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Gene Section
Mini Review

NCOA4 (Nuclear Receptor Coactivator 4)

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Identity

Other names: ARA70, DKFZp762E1112, ELE1, PTC3, RFG

HGNC (Hugo): NCOA4

Location: 10q11.23

DNA/RNA

Description

10 exons, 3431bp.

Transcription

Isoforms due to alternative splicing.

Protein

Description

Two isoforms:
- Isoform alpha (614 aa, mass around 70kD)
- Isoform beta: missing of aa 239-565 (mass around 32kD)

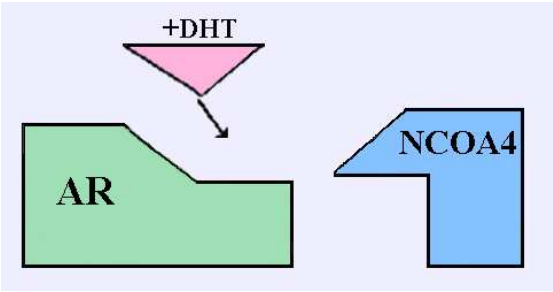
Expression

NCOA4 is widely expressed in several tissues, including testis, adrenal and thyroid glands, thymus, prostate. A truncated NCOA4 corresponding to the beta isoform is fused to RET exon 12 and is aberrantly expressed in papillary thyroid carcinoma as a consequence of intrachromosomal rearrangements at 10q11.2 (RET/NCOA4).

Function

NCOA4 is involved in the androgen receptor signaling pathway and in the development of the male gonade. It is a ligand-dependent associated protein for the androgen receptor (AR), that functions as coactivator to enhance AR transcriptional activity (7-10 fold in human prostate cancer cells) and protein stability. NCOA4 also enhances the agonist activity of anti-androgens in human prostate cancer cells (3-30 fold in the prostate cancer cell line DU145), with relevant implications for hormonal treatment of prostate cancer. Albeit to a lesser degree (up to 2-fold), NCO4 also enhances transcription activity of other steroid receptors, such as glucocorticoid receptor (GR), progesterone receptor (PR) and oestrogen receptor (ER).

In addition to the interaction with steroid hormone receptors, NCOA4 functions as coactivator of peroxisome proliferator-activated receptor gamma (PPARG). PPARG is a peroxisome proliferator-activated receptor and as such belongs to the nuclear hormone receptor superfamily. PPARG is highly expressed in adipose tissue (were it is involved in adipogenesis and in the regulation of adipocyte-specific genes), as well as in other human tissues. Interestingly, PPARG is rearranged with PAX8 in a subset of follicular thyroid tumors.



Ligand-specific interaction between AR (Androgen receptor), NCOA4, and the androgen receptor ligand DHT (dihydrotestosterone).

Unlike the AR-NCOA4 interaction, which requires the presence of androgen, the PPARG-NCOA4 interaction

can occur in the absence of exogenous ligand. However, the presence of the ligand enhances PPARG-NCOA4 transactivation and NCOA4 is thus regarded as a ligand-enhanced coactivator of PPARG.

Mutations

Germinal

LINE S94L; F154L; C350R; P474R; L561P.

Somatic

NCOA4 breakpoint for rearrangement to form RET/NCOA4 oncogene at cDNA bp791, corresponding to aa 238-239.

Implicated in

inv(10)(q11q11) with RET/NCOA4 rearrangement in thyroid cancer

Disease

Papillary thyroid carcinoma. RET/NCOA4 may occur in non radiation-associated carcinomas but it is particularly common in radiation-associated tumors like those linked to the Chernobyl nuclear accident (1986).

Prognosis

RET/NCOA4 may be associated with aggressive behaviour. Among post-Chernobyl papillary carcinomas, RET/NCOA4 has been associated with tumors that were of shorter latency after radiation exposure, of larger size, with extrathyroidal extension, and that were classified as solid variant papillary carcinomas.

Cytogenetics

Simple karyotypes with balanced chromosomal inversions due to structural rearrangement of NCOA4 and RET gene on chromosome 10 [inv(10)(q11.2-q21)], resulting in RET/NCOA4.

Hybrid/Mutated gene

RET/NCOA4.

Abnormal protein

NCOA4/RET (RP3).

Oncogenesis

RET/PTC oncogenes are generated by chromosomal rearrangements resulting in the fusion of the RET tyrosine-kinase (RET-TK) domain to the 5'-terminal region of heterologous genes (e.g. H4, RIa, RFG5, hTIF1, RFG7, ELKS). All are balanced inversions or translocations which involve the 3.0 kb intron 11 of RET. RET-fused genes are widely expressed in human tissues, including thyroid follicular cells, and have putative dimerization domains. As the chimeric forms of RET-TK are translated into fusion proteins, these domains of the translocated amino terminal regions allow dimerization and thus ligand independent activation of RET-TK, which is considered essential for the transformation of thyroid cells. To date, at least 16 chimeric mRNAs involving 10 different genes have been reported, of which RET/PTC1 (consisting in the fusion of RET with H4) and RET/NCOA4 (consisting in the fusion of RET with NCOA4) are by far the most common.

ANIMAL MODELS RET/NCOA4 transgenic mice have been generated by Powell and coworkers using a construct with the RET/NCOA4 fusion gene downstream and under the control of the bovine thyroglobulin gene regulatory region; they express RET/NCOA4 selectively in the thyroid gland and develop thyroid hyperplasia and solid tumor variants of papillary carcinomas.

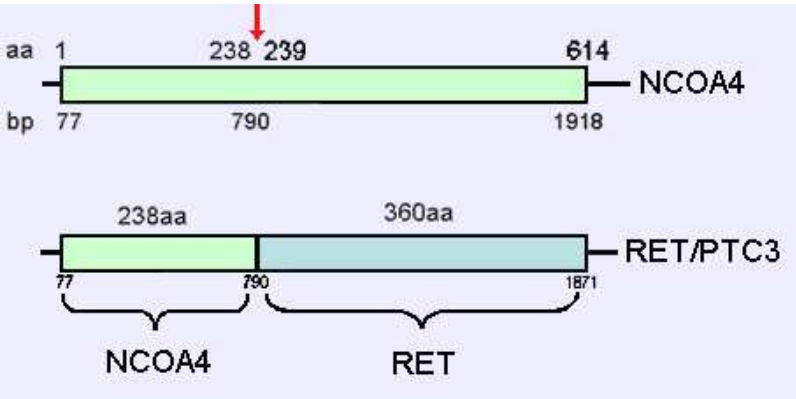


Diagram of RET/NCOA4 oncogene. The red arrow indicates the breakpoint region.

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