Leoni *et al*. 2011), both in normal conditions and upon and I^- excess, known as the Wolff–Chaikoff effect (Wolff & Chaikoff 1948, Leoni *et al*. 2011).

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Ovary and fallopian tube

I^- metabolism is also essential in several reproductive organs. We have shown that I^- is transported by BL NIS in ovarian surface epithelial cells and in secretory cells of fallopian fimbriae (Riesco-Eizaguirre *et al*. 2014) (Fig. 2, ovarian and fallopian tube panel). The role of I^- in the female reproductive tract (FRT) could be twofold, on the one hand, it could contribute to I^- body-pool recycling, and on the other hand, it may be implicated in maintaining sterile conditions throughout the FRT. NIS expression and therefore I^- accumulation are hormonally regulated during the menstrual cycle, at least by estradiol. This regulation may be concurrent with that of the immune response throughout the FRT, which is synchronized with reproduction function to optimize the conditions for sperm migration, fertilization, implantation and pregnancy (Wira *et al*. 2010). We showed that NIS is functional in the FRT (Riesco-Eizaguirre *et al*. 2014), and it is also expressed in the uterine/cervix region (unpublished observations), possibly extending its protective role to these areas. Similarly, DUOX2 mRNA has been identified by microarray and RNA-sequencing analysis in the ovary (www.genecards.org), and peroxidase activity (with an antimicrobial effect in the presence of I^-) has been reported in the uterine fluid of rats (Klebanoff & Smith 1970).

A low level of CFTR expression has been observed in the ovary; however, CFTR is overexpressed in ovarian cancer (Xu *et al*. 2015). ANO1 and PENDRIN protein have been detected by immunohistochemical analysis in the Ap surface of the ovary and fallopian tube follicular cells (www.proteinatlas.org), but nothing is yet known about their role in these tissues.

Placenta

The fetal thyroid gland initiates TH biosynthesis at around 17 weeks of gestation (Chan *et al*. 2009). This follows through the placental expression of NIS and PENDRIN, which transports I^- from the mother to the fetus (Fig. 3, placenta panel). Expression of NIS remains stable during pregnancy; in the first trimester, relatively low expression of NIS is localized at the Ap membrane of villous syncytiotrophoblasts (maternal-facing) and high expression is detected in villous syncytiotrophoblast cells (Bidart *et al*. 2000, Degrelle *et al*. 2013). Furthermore, PENDRIN is expressed at the Ap surface of cytotrophoblasts and its expression is higher at term. In early pregnancy (8–10 weeks), extra-villous villous syncytiotrophoblasts express high levels of NIS protein, at a time when the fetus is still unable to synthesize TH. This suggests that early I^- accumulation may have an additional role during pregnancy. One hypothesis is that the placenta may store I^- to prevent the fetus from experiencing insufficient I^- coming from the maternal diet, thereby preventing future iodide deficiency during pregnancy. It is also possible that I^- participates as an antioxidant and as a defense against infections. Indeed, all the necessary components of this system are also present in placenta: DUOX2 mRNA expression has been found by microarray analysis (www.genecards.org), XO activity has been reported in trophoblast cells (Many *et al*. 1996) and myeloperoxidase has been isolated in placenta (Joseph *et al*. 1993). Interestingly, placental peroxidation is more active in the early phases of gestation, which may coincide with placental I^- accumulation by NIS in the first trimester. *CFTR* and *ANO1* mRNAs have also been detected in the placenta (Mylona *et al*. 1996, Fagerberg *et al*. 2014).

Lactating mammary gland

Similar to the findings observed in the placenta, NIS expression in the mammary gland acts primarily to provide I^- to the newborn during lactation, until it can synthesize its own TH (Tazebay *et al*. 2000) (Fig. 3, lactating mammary gland panel). Accordingly, NIS expression is located at the BL surface of the mammary alveolar cells (Vayre *et al*. 1999). To transport I^- to the milk, other transporters such as CFTR and ANO1 are expressed on the Ap membrane of epithelial cells, both in alveoli and ducts (Kamikawa *et al*. 2016). Analogous to NIS expression, PENDRIN expression on the Ap membrane of the alveolar mammary gland occurs after pregnancy and during lactation (Rillema & Hill 2003). These three transporters, as in many of the mentioned tissues, are chiefly tasked with Cl^- secretion, in this case into the milk. However, NIS expression occurs not only during lactation but also in late pregnancy, which may suggest that I^- participates in other processes. Indeed, it is plausible that I^- and SCN^- also participate as protective agents against a wide variety of microorganisms such as bacteria, fungi and viruses (Kussendrager & van Hooijdonk 2000, Shin *et al*. 2002). Strengthening this notion, LPO is abundant in milk, and it may convert I^- or SCN^- into the antibacterial IO^- or $SCNO^-$ using H_2O_2. Whereas DUOX2 is not present in the mammary gland, mammary XO can produce the required H_2O_2 using xanthine and hypoxanthine as substrates, both of

