Loss of Function of TP53 in Cancer

Loss of function of TP53 in cancer due to loss of tetramerization ability

Orlic-Milacic, M., Sakaguchi, K.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

07/09/2021

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

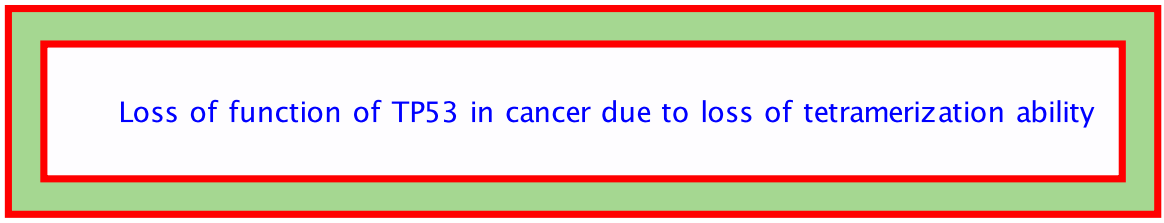
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Loss of Function of TP53 in Cancer ↗

Stable identifier: R-HSA-9723907

Diseases: cancer



TP53 is the most frequently mutated tumor suppressor gene, with mutations present in more than 50% of human tumors and germline mutation in TP53 being underlying cause of the cancer-predisposing Li-Fraumeni syndrome (reviewed in Monti et al. 2020). The TP53 gene maps to chromosomal band 17p13 and encodes a transcription factor that contains four functional domains. A transactivation domain (TAD) involves amino acid residues 1-61 and is involved in interaction with components of the transcription machinery. A DNA binding domain (DBD) involves amino acid residues 94-290 and interacts with specific DNA target sequences called p53 response elements. A C-terminal domain (CTD) involves residues 357-393 and regulates DNA binding (reviewed in Monti et al. 2020). A tetramerization domain (TD) involves amino acids 325-355 and is needed for the formation of TP53 homotetramers. TP53 is considered the “guardian of the genome” (Lane 1992) as it is activated by DNA damage to initiate, depending on the amount of damage, cell cycle arrest, senescence or apoptosis (reviewed in Reinhardt and Schumacher 2012). In addition, TP53 regulates the expression of DNA repair genes, and is involved in the regulation of metabolism and autophagy (reviewed in Monti et al. 2020).

Most cancer-derived TP53 mutations are missense mutations that affect the central DNA binding domain of TP53 (amino acid residues 94-312). Eight hotspot amino acid substitutions in this region (R175H, G245S, R248Q, R248W, R249S, R273H, R273S and R282W) are found in close to 30% of TP53-mutated cancers. Based on their functional impact, TP53 mutations can be classified as 1) loss-of-function (LOF), 2) partial LOF (which may involve temperature sensitivity); 3) wild type-like (WT-L) or super-transactivating (ST) mutants; 4) mutants with altered specificity (AS), which are active or partially active on some but inactive on other TP53 target genes; 5) dominant-negative (DN) mutants, able to tetramerize with and inhibit the activity of the wild type TP53 protein. Some of the TP53 mutants, especially in the category of ST and AS mutants, are gain-of-function (GOF) mutants, able to interact with novel target genes and/or novel components of the transcriptional machinery (reviewed in Monti et al. 2020, and Gencel-Augusto and Lozano 2020).

Due to the complex function of WT-L, ST, AS and DN mutants of TP53, we have so far focused on annotating LOF mutants of TP53 which are unable to oligomerize due to mutations in the TD. Although accounting for a small percent of TP53 mutants, TD mutant are therefore considered to be completely defective in transcriptional activity, with no possibility of AS, DN and GOF effects (Chène and Bechter 1999, reviewed in Chène 2001, and Kamada et al. 2016). However, when overexpressed, some missense TD mutants of TP53 can form homotetramers and heterotetramers with the wild type TP53 which are partially functional and some extent of AS, DN and GOF effects may not be excluded for those mutants (Atz et al. 2000, reviewed in Chène 2001). In addition, the synthetic mutant p153(1-320) which consists of the

first 320 amino acids and lacks the TD and CTD, while unable to tetramerize, can form stacked oligomers at the recombinant target gene promoter and induce transcription at a low level. Stacked oligomers are formed through interactions that involve amino acid residues outside the TD, which are facilitated by the presence of a target DNA sequence (Stenger et al. 1994).

Literature references

Chène, P., Bechter, E. (1999). p53 mutants without a functional tetramerisation domain are not oncogenic. *J Mol Biol, 286*, 1269-74. ↗

Monti, P., Menichini, P., Speciale, A., Cutrona, G., Fais, F., Taiana, E. et al. (2020). Heterogeneity of TP53 Mutations and P53 Protein Residual Function in Cancer: Does It Matter?. *Front Oncol, 10*, 593383. ↗

Atz, J., Wagner, P., Roemer, K. (2000). Function, oligomerization, and conformation of tumor-associated p53 proteins with mutated C-terminus. *J Cell Biochem, 76*, 572-84. ↗

Gencel-Augusto, J., Lozano, G. (2020). p53 tetramerization: at the center of the dominant-negative effect of mutant p53. *Genes Dev, 34*, 1128-1146. ↗

Chène, P. (2001). The role of tetramerization in p53 function. *Oncogene, 20*, 2611-7. ↗

