RNA mediated trans-activation: its therapeutic potential in anaplastic thyroid cancer

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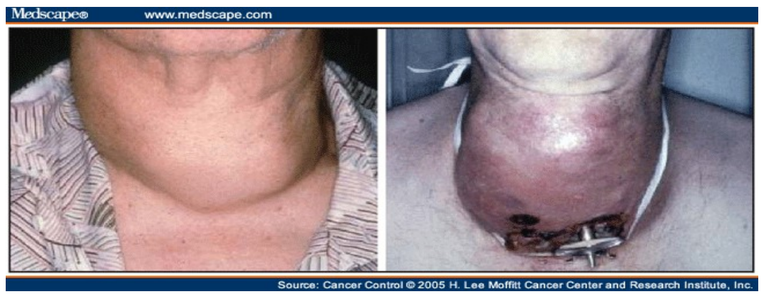
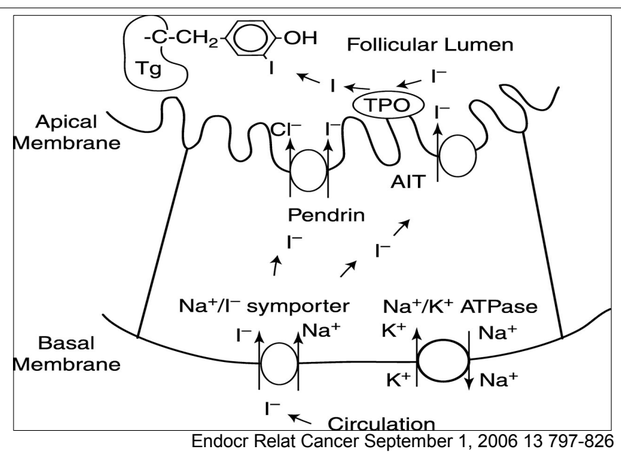


Anaplastic thyroid carcinoma (ATC) is a rare thyroid cancer characterized by a rapid fatal course. It is an undifferentiated form of cancer resistant to radiotherapy and chemotherapy.
Surgery is rarely performed.
It is resistant to the radio-iodine therapy because it is lacking of the NIS symporter, marker of differentiated thyroid.
Radio-iodine therapy id the therapy of election for the treatment of Thyroid cancers.

Proc Natl Acad Sci U S A. 1990 Dec;87(24):9923-7.

Trans-activation: A New Epigenetic Phenomenon Underlying Transcriptional Memory (Arancio W, Onorati MC, Corona DF et Al; manuscript in preparation).

Using PEV assays, non-functional alleles can trans-activate the expression of wild type copy of the same gene. Data strongly suggest that cells can 'read' the presence of RNAs and can use them to maintain their transcriptional memory after cell division. If the phenomenon is conserved, it could be used as a therapeuthical strategy for ATC.



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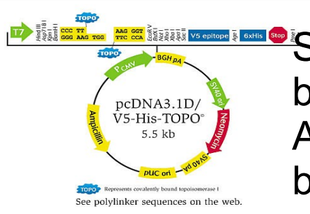
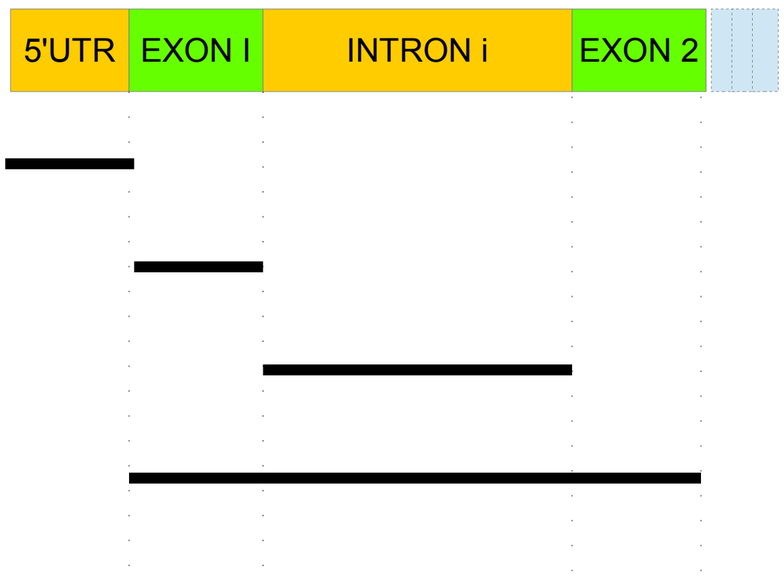
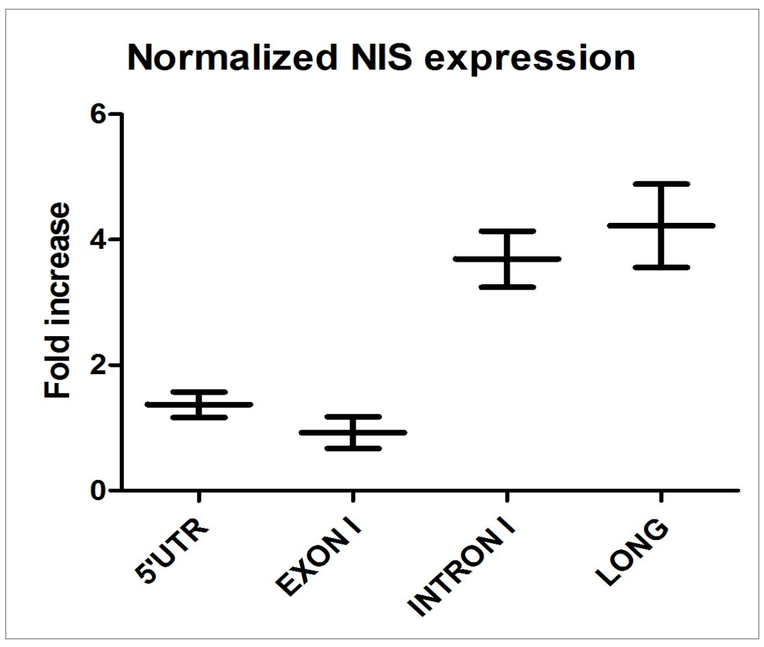
The sodium/iodide symporter (NIS) mediates iodide uptake in the thyroid gland. NIS is detected in most thyroid cancer specimens, and it is sufficient to utilize radioactive iodide for the treatment of residual and metastatic disease. Approximately 10% of differentiated thyroid cancers and all ATC, do not express the NIS gene. These tumors are generally associated with a poor prognosis.