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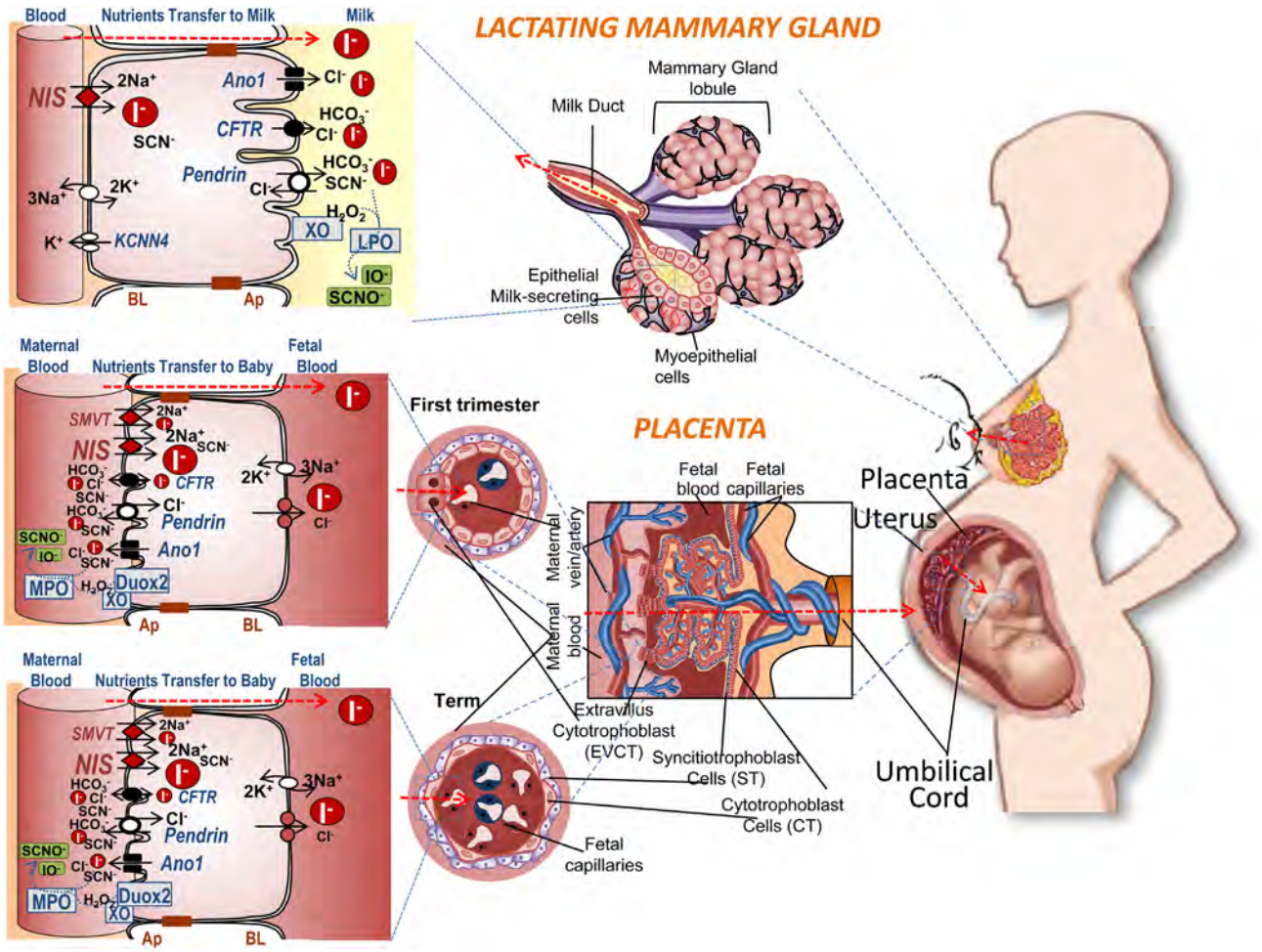

Figure 3

Schematic overview of I^- metabolism in reproduction and lactation: Placenta and lactating mammary gland. I^- is transferred from mother to fetus via the placenta (bottom panels). I^- from maternal blood is translocated across the apical (Ap) membrane of the cytotrophoblasts. SMVT and CFTR may participate in Ap I^- translocation. An unidentified channel at the basolateral (BL) side may translocate I^- to the fetal blood. During the first trimester, the fetus does not yet synthesize its own TH, so the role of I^- accumulation will be to prevent iodine deficiency in the fetus and to contribute to redox homeostasis via its antioxidant properties. Additionally, I^- and SCN^- conversion to IO^- and $OSCN^-$, respectively, by myeloperoxidase (MPO) with the H_2O_2 generated by DUOX2 and xanthine oxidase (XO) may contribute to prevent microbial infections, at least at the maternal blood side. At term, the main role of I^- will be to supply the fetal thyroid, to be able to synthesize TH. During lactation, the mother provides I^- to the baby through the milk (top panels). I^- from the bloodstream is translocated across the BL membrane of the alveolar epithelial milk-secreting cells by NIS. Then, I^- exits the Ap side through PENDRIN, ANO1 and CFTR to the milk. Additionally, using the H_2O_2 generated by XO, lactoperoxidase (LPO) produces IO^- and $OSCN^-$ to prevent mammary and infant infections.

which are abundantly present in neonatal saliva during breast feeding. Supporting this idea, mammary gland XO expression in the outer surface and its antioxidant and antimicrobial ability has recently been demonstrated (Al-Shehri *et al.* 2015). Interestingly, I^- accumulation is considerably faster in the lactating mammary gland (around 5 min in mouse) than in the thyroid (around 30 min in mouse) (Tazebay *et al.* 2000). This suggests that in cases of partial I^--deficient diets, the newborn would be sufficiently supplied, but the mother would not, which in turn could cause maternal transitional hypothyroidism.

