13. THYROIDAL IODIDE TRANSPORT AND THYROID CANCER

ORSOLYA DOHÁN AND NANCY CARRASCO

Department of Molecular Pharmacology Albert Einstein College of Medicine Bronx, NY 10461, USA

INTRODUCTION

The current treatment for metastatic papillary and follicular thyroid carcinomas, consists of total thyroidectomy followed by administration of radioiodide for the ablation of any remaining thyroid cancer cells or metastases (1). Radioiodide treatment of thyroid cancer has been employed for over 60 years (2), and this is the most effective targeted and curative radiotherapeutic modality available for any cancer. Radioiodide also destroys any remaining normal thyroid tissue, thus increasing the sensitivity of subsequent ^{131}I scanning and serum Tg measurements for the detection of recurrent or metastatizing disease. This is because, if normal thyroid cells remained after thyroidectomy, they would tend to prevent cancerous cells from being detected by either method. The success rate of this treatment is impressive: the mortality of patients with metastatic thyroid cancer who are treated with ^{131}I is just 3%, as opposed to 12% for those who are not treated (3). Side-effects resulting from this therapy, such as mild sialadenitis, are minimal (3); in most instances they resolve within a few weeks of termination of the treatment.

Two key characteristics of the thyroid contribute to the success of this approach. First, thyrocytes, both normal and cancerous, exhibit a remarkable ability to actively transport iodide (I^-). Thus, when radioiodide is administered, it is actively taken up almost exclusively by thyrocytes without affecting other cells. This makes radioiodide therapy a distinctively specific targeted method that delivers radiation from within the cancerous cells themselves. Even though I^- transport activity is significantly lower in the

majority of cancerous thyrocytes than in normal ones, the activity remains high enough for accumulated radioiodide to destroy cancerous thyrocytes as well. The decreased ability of cancerous thyrocytes results in the presence of "cold nodules" at tumor sites on thyroid scintigraphic scans. Second, although the thyroid is physiologically crucial, its function can be fully restored after thyroidectomy by thyroid hormone substitutive therapy, thus keeping patients in a euthyroid state.

It has long been well known that active I^- transport is a key attribute of differentiated thyrocytes, as I^- is essential for thyroid hormone biosynthesis. The Na^+/I^- symporter (NIS) is the plasma membrane glycoprotein that mediates active I^- transport from the bloodstream into the cytoplasm of thyrocytes. Using expression cloning in *Xenopus laevis* oocytes, our group isolated the cDNA encoding NIS from rat-thyroid-derived FRTL-5 cells (4). On the basis of a high degree of homology with the rat NIS cDNA, the human, mouse, and pig NIS cDNAs were subsequently cloned (5, 6, 7). NIS-mediated active I^- transport has also been documented in a few other tissues, including salivary glands, gastric mucosa, and lactating (but not non-lactating) mammary gland (8, 9). These findings and the generation of high affinity anti-NIS Abs have led to a thorough molecular characterization of NIS (10) (11)and to the analysis of both thyroidal and extrathyroidal I^- transport in health and disease (9, 12–14).

FUNCTION AND STRUCTURE OF NIS

NIS couples the inward translocation of Na^+ down its electrochemical gradient to the simultaneous inward "uphill" translocation of I^- against its electrochemical gradient. NIS activity is inhibited by the "classic" competitive inhibitors perchlorate and thiocyanate (9, 15–18). Two Na^+ are transported per each I^- (19). The Na^+ gradient that provides the driving force for I^- uptake is maintained by the Na^+/K^+ ATPase. In the thyroid, both NIS and the Na^+/K^+ ATPase are located on the basolateral side of the thyroid follicular cells, facing the blood supply (20). Rat NIS (rNIS) is a 618-amino acid protein (relative molecular mass 65,196) (4); both human and pig NIS, which contain 643 amino acids each, are highly homologous (75.9% and 74.2%, respectively) to rNIS (6, 7). Based on extensive experimental testing, we have proposed a NIS secondary structure model with 13 transmembrane segments (Figure 1) (12). The amino and carboxy termini face extra- and intracellularly, respectively (10). NIS is a glycoprotein; three of its Asp residues (225, 485, 497) are glycosylated in the endoplasmic reticulum (21). However, glycosylation is not essential for proper NIS function, as indicated by the observation that a non-glycosylated NIS protein is properly targeted to the plasma membrane and displays I^- transport activity with an identical K_m value (~20–30 μM) to that of wild-type (WT) NIS (21). The ca 70-amino acid hydrophilic carboxy terminus is the main phosphorylated region of the protein (22). Freeze-fracture electron microscopy studies of NIS-expressing *Xenopus laevis* oocytes revealed the appearance of 9-nm intramembrane particles corresponding to NIS (19). The size of these particles suggested that NIS may function as a multimeric protein. Recent co-immunoprecipitation experiments indicate that NIS is indeed an oligomer (23). A putative leucine zipper motif constituted by leucines at positions 199, 206, 213 and 220 may be the structural basis for NIS oligomerization (4).