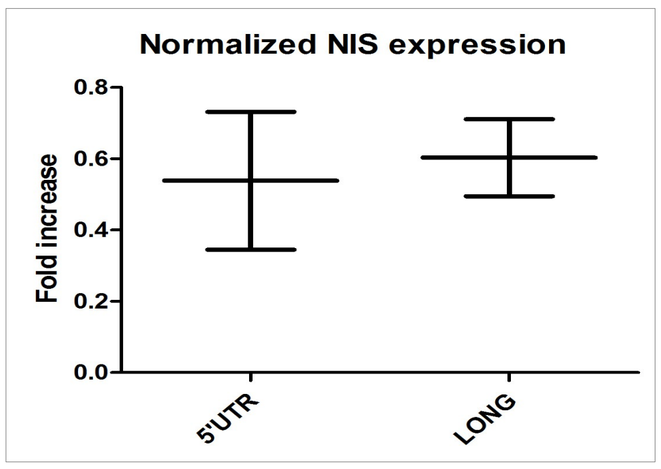
Several constructs have been made from NIS gene. ATC cell line SW1736 have been transiently transfected



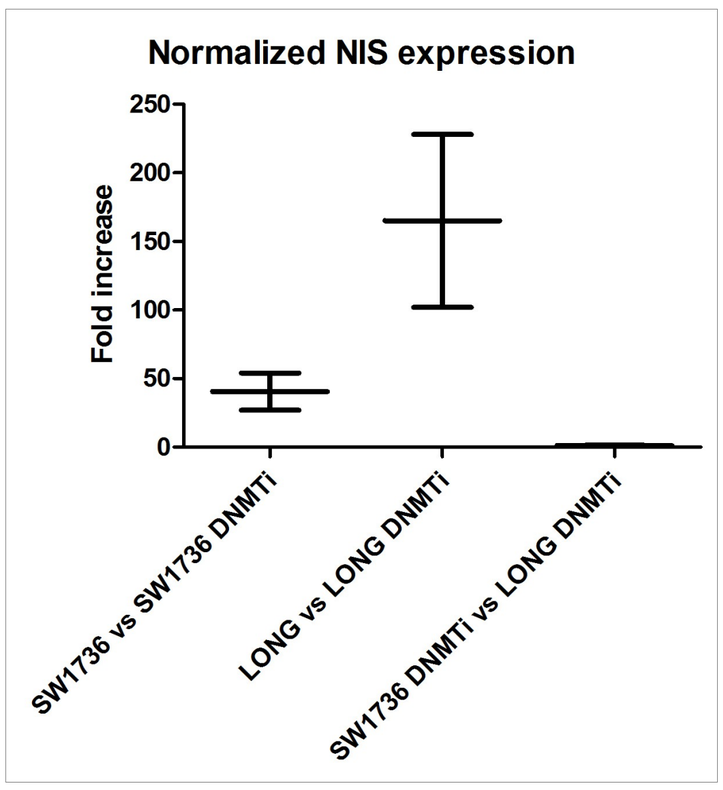
The effects of transient transfection have been tested in RT-PCR using specific primers able to discriminate between constructs and genomics



The effects of stable transfection have been tested in RT-PCR. Unexpectedly, the effect was nullified by an unknown mechanism.



We tested if DNA methylase inhibitors can rescue the phenotype.



ZEBularine 100 uM + RG108 50uM; 72 Hrs

DNMTi cocktail is highly citotoxic for the SW1736 ATC cell line and strongly induce NIS expression

We identified a cocktail of DNA methyl transferase inhibitors (nucleotidic and not nucleotidic) that strongly induce the expression of NIS in the ATC cell line SW1736 (45X), independently from the transfection.

The expression is even 3 times greater than the expression of NIS in control thyroids (data not shown).

Moreover the cocktail results to be extremely toxic to the ATC cell line even at very low concentration (data not shown).

CONCLUSIONS

ATC is up to date an untreatable form of cancer, resistant to any therapy, with poor prognosis and rapid fatal course.
Our preliminary data suggest that a specific cocktail of DNA methyl transferase inhibitors can kill ATC cells per se.
Moreover the treatment strongly induce the expression of NIS, sensitizing them to the treatment with radio-iodine.
These data suggest a possible pharmacological healing strategy for ATC.

To Do list...

- Testing Dose and Time dependence
- Testing other ATC cell lines
- Testing expression of NIS protein
- In vitro Functional assays
- In vivo assays
- Et cetera...