Airways

I^- metabolism has been shown to play a role in airway epithelia, which also express the necessary transporters. Accordingly, NIS expression has been localized to ciliated columnar cells of the bronchial mucosa, although its precise localization remains controversial (Kang *et al.* 2009). Moreover, ANO1, CFTR, PENDRIN and DUOX2/DUOX1 are expressed in the Ap membrane of bronchial epithelial cells (Lee *et al.* 2015, Brennan *et al.* 2016), and LPO is secreted primarily in tracheal and bronchial submucosal glands (Wijkstrom-Frei *et al.* 2003). This situation

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would allow for the transport of I^- and/or SCN^- across the airway epithelium, and their transformation to HOI^- and $OSCN^-$. Surprisingly I^-, but not SCN^-, has been proven to inhibit viral infections by encapsulating and enveloping respiratory virus particles in the airway epithelium (Fischer *et al.* 2011). In addition, SCN^- transported across the airway epithelium by CFTR, among others, is oxidized to $OSCN^-$ by LPO, which kills gram-positive and gram-negative bacteria (Moskwa *et al.* 2007).

Alterations in the expression of proteins implicated in I^- metabolism in cancer

In relation to human disease, the most important observations made do date are that alterations in the expression levels of proteins involved in I^- metabolism have critical roles in cancer (Fig. 4) and are associated with tumor progression, although not always in the same way.

CFTR

CFTR plays a tumor-suppressing role in prostate cancer development (Xie *et al.* 2013), whereas it is significantly downregulated in breast cancer and is associated with poor prognosis (Zhang *et al.* 2013). Moreover, CFTR expression is significantly higher in ovarian cancer than in benign ovarian tumors and normal ovaries and again correlates with cancer progression and aggressiveness (Xu *et al.* 2015). Accordingly, CFTR knockdown suppresses the malignant behavior of ovarian tumor cells, such as cell invasion, motility and proliferation, pointing to CFTR as a novel tumor marker for ovarian cancer, particularly for aggressive carcinoma. This may have important implications for RAI treatment in NIS-expressing tumors, as downregulation of CFTR would improve radioiodide retention and therefore more efficient effects.

ANO1

ANO1 gene amplification and overexpression have been described in many types of cancers (Fig. 4). Indeed, it was initially discovered as an overexpressed molecule in several tumors and was recognized as a tumor marker and even as an oncogene (Simon *et al.* 2013). Overexpression of ANO1 promotes breast, colorectal cancer, and head and neck squamous cell carcinoma, tumorigenesis and invasion (Duvvuri *et al.* 2012, Britschgi *et al.* 2013, Sui *et al.* 2014). Also, its overexpression may be a potential marker for good prognosis in progesterone receptor-positive or human epidermal growth factor receptor 2-negative breast cancer following tamoxifen treatment (Wu *et al.* 2015). ANO1 is also ubiquitously overexpressed in gastrointestinal stromal tumors (West *et al.* 2004), and its overexpression is associated with modulation of cell proliferation via ERK1/2 activation (Duvvuri *et al.* 2012). Conversely, inhibition of ANO1 leads to a decrease in tumor cell viability, suggesting that its suppression could be used as a potential target for anticancer therapies. An important open question, however, is whether its ability to transport I^-, although limited compared with NIS, can be used as a molecular target in RAI therapy by reversing the I^- flux in tumors that do not express NIS but overexpress this transporter. However, in these cases, improved cytoplasmic oxidation of I^- could be also necessary for effective RAI.

PENDRIN

PENDRIN expression is reduced both in thyroid (Arturi *et al.* 2001) and in all breast cancer subtypes (Gorbatenko *et al.* 2014) (Fig. 4). This has been attributed, at least in part, to aberrant hypermethylation of the gene early during tumor progression (Xing *et al.* 2003). Mechanistically, low levels of PENDRIN could be a strategy for tumor cells to maintain an elevated pH by inhibiting Cl^-/HCO_3^- exchange rather than by inhibiting I^- transport.

NIS

As mentioned earlier, RAI has been successfully used for decades in the treatment of differentiated thyroid cancer (Seidlin *et al.* 1946), where it is utilized following thyroidectomy for remnant tumor ablation and for residual or metastatic thyroid disease (Riesco-Eizaguirre & Santisteban 2007, Spitzweg *et al.* 2014). The side effects of RAI therapy are moderate and usually temporary, affecting mainly extrathyroid NIS-expressing tissues, particularly salivary glands, lacrimal gland, lungs and ovaries (Albano *et al.* 2017), where I^- crosses the epithelial cells without major accumulation and has very little chance to be intracellularly oxidized/organified. NIS has a unique role in RAI therapy based on its high capacity to accumulate I^-. Indeed, by exploiting NIS, RAI is one of the most successful modalities for targeted therapy and molecular imaging in oncology (Riesco-Eizaguirre & Santisteban 2007, Chung & Cheon 2014). Accordingly, NIS is a preferred tool in new targeted modalities, such as adenovirus and oncolytic virus therapy, stem cell therapy and regenerative medicine (Spitzweg & Morris 2001, Montiel-Equihua *et al.* 2008, Baril *et al.* 2010,

