Heart failure drug restores sensitivity to radioactive iodide treatment in aggressive thyroid cancer

Patients diagnosed with thyroid cancer generally have a good prognosis as a result of implementing treatment regimens consisting of surgery and radioactive iodide (RAI) ablation. However, in about 30% of cases, these tumors develop resistance to RAI treatment. As a consequence, treatment success and overall survival of RAI-resistant thyroid cancer patients is poor since no other efficient treatments are available, leading to recurrences, persistent disease and death. Mechanistically it is well established that RAI-resistance is accompanied by severe tumor dedifferentiation, i.e. the loss of thyroid-specific features, and, hence, these tumors are denoted as poorly differentiated thyroid cancer. Strategies for restoring thyroid-specific features, designated as redifferentiation, are therefore considered as a promising treatment modality to improve clinical responses to RAI treatment.

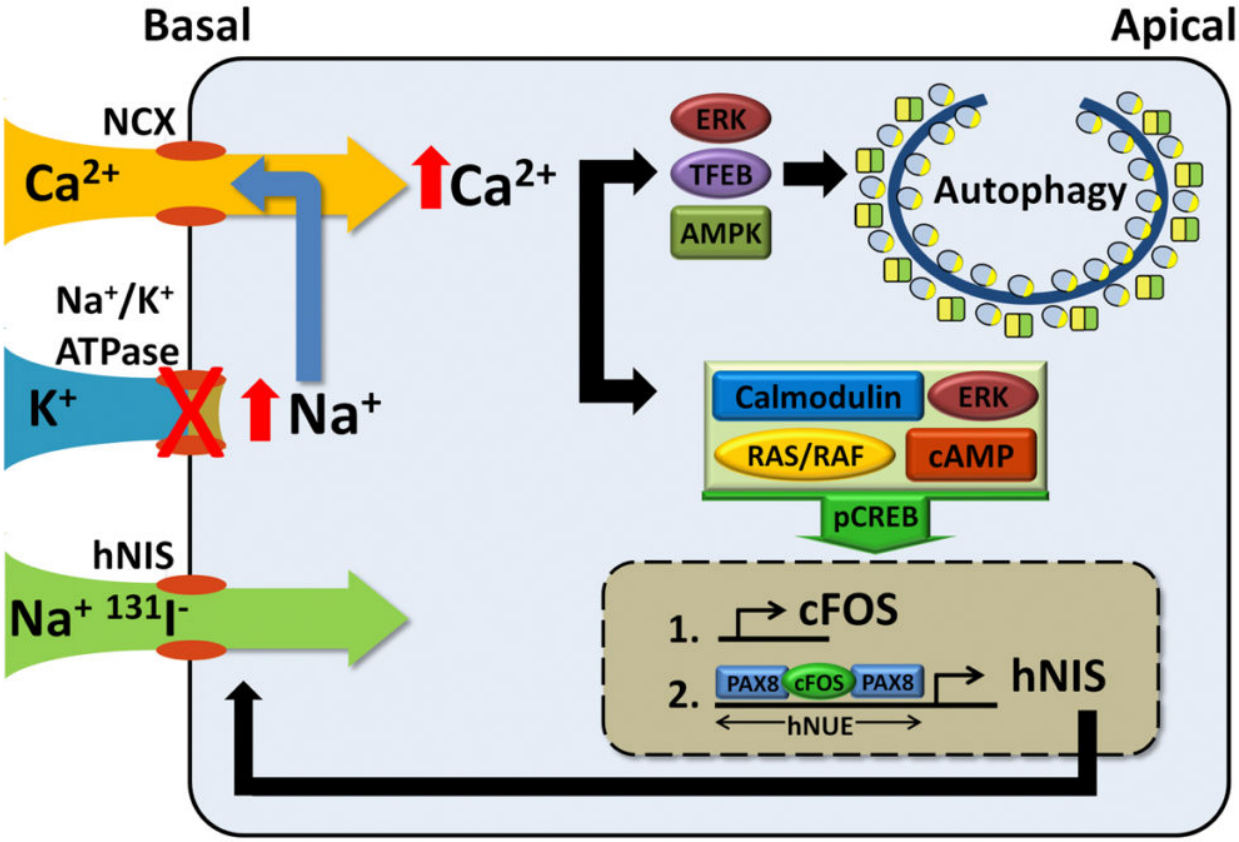

Fig. 1. Schematic representation of mechanisms induced by digoxin that activate autophagy and restore tumor sensitivity to radioactive iodide treatment in aggressive, poorly differentiated thyroid

cancer.

In the present study, we have demonstrated that TC redifferentiation is accomplished by activating a biological mechanism designated as autophagy. Autophagy is a recycling process that occurs within cells to keep themselves well organized by processing of waste components and replacing them with newly build components. In many cancer types, cancer cells have defects in autophagy, which contributes to their cancerous properties. In a previous study we have indeed shown that in thyroid cancer the development of RAI-resistance is specifically accompanied by defective autophagy.

We have established activation of autophagy by an existing FDA-approved drug called digoxin, which is currently prescribed to patients with heart failure or heart arrhythmia. As a result of digoxin treatment, thyroid-specific features are reactivated and sensitivity to RAI treatment is restored. Treatment with digoxin is therefore a highly promising approach to effectively treat and cure aggressive, poorly differentiated thyroid cancer patients that initially have a poor response to RAI treatment.

We have further characterized the important biological mechanisms that are influenced in thyroid cancer cells by digoxin treatment and have shown that autophagy, intracellular calcium and the protein called FOS are crucial factors.

The additional benefit of digoxin is that this is an existing off-label drug approved for treatment of heart disease with well established profiles of dose response and side effects, which means that the use of this drug can be easily and rapidly repositioned and introduced into another patient group (aggressive, poorly differentiated thyroid cancer) for a different purpose (improve sensitivity to RAI treatment by redifferentiation).

Future studies are aimed at validating these findings in mouse models and tumor material of thyroid cancer patients. These novel insights provide the required knowledge to establish an effective treatment regimen for thyroid cancer patients with a initially poor response to RAI treatment and will lead to improved survival and cure rates among patients with aggressive, poorly differentiated thyroid cancer.

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Publication

Digitalis-like Compounds Facilitate Non-Medullary Thyroid Cancer Redifferentiation through Intracellular Ca2+, FOS, and Autophagy-Dependent Pathways.
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