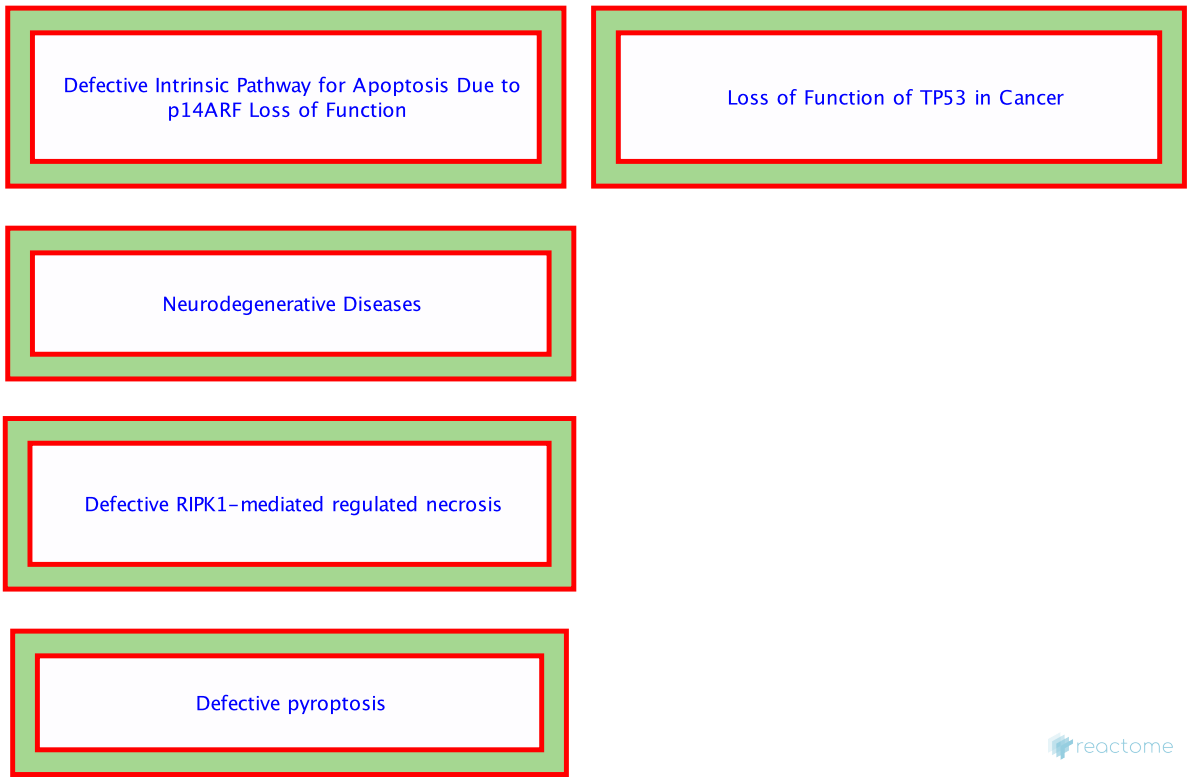
Diseases of programmed cell death



Bennett, DC., D'Eustachio, P., Kanneganti, TD., Lalaoui, N., Orlic-Milacic, M., Rizos, H., Sakaguchi, K., Shamovsky, V., Shao, F., Shorser, S., Zhang, Z.

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13/09/2021

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.