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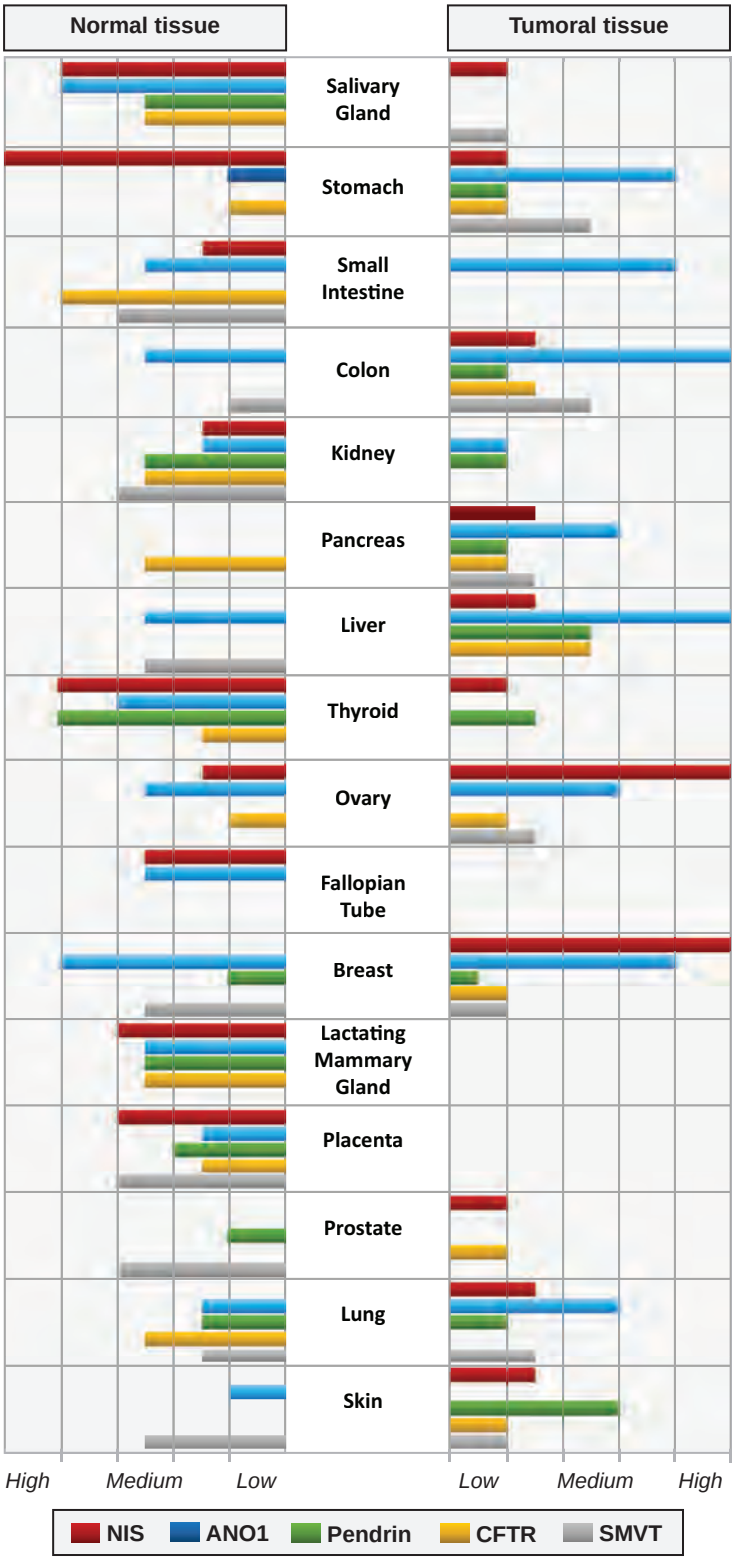

Figure 4
Protein expression of the transporters implicated in iodide metabolism in normal and tumor tissues. Relative levels of NIS (red bars), ANO1 (blue bars), PENDRIN (green bars), CFTR (yellow bars) and SMVT (gray bars) protein expression observed in normal and tumor tissues. Data were obtained from articles cited in the text or from the human protein atlas database (www.proteinatlas.org). Absence of bars indicates not detected or not analyzed.

Riesco-Eizaguirre *et al*. 2011). RAI may also be successful for extrathyroidal endogenous NIS-overexpressing tumors such as in breast (Tazebay *et al*. 2000, Renier *et al*. 2016) and ovarian cancer (Riesco-Eizaguirre *et al*. 2014) (Fig. 4).

Downregulation of NIS expression in thyroid cancer is proportional to the tissue dedifferentiation. Despite this loss, >70% of differentiated thyroid cancers can accumulate I^- to some extent, which is sufficient to

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achieve appropriate ^{131}I accumulation for treatment (Kogai *et al*. 2006). In addition to gene downregulation, an alteration in NIS trafficking to the plasma membrane (Dohan *et al*. 2001) is believed to be responsible for the 'cold' thyroid nodule pattern on a radioiodine image and the associated decrease of ^{131}I accumulation in thyroid cancers. Meta-analysis has found an increased risk of second primary malignancies in thyroid cancer patients treated with RAI (Sawka *et al*. 2009); however, this may be associated with extremely high RAI doses. Multimodal thyroid cancer treatment, including thyroidectomy, TH treatment and RAI therapy results in a remarkable >90% 10-year patient survival. Nevertheless, about 30–40% of metastatic differentiated thyroid cancers are refractory to RAI therapy and, unfortunately, this patient group presents significantly decreased survival (Durante *et al*. 2006). This complication is due mainly to decreased NIS gene expression and/or impairment in NIS plasma membrane trafficking (Dohan *et al*. 2001, 2003).

