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Asset #37
Dana-Farber Cancer Institute

Targeting TIRR for Cancer Therapy: A Novel Target for p53 Reactivation

Therapeutic Area	Oncology	**Indications**	Cancer
Modality	Small Molecule	**Development Stage**	Target Identification/Validation

Overview

Background

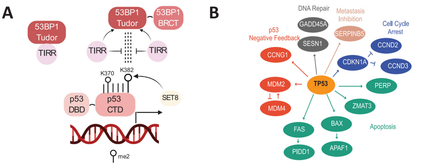
- Tudor-interacting repair regulator (TIRR) is a key modulator of p53, a tumor-suppressor gene that plays an important role in a variety of cancers. Due to the powerful apoptotic response that can be driven by p53, p53 reactivation remains a compelling strategy for cancer therapy. In cells, p53 activity is regulated by a complex that forms between p53 and p53-binding protein 1 (53BP1). Dana-Farber scientists have discovered that TIRR inhibits the formation of the 53BP1-p53 complex. As a result, TIRR negatively affects the expression of key p53 target genes in multiple tumor types, including breast, prostate, and renal cancers. Furthermore, elevated TIRR protein levels and gene amplifications are observed in cancers that maintain at least one wild-type copy of p53, suggesting cancers use TIRR overexpression as a mechanism to suppress p53 activity. Therefore, inhibition of TIRR results in reactivation of p53 leading to cancer cell death.

Technology Advantages

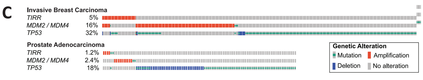
- There have been two main approaches to reactivate p53 in cancer; (1) inhibiting MDM2/MDM4, negative modulators of p53 and (2) directly interacting with mutant p53 to restore its transactivation functions. While these approaches to selectively activate p53 have proven efficacious in animal models and in some human clinical trials, the use of these inhibitors remains limited by on-target toxicity observed in clinical trials. This is consistent with results showing MDM2/MDM4 knockout mice have early embryonic lethality.
  Based on the mechanism of p53 regulation by TIRR and the observation that TIRR knockout mice are viable, targeting TIRR offers an alternative approach to activate p53 and is expected to be well tolerated in the clinic.

Key Data

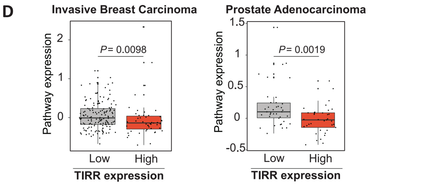
TIRR negatively regulates p53 signaling in cancer

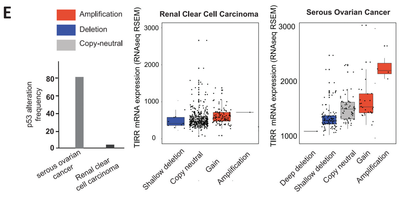


(A) Model depicting TIRR as an upstream regulator of the 53BP1-p53 axis involved in p53 transactivation. (B) Genes belonging to the p53 pathway.

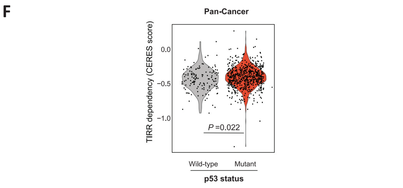


(C) OncoPrint showing the frequency at which TIRR, MDM2/ MDM4, and TP53 are altered in invasive breast carcinoma and prostate adenocarcinoma cohorts from TCGA. (D) Pathway expression in invasive breast carcinoma and prostate adenocarcinoma samples with and without TIRR amplification. Pathway expression scores were calculated as the average mRNA expression of p53 pathway members.





(E) The level at which loss of TIRR is tolerated in human cancers is dependent on p53 status. Cancers with high frequencies of p53 alterations (serous ovarian cancer, right) can tolerate changes in TIRR expression through genomic loss, as a compensating mechanism for p53 activity. However, cancers with low frequencies of p53 alterations (renal cancer, left) do not tolerate changes in TIRR expression that cause changes in p53 activity.



(F) Comparison of TIRR dependency scores (CERES) between 136 p53 WT and 633 p53 mutant cancer cell lines. p53 WT cell lines have a significantly higher dependency on TIRR.

IP Status & Publication(s)

Intellectual Property

Patent Number
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Patent Family
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Publication(s)

- Drané, P., et al. (2017). TIRR regulates 53BP1 by masking its histone methyl-lysine binding function. Nature, 543(7644), 211–216.
- Nishita Parnandi et al. (2021). TIRR inhibits the 53BP1-p53 complex to alter cell-fate programs. Mol Cell. Jun 17;81(12):2583-2595.e6