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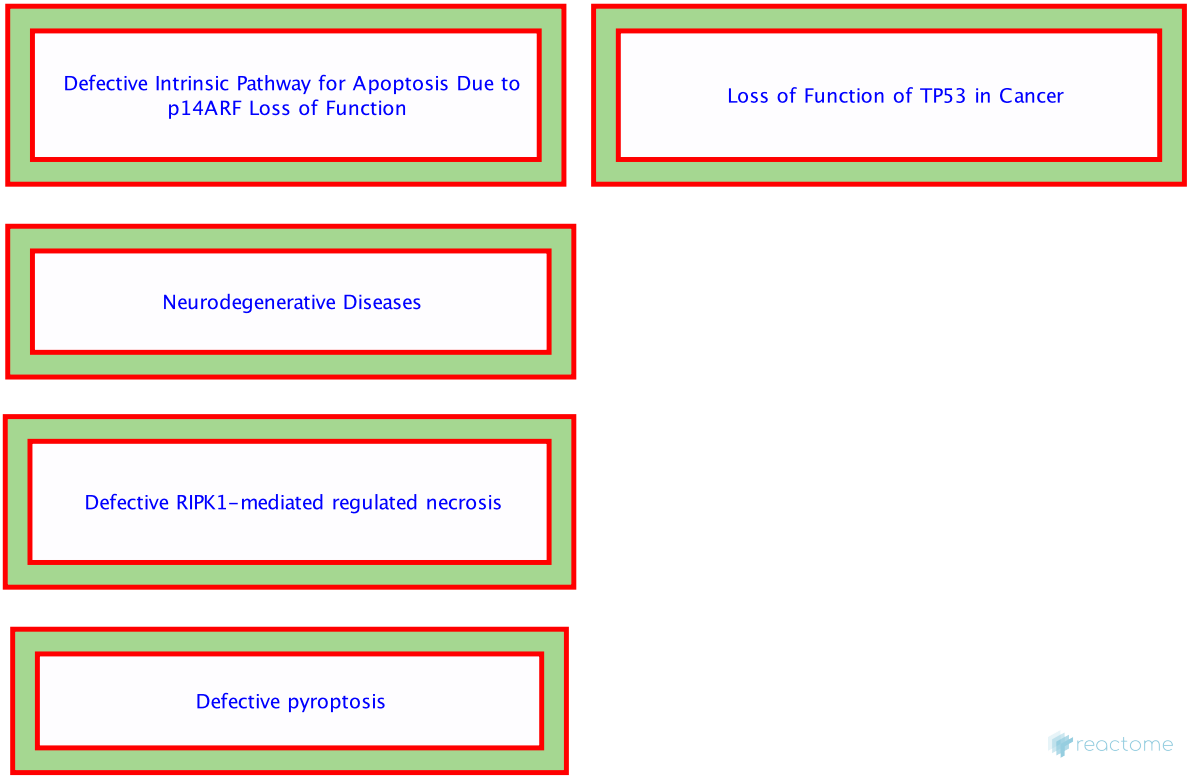
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Diseases of programmed cell death

Stable identifier: R-HSA-9645723

Diseases: neurodegenerative disease, cancer



Programmed cell death is frequently impaired in cancer and is thought to significantly contribute to resistance to chemotherapy. Mutations and perturbations in expression of different proteins involved in programmed cell death, such as TP53 (p53), BH3-only family proteins, caspases and their regulators enable malignant cells to evade apoptosis (Ghavami et al. 2009, Chao et al. 2011, Wong 2011, Fernald and Kurokawa 2013, Ichim and Tait 2016).

Literature references

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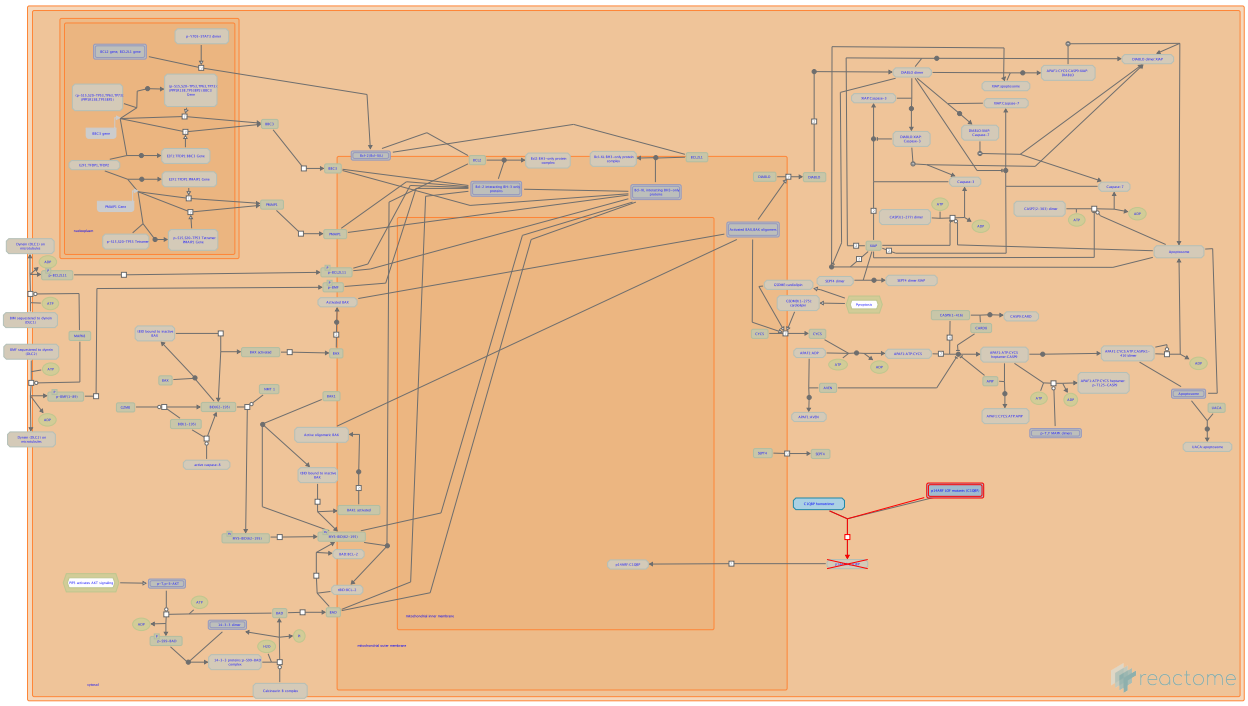
Defective Intrinsic Pathway for Apoptosis Due to p14ARF Loss of Function ↗