We and others have shown that several signaling pathways are implicated in NIS downregulation in differentiated thyroid cancers. The most frequent genetic event in thyroid cancer is an activating mutation in the serine–threonine kinase BRAF-V600E, which is associated with advanced clinical stages, extrathyroidal extension and a high risk of recurrence (Riesco-Eizaguirre *et al*. 2009, Xing *et al*. 2013). Although many strategies to 'redifferentiate' refractory metastatic thyroid cancer have been attempted, only retinoids and lithium have yielded an effect, albeit very modest, which limits their use in clinical practice. As downstream signaling of BRAF-V600E involves BRAF and MAPK activation, an approach used to redifferentiate thyroid tumor cells has been the use of kinase inhibitors, with varying success. Thus, sorafenib, a multikinase inhibitor that targets BRAF and that is increasingly used in patients with advanced thyroid cancer, fails to re-induce iodine uptake (Hoftijzer *et al*. 2009). By contrast, the MAPK inhibitor selumetinib has shown significant clinical benefit in promoting radioiodine uptake in refractory metastatic thyroid cancers, exerting its effects after a short treatment period (1 month) and so greatly reducing the side effects of this inhibitor (Ho *et al*. 2013). Moreover, selumetinib was effective in >40% of the patients and seemed to be most beneficial in a subgroup of patients harboring a RAS mutation and in those with detectable iodine uptake at baseline. However, it was ineffective in patients with BRAF-positive tumors and no detectable iodine uptake at baseline, save for one patient (Ho *et al*. 2013). A perplexing question was why the treatment was ineffective in patients with a BRAF mutation, given that inhibitors of the canonical MEK-ERK pathways could restore radioiodine uptake in a mouse model of papillary thyroid cancer (PTC) generated by conditional BRAF-V600E activation (Chakravarty *et al*. 2011). This was answered in a later study that demonstrated that a greater effect was achieved with a stronger and more sustained inhibition of MAPK signaling (Nagarajah *et al*. 2016). The MEK inhibitor, CKI (CH5126766), seems to be even more effective and longer-lasting than selumetinib in restoring iodide uptake in transgenic mice (Nagarajah *et al*. 2016). CKI is an allosteric MEK inhibitor that adopts a conformation that cannot be phosphorylated by RAF, reducing feedback reactivation of ERK signaling. This finding underscores the importance of having robust and sustained MAPK signaling inhibition such that RAI is more effective. Whether this strategy would also be beneficial in patients remains to be determined.

We previously demonstrated that the BRAF-V600E mutation induces TGFβ secretion, leading to NIS downregulation in an autocrine TGFβ loop that is MEK-ERK-independent but cooperates with the MEK-ERK pathway to induce strong tumor cell invasion *in vitro* (Riesco-Eizaguirre *et al*. 2009). This mechanism was later confirmed in a transgenic mouse model (Chakravarty *et al*. 2011). Very recently, it has been shown that NOX4 expression is also upregulated by BRAF-V600E via the TGFβ/Smad3 signaling pathway (Azouzi *et al*. 2017). Therefore, ROS production by NOX4 participates in the downregulation of thyroid differentiation genes, such as NIS. PI3K downregulates NIS transcription in thyroid (Garcia & Santisteban 2002), and inhibition of this pathway improves I^- accumulation in differentiated thyroid cancer cell lines (Kogai *et al*. 2008). Inhibition of mTOR, a downstream serine–threonine protein kinase activated by PI3K was also found to stimulate I^- accumulation in thyroid cells (de Souza *et al*. 2010).

Several microRNAs are abundantly expressed in PTC, the most common thyroid malignancy, and target different genes involved in iodine metabolism, including NIS (Asa *et al*. 2015, Riesco-Eizaguirre *et al*. 2015). Among them, miR-146b is one of the most studied miRNAs in PTC and appears to be a prognostic factor associated with poor clinical outcome. Underscoring its importance in thyroid cell transformation, we recently showed that miR-146b specifically represses *PAX8* and *NIS*, two genes essential for modulating the differentiation phenotype of thyroid cancer (Riesco-Eizaguirre & Santisteban 2016). Conversely, miR-146b antagonism in human thyroid cancer cells was found to re-induce NIS-mediated iodide uptake (Li *et al*. 2015). In addition to NIS, we found that miR-146b is

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predicted to repress other iodide-metabolizing proteins such as DEHAL and DIO2 (Riesco-Eizaguirre *et al*. 2015). Examples of additional miRs implicated in the repression of genes involved in iodine metabolism include miR-182, which is predicted to repress PAX8 and DEHAL, and miR-375, which is predicted to repress both NKX2.1 and DEHAL (Riesco-Eizaguirre & Santisteban 2016).

