# 12. TRK ONCOGENES IN PAPILLARY THYROID CARCINOMA

ANGELA GRECO, EMANUELA ROCCATO AND MARCO A. PIEROTTI

*Istituto Nazionale Tumori, Department of Experimental Oncology Operative Unit #3*
*Via G. Venezian, 1 20133 Milan Italy*

## INTRODUCTION

The NTRK1 gene encodes the high affinity receptor for Nerve Growth Factor, and its action regulates neural development and differentiation. Deregulation of NTRK1 activity is associated with several human disorders. Loss of function mutations cause the genetic disease Congenital Insensitivity to Pain with Anhidrosis (CIPA). Constitutive activation of NTRK1 has been detected in several tumor types. An autocrine loop involving NTRK1 and NGF is responsible for tumor progression in prostate carcinoma and in breast cancer. Somatic rearrangements of NTRK1, producing chimeric oncogenes with constitutive tyrosine kinase activity, have been detected in a consistent fraction of papillary thyroid tumors.

The topic of this review is the thyroid TRK oncogenes; the modalities of activation, the mechanism of action, and the contribution of activating sequences will be discussed.

### NTRK1 proto-oncogene

NTRK1 (also known as TRKA) is the prototype of a family of genes which also includes NTRK2 (TRKB) and NTRK3 (TRKC), encoding tyrosine kinase receptors for the neurotrophins of the Nerve Growth Factor (NGF) family. NGF is the preferred ligand for NTRK1, brain-derived neurotrophic factor and NT4/5 are ligands for NTRK2, and NT3 is the ligand for NTRK3. Interestingly, NT3 is also capable of binding to NTRK1 and NTRK2, although with low affinity (Barbacid, M., 1995).

All the neurotrophins bind also the p75 low affinity receptor, which belongs to the TNF receptor family, and is devoid of kinase activity (Kaplan, D. R. et al., 2000).

Neurotrophins are responsible for the survival, differentiation and maintenance of specific population of neurons in the developing and adult nervous system (Davies, A. M., 1994). In particular, the NGF/NTRK1 signaling supports survival and differentiation of sympathetic and sensory neurons responsive to temperature and pain. In addition to its neurotrophic functions, NGF also stimulates proliferation of a number of cell types such as lymphocytes, keratinocytes and prostate cells (Otten, U., et al., 1989; Di Marco, E. et al., 1993; Djakiew, D. et al., 1991).

NTRK1 was originally isolated from a human colon carcinoma as a transforming oncogene activated by a somatic rearrangement that fused a non-muscle tropomyosin gene to a novel tyrosine kinase receptor (Martin-Zanca, D. et al., 1986). Cloning of the full length gene (Martin-Zanca, D. et al., 1989) and identification of the NGF as a ligand occurred few years later (Kaplan, D. R. et al., 1991).

The NTRK1 gene is located on chromosome 1q21–22 (Weier, H.-U. G. et al., 1995) and consists of 17 exons distributed within a 25 kb region (Greco, A. et al., 1996). The NTRK1 receptor is a glycosylated protein of 140 kDa, comprising an extracellular portion, including Ig-like and Leucine rich domains for ligand binding, a single transmembrane region, a juxta-membrane domain, a tyrosine kinase domain and a C-terminal tail. Following NGF binding, NTRK1 undergoes dimerization and autophosphorylation of five tyrosine residues (Y490, Y670, Y674, Y675, and Y785). Activated receptor initiates several signal transduction cascades, including the Mitogen Activated Protein Kinase (MAPK), the phosphatidylinositol 3-kinase (PI3K) and the PLC-$\gamma$ pathways. These signaling cascades culminate in the activation of transcription factors that alter gene expression (Kaplan, D. R. et al., 2000).

**NTRK1 in human diseases**

Deregulation of NTRK1 activity is associated with several human diseases. Mutations affecting different NTRK1 domains are associated with CIPA (Congenital Insensitivity to Pain with Anhidrosis), a rare recessive genetic disease characterized by loss of pain and temperature sensation, defects in thermal regulation and occasionally mental retardation (Indo, Y. et al., 1996). CIPA is the consequence of a genetic defect in the differentiation and migration of neural crest elements. By studying the effects of different CIPA mutations on NTRK1 biochemical and biological properties, the molecular mechanisms responsible for the disease have been unveiled. CIPA mutations cause inactivation of the NTRK1 receptor by at least three different mechanisms, such as complete inactivation, protein processing alteration, and reduction of receptor activity (Greco, A. et al., 1999; Greco, A. et al., 2000; Miranda, C. et al., 2002a; Miranda, C. et al., 2002b).

NTRK1 gain of function mutations have been described in some human tumors. Activation through genomic rearrangements producing chimeric oncogenes has been detected in a consistent fraction of human papillary thyroid carcinoma, and it will be described later. A 75 amino acids deletion in the extracellular domain of the NTRK1 receptor, resulting in a mutated protein with in vitro transforming activity, has been