Overexpression of Neurotrophic Tyrosine Receptor Kinases (NTRKs) as a Potential Therapeutic Target for Cancer

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Abstract

Neurotrophic tyrosine receptor kinases (NTRKs), or Tropomyosin receptor kinases (Trks), belong to a family of tyrosine kinases that regulate synaptic strength and plasticity during neural development. Deregulated kinase activity of the family members due to chromosomal rearrangements, gene mutations, splice variants and overexpression has been shown to be associated with cancer cell proliferation, survival, invasion and chemo-resistance in a number of cancer types. For example, chromosomal rearrangements involving NTRK1-3 have been reported in lung, colorectal, papillary thyroid, glioblastoma, melanoma and other cancers, and have been demonstrated to function as oncogenic drivers in these tumors. Moreover, overexpression of TrkA, TrkB and/or their corresponding ligands has been observed in a number of solid tumors such as breast, lung, prostate and pancreatic cancers. However, the functional implication of Trk overexpression has not been well defined or fully explored as a potential target of a therapeutic strategy.

To characterize the expression, signaling and function of full-length Trks in cancer, a series of stable cell lines with full-length NTRK genes were established. The engineered cell lines were characterized for Trk expression, Trk phosphorylation and their response to ligand stimulation. Moreover, cell proliferation, cell transformation and growth inhibition by entrectinib (RXDX-101), a clinical stage, potent and selective pan-Trk inhibitor, were assessed. Trk downstream effectors, such as PLCγ, AKT and ERK, were also evaluated in the relevant settings. Furthermore, several cancer cell lines with endogenous overexpression of full-length Trks or rearranged Trks were identified and functionally characterized.

Our studies highlight the similarities and differences between Trk rearrangement and overexpression as potential oncogenic drivers and support further exploration of entrectinib in cancers with Trk overexpression.

Methods to Study Rearranged (Fusion) and Wild-Type (WT) Trks

Entrectinib Inhibits Proliferation of NGF-Stimulated TrkA Expressing Cell Lines (including an AML Cell Line) at Low Nanomolar Concentrations

Entrectinib Inhibits TrkA Phosphorylation and Downstream Signaling Pathways in NGF-Stimulated TrkA-Expressing Cell Lines

Conclusions

• We have demonstrated that both wild-type TrkA and TrkB can transform BaF3 cells in the presence of their respective ligands.

• Entrectinib (RXDX-101) effectively inhibits the proliferation of cells expressing rearranged (fusion) and over-expressed wild-type Trks.

• Our data support further exploration of entrectinib in cancers with NTRK rearrangements as well as tumors with Trk overexpression.

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