The abovementioned data suggest that many events occur in thyroid cancer to frustrate iodine uptake, and therefore, an understanding of NIS regulation and trafficking to the membrane is imperative to recover its function for the clinical effectiveness of ablative RAI therapy. In this regard, two proteins have been identified to interact with NIS and to participate in thyroid cancer. PBF (pituitary tumor-transforming gene (PTTG)-binding factor) is a proto-oncogene that appears to post-translationally repress NIS membrane targeting, decreasing I^- accumulation (Smith *et al*. 2013). In addition, the guanine nucleotide exchange factor LARG (leukemia-associated RhoGEF) interacts with NIS and regulates cancer cell invasion and migration in NIS-expressing cells (Lacoste *et al*. 2012). Furthermore, we showed that NIS BL localization is mediated by the Clathrin adaptor proteins AP-1A and AP-1B (Koumarianou *et al*. 2014).

NIS is constitutively expressed at relatively high levels in salivary glands and stomach and, similar to what is observed in thyroid cancer, its expression is reduced in benign and malignant neoplasms of ductal origin in salivary glands (La Perle *et al*. 2013), in gastric cancers and in intestinal metaplasia (Altorjay *et al*. 2007) (Fig. 4). Conversely, in tissues where NIS is hormonally regulated and expressed only during certain periods, it is found overexpressed in tumors arising from these tissues. As mentioned earlier, NIS expression in breast tissue is exclusively observed during late pregnancy and lactation where it is regulated by lactogenic hormones (estradiol, oxytocin and prolactin) (Tazebay *et al*. 2000). More than 85% of breast tumor samples and their metastases overexpress NIS (Tazebay *et al*. 2000, Renier *et al*. 2010), suggesting that RAI could be used as an anti-breast cancer therapy in these tumors. Nevertheless, an extensive immunohistochemical study showed that only around 25% of NIS-positive tumors accumulate I^- (Wapnir *et al*. 2003), meaning that it would be necessary to determine the functionality of NIS to correctly assess the potential of RAI in breast cancer.

Ovarian NIS expression is hormonally regulated during the menstrual cycle, with the strongest expression, and therefore, I^- accumulation, coinciding with the rise in estradiol levels (Riesco-Eizaguirre *et al*. 2014). This finding has a very important implication in the treatment of thyroid cancer since avoiding ^{131}I treatment during this period could considerably minimize the side effects in ovarian function and fertility, as frequently occurs in RAI therapy. We showed that overexpression of NIS is detected in >98% of ovarian cancer tissues analyzed and is present at the plasma membrane in one-third of them, even at early stages of tumor development (Riesco-Eizaguirre *et al*. 2014). This recent evidence opens avenues for the use of RAI in the diagnosis and treatment of ovarian cancer, which has one of the lowest 5-year survival rates after diagnosis.

Interestingly, mutations in any one of the transporters involved in I^- metabolism can cause cancer per se (Russo *et al*. 2001, Schubert *et al*. 2014, Huang & Jap 2015). In some cases, a mutation may lead to dysfunctions at the plasma membrane and, indirectly, can be associated with tumor progression because of dysregulated protein expression (Dohan *et al*. 2003, De la Vieja *et al*. 2005). A potentially important question that remains to be addressed is how these mutations affect the potential roles of NIS, PENDRIN, ANO1 and CFTR as defense agents against microorganisms and ROS, which is frequently observed to be elevated in cancer cells.

All of the above data suggest that tumors use the nutrients acquired by the overexpression of some of these transporters to their advantage to promote survival, proliferation and invasion. Accordingly, overexpression of PENDRIN, CFTR and ANO1 and reverse I^- transport by malignant cells may provide opportunities to explore the use of RAI in tumors that do not express NIS. However, I^- oxidation systems will likely be necessary in the tumor cells to improve I^- retention and RAI efficiency.

Iodide and iodine diet effect in cancer

Daily iodine intake recommendations by WHO are 90 µg for infants until year 5, 120 µg for children (6–12 years), 150 µg for adolescents and adults and 250 µg for pregnant and lactating women (Zimmermann 2013). This intake translates to sufficient iodine nutrition when the urinary I^- concentration (UIC) is 100–299 µg/L. Higher UIC poses a risk for developing hyperthyroidism and autoimmune thyroid disease, whereas lower or excess (supraphysiological) amounts of iodine intake are associated with several different pathologies.

Deficiency in I^- intake leads to goiter and hypothyroidism to different degrees. Congenital hypothyroidism due to iodine deficiency is the most common preventable cause of mental retardation

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(WHO, www.who.int). I^- deficiency during pregnancy is associated with miscarriage, stillbirth, preterm delivery and fetal congenital abnormalities. Accordingly, the newborn can present impaired growth, hearing and speech problems and mental retardation, and in the most severe form, cretinism (Morreale de Escobar *et al.* 2008, Berbel *et al.* 2010).