Editions

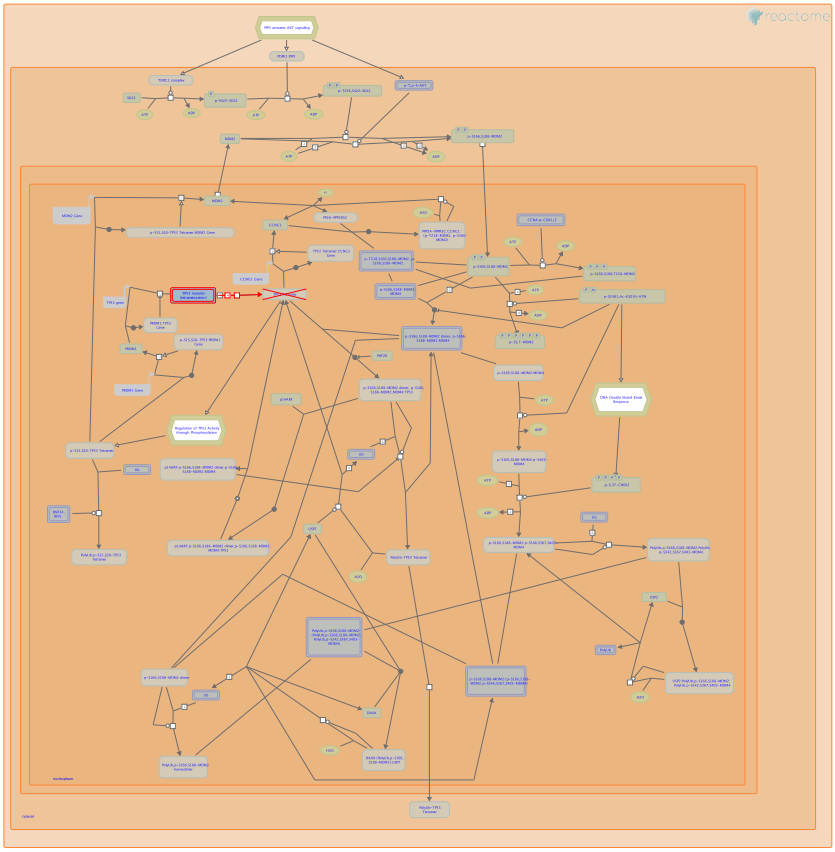
2021-04-07	Authored	Orlic-Milacic, M.
2021-04-30	Reviewed	Sakaguchi, K.
2021-05-03	Edited	Orlic-Milacic, M.

Loss of function of TP53 in cancer due to loss of tetramerization ability ↗

Location: Loss of Function of TP53 in Cancer

Stable identifier: R-HSA-9723905

Diseases: cancer



The physiologically active form of TP53 is homotetramer, which represents a dimer of dimers (Lee et al. 1994, Clore et al. 1994, Jeffrey et al. 1995), with the dimer considered to represent a transient intermediate (Mateau et al. 1998, Mateau et al. 1999, Natan et al. 2009). The tetramerization domain (TD) of TP53 localizes to the C-terminal region and involves amino acid residues 325-355 and is connected to the DNA binding domain (DBD) via a short unstructured region (reviewed in Wang et al 1993). The destabilizing effects of some of the DBD mutations in TP53 can only be observed in the context of the TP53 tetramer, but not in monomeric TP53 (Lubin et al. 2010). A number of nonsense and frameshift truncations result in mutant TP53 proteins that lack the tetramerization domain. In addition, several missense mutations affect the tetramerization domain, some of which, like R342P and L344P, have been shown to impede tetramerization (Chène and Bechter 1999; Lubin et al. 2010). Oligomerization-defective TP53 TD mutants are considered to be complete loss-of-function mutants in terms of their transcriptional activity, without altered specificity, dominant-negative or gain-of-function effects (Chène and Bechter 1999, reviewed in Chène 2001). However, when overexpressed, some missense TD mutants of TP53 can form homotetramers and heterotetramers with the wild type TP53 which are partially functional and some extent of AS, DN and GOF effects may not be excluded for those mutants (Atz et al. 2000, reviewed in Chène 2001). In addition, the synthetic mutant p153(1-320) which consists of the first 320 amino acids and lacks the TD and the C-terminal domain (CTD), while unable to tetramerize, can form stacked oligomers at the recombinant target gene promoter and induce transcription at a low level. Stacked oligomers are formed through interactions that involve amino acid residues outside the TD, which are facilitated by the presence of a target DNA sequence (Stenger et al. 1994). Recombinant TP53 that consists of amino acid residues 83-323 also predominantly exists as a monomer (reviewed in Wang et al. 1994).

Literature references

Lubin, DJ., Butler, JS., Loh, SN. (2010). Folding of tetrameric p53: oligomerization and tumorigenic mutations induce misfolding and loss of function. *J Mol Biol, 395*, 705-16. ↗

Chène, P., Bechter, E. (1999). p53 mutants without a functional tetramerisation domain are not oncogenic. *J Mol Biol, 286*, 1269-74. ↗

Chène, P. (2001). The role of tetramerization in p53 function. *Oncogene, 20*, 2611-7. ↗

Atz, J., Wagner, P., Roemer, K. (2000). Function, oligomerization, and conformation of tumor-associated p53 proteins with mutated C-terminus. *J Cell Biochem, 76*, 572-84. ↗

Stenger, JE., Tegtmeyer, P., Mayr, GA., Reed, M., Wang, Y., Wang, P. et al. (1994). p53 oligomerization and DNA looping are linked with transcriptional activation. *EMBO J., 13*, 6011-20. ↗

Editions

2021-04-07	Authored	Orlic-Milacic, M.
2021-04-30	Reviewed	Sakaguchi, K.
2021-05-03	Edited	Orlic-Milacic, M.

Table of Contents