Excess I^- intake is generally well tolerated, except in certain susceptible individuals such as those with pre-existing thyroid disease, the elderly, fetuses and neonates, who may have an increased risk of thyroid dysfunction (Leung & Braverman 2014). Excess or supraphysiological I^- intake triggers the Wolff–Chaikoff effect, which is a transient (lasting around 24 h) reduction of TH synthesis (Wolff & Chaikoff 1948). This mechanism has been attributed to the inhibition of TH synthesis by several iodo-compounds such as iodolactone and iodolipids (Dugrillon 1996) and also by TPO inhibition. A recent study from our laboratory showed that supraphysiological I^- intake results in the rapid functional inhibition of NIS at the plasma membrane (Leoni *et al.* 2011), suggesting that the effect could also occur in extrathyroid NIS-expressing tissues, as has been demonstrated in the intestine (Nicola *et al.* 2009). TH production resumes after this transient period by the normalization of intra-iodide concentrations mediated by a decrease and stabilization of NIS mRNA (Eng *et al.* 1999). We demonstrated that during the Wolff–Chaikoff effect, thyroidal ROS production is increased and is balanced by TXNRD1 in parallel to NIS recovery (Leoni *et al.* 2011). Our results showed that adequate selenium homeostasis may thus contribute both to selenoprotein expression and activity and to NIS expression and recovery (Leoni *et al.* 2016). Aside from NIS, PENDRIN expression and function increase to regulate the apical thyroid efflux in conditions of I^- excess (Calil-Silveira *et al.* 2016). These mechanisms directly involving NIS could also be responsible for the phenomenon known as 'thyroid stunning', which is generally defined as the inhibition of the uptake of an ablative dose of ^{131}I by the prior uptake of a diagnostic dose (Norden *et al.* 2007). In another study, moderate high I^- concentration (2- to 10-fold over physiological conditions) were found to regulate thyroid activity directly by inhibiting Duox2 function and indirectly by reducing the mRNA expression of NIS and TPO (Morand *et al.* 2003). Although additional work is necessary to elucidate the mechanisms involved.

It is well known that Japan has the highest life expectancy and the lowest infant mortality in the world (WHO, www.who.int). Interestingly, the daily intake of I^- in the Japanese population is more than 2 mg, 10 times higher than the WHO recommended dose, without apparent thyroid dysfunction (Tsubota-Utsugi *et al.* 2013). Moreover, autoimmune thyroiditis incidence is low in the Japanese population (Konno *et al.* 1993), and Japanese women have a low incidence of benign and malignant breast diseases, which is lost when they migrate to other countries (LeMarchand *et al.* 1985, Minami *et al.* 1996). The protective antineoplastic effect of iodine has also been reported in epidemiological studies in which high iodine intake was related to low incidence of breast cancer (Eskin *et al.* 1995, Cann *et al.* 2000), and this has been confirmed in animal models (Garcia-Solis *et al.* 2005). These findings are consistent with results showing that incidence of prostate, endometrium, ovary and breast cancer is lower in populations with high iodine intake (Stadel 1976). The antineoplastic effect is believed to be mediated by I_2, but not I^-, via increases in the expression of peroxisome proliferator-activated receptor gamma, which triggers apoptosis pathways (Garcia-Solis *et al.* 2005, Aceves *et al.* 2009). LPO has also been shown to be involved in the protective mechanism by I_2 in mammary tumors (Soriano *et al.* 2011). Nevertheless, the transporters reviewed here are unable to transport I_2, and so the next challenge is to discover which molecule/s is/are implicated in I_2 translocation.

The remarkable role of NIS in anti-tumoral targeted therapies

Radioiodide and other radiolabeled NIS-translocated isotopes represent one of the major advances in therapeutic nuclear oncology in the last two decades. NIS has a unique and dual role in this process, both as a reporter and as a therapeutic modality. Accordingly, NIS can be used as a reporter for noninvasive imaging and also as a diagnostic tool for PET/SPECT. The use of NIS has some advantages over other reporter genes that can be monitored by PET/SPECT, which have less resolution and penetrance by bioluminescence and fluorescence (Baril *et al.* 2010). Three types of reporter genes are currently in general use: (1) those based on enzymatic activities (HSV-1-tk and TK2); (2) those based on the presence of specific receptors (somatostatin receptor 2 (SSTR2) and dopamine receptor-2 (D2)) and (3) those based on ionic transport (NIS and the norepinephrine transporter). For the latter reporter system, only NIS offers a variety of affordable substrates (^{124}I, ^{125}I, ^{131}I, $^{99m}TcO_4$, $^{188}ReO_4^-$ and $B_{18}F_4^-$) that additionally can provide detailed functional and molecular information on the evolution of infection *in vivo*. Furthermore, these radioisotopes present different energy levels, half-lives and

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tissue penetration radius, which allows one to choose the imaging system and optimize the treatment strategy. The use of NIS reporter gene imaging has rapidly advanced to provide unprecedented insight into spatial and temporal biodistribution (Miller & Russell 2016).

NIS can also be used as a therapeutic tool through its ability to concentrate radioiodide in specifically targeted cells. An additional advantage in using NIS is that the anti-tumoral effects of RAI in targeted cells and potential side effects in other tissues have been extensively explored over the last seven decades. Overall, these attributes have made NIS a very attractive tool in several types of targeted therapy using viral and cellular vectors and nanoparticles. It is important to state that the efficiency of RAI therapy could be greater if the I^- oxidation, therefore retention, within the tumor cells is increased. Further research should be focused in this direction. In NIS-targeted therapies, higher amounts of radioiodide are commonly used to compensate for this limitation.

Viral vectors

The use of viral vectors in gene therapy has met with increasing success, with the initial challenges of immunogenicity addressed and with the introduction of new generation vectors, such as non-integrative viral vectors (adenovirus, Herpes Simplex virus and vaccinia virus), which do not integrate into the genome of the target cells. This makes them very useful for short-term therapy such as suicide therapy. By contrast, integrative viral vectors (retrovirus, lentivirus and adeno-associated virus) allow longer-term expression and higher therapeutic efficiency that is suitable for the treatment of chronic diseases. However, insertion of the vector may cause deleterious mutagenesis. Oncolytic, replication-competent, viruses preferentially replicate in tumor tissues, and subsequent intratumoral replication and spread of replicating vectors amplifies the antitumor effect of the initial administered dose (Baril *et al*. 2010).

In contrast to drug therapies, viral therapies need continued pharmacologic monitoring to track pharmacokinetics, safety, efficacy and toxicity. Against this background, NIS is the gene of choice and allows the determination of the precise localization of the virus and its fate using noninvasive monitoring by PET/SPECT. Many NIS-expressing viruses have been used in preclinical and clinical trials (Miller & Russell 2016). Indeed, >20 types of cancers are currently being treated using viruses expressing NIS, used both as a reporter and also as a treatment in preclinical studies (Baril *et al*. 2010, Riesco-Eizaguirre *et al*. 2011). These include at least 28 adenoviruses, 1 herpes simplex virus, 2 measles viruses, 2 vesicular stomatitis viruses and 3 vaccinia viruses. More importantly, fourteen clinical trials, 10 of which are ongoing, are utilizing oncolytic viruses expressing NIS (Miller & Russell 2016, Msaouel *et al*. 2017). The types of cancer being treated in clinical trials include ovarian, cutaneous T cell lymphoma, glioma, myeloma, mesothelioma, breast, squamous cell head and neck and malignant peripheral nerve sheath tumors. The completed or terminated trials using NIS as a reporter gene have allowed the unparalleled optimization of therapy protocols at several levels: in the dynamic nature of the viruses, the best treatment administration route and virus dose and improving virus design. These trials should enhance our understanding of the oncolytic activity of these viruses and guide future clinical treatments.

Nonviral/nanoparticles vectors

Synthetic nonviral vectors have low cytotoxicity, low immunogenicity and are easy to manipulate. This allows for better efficacy and rapid, large-scale, production. Nanoparticles are smaller than 1 micron, usually between 1 and 100 nm, and they can be organic (such as polymers, dendrimers, cationic liposomes) or inorganic (such as silica, iron oxide, gold or carbon nanoparticles) in nature and are designed to bind DNA/RNA. Due to their size, they have been used successfully in anticancer therapies attributed, in part, to the phenomenon known as enhanced permeability and retention effect, which permits preferential tumor retention.

Nanoparticles composed of third-generation polypropylenimine dendrimers loaded with NIS have been shown to specifically accumulate NIS-dependent [^{99m}Tc]pertechnetate in tumor-bearing mice (Chisholm *et al*. 2009). In a hepatocellular carcinoma mouse model, a nonviral vehicle based on linear polyethylenimine, polyethylene glycol and coupled to the synthetic peptide B6, with NIS as a theranostic gene, was able to induce tumor-specific radioiodide accumulation (Urnauer *et al*. 2017). Significant delay of tumor growth and improved survival was observed after 4 cycles of ^{131}I therapy. This creates a new set of tools for gene delivery with therapeutic benefits not only in primary tumors but also, more importantly, in metastatic tumors. Moreover, these strategies allow the possibility to load a combination of several targeting ligands to improve the selectivity and efficiency of therapeutic approaches.

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Cellular vectors

Mesenchymal stem cells (MSCs) have been studied as vehicles to express or deliver target genes in light of their low immunogenic potential and their propensity to migrate to injured and inflamed tissues (Aquino *et al*. 2010). Moreover, MSCs have natural tropism for tumors and their metastases, which can be focused by expression of different receptors and using tumor stroma-specific gene promoters linked to unique differentiation pathways that are activated as MSCs respond to tumor microenvironments (Reagan & Kaplan 2011, Knoop *et al*. 2015). Additionally, MSCs are easy to extract, expand and transduce in tissue culture and can be easily engineered to deliver viral or nonviral vectors containing a target gene.

Along this line, MSCs have been engineered to transduce NIS in hepatocellular cancer (Knoop *et al*. 2011, Knoop *et al*. 2015, Muller *et al*. 2016) and breast cancer (Dwyer *et al*. 2011) mouse models with specific ^{131}I tumor accumulation and significant delay of tumor growth. In addition, NIS has been used successfully used as a reporter to monitor MSC biodistribution and fate using lentiviral vectors (Shi *et al*. 2014) and baculovirus (Pan *et al*. 2013).

Future directions

As an essential component of TH signaling I^- has been studied extensively for many years. The defensive role of I^- as an antioxidant and antimicrobial in the form of IO^- is becoming more relevant, and it would be interesting to explore how it affects the body's redox homeostasis through dietary I^-. It will also be important to determine to what extent I^- deficiency affects other health problems, such as inflammatory diseases, and the predisposition to neurodegeneration and certain cancers that have been linked to other molecules implicated in I^- metabolism. New I^- transporters have been recently identified, and it will be central to understand better their precise role in I^- homeostasis and to comprehend the relationships between them. Given that some of these transporters are highly expressed in cancer, it will also be crucial to know why tumor cells use I^- for survival and progression. Finally, the use of NIS as a therapeutic tool in antitumor treatments is now beginning to give encouraging results in ongoing clinical trials. Broadening the applications of NIS-mediated modalities to extrathyroidal cancers, both as a reporter and a therapy, will be a necessary next step.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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