Location: Diseases of programmed cell death

Stable identifier: R-HSA-9645722

Diseases: cancer



Cancer-derived missense mutations in the CDKN2A gene that affect the C-terminal arginine-rich region of p14ARF (also known as CDKN2A transcription isoform 4, CDKN2A-4, p14 or ARF) impair p14ARF binding to the mitochondrial matrix protein C1QBP and interfere with p53-mediated apoptosis. Many mutations in the CDKN2A locus that affect C-terminal arginines of p14ARF are silent in p16INK4A (CDKN2A-1) (Itahana and Zhang 2008).

Literature references

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Editions

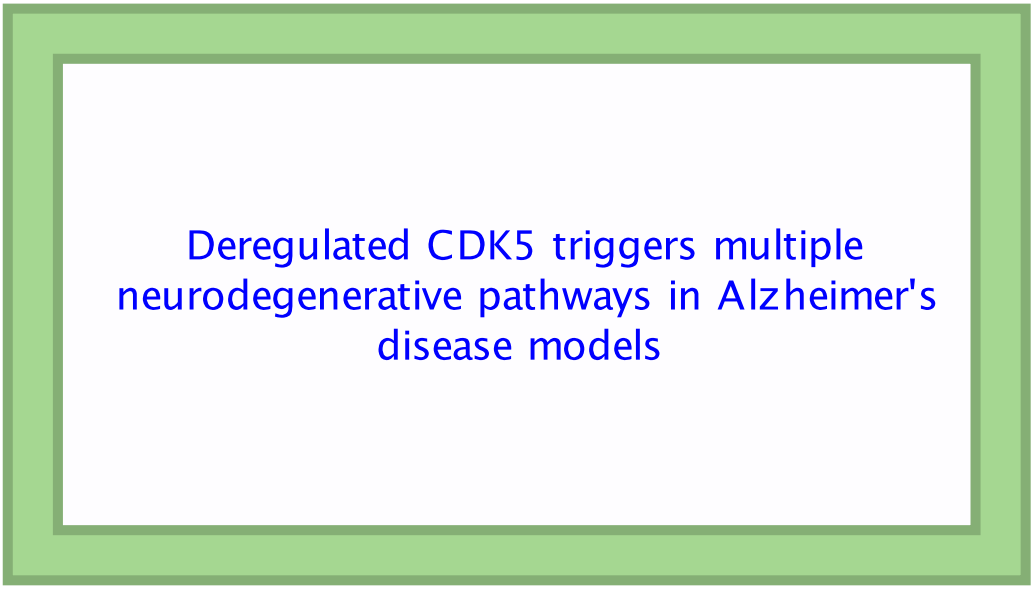
2019-06-28	Authored	Orlic-Milacic, M.
2019-07-08	Reviewed	Rizos, H.
2019-07-16	Edited	Orlic-Milacic, M.
2019-08-12	Reviewed	Bennett, DC.

Neurodegenerative Diseases ↗

Location: Diseases of programmed cell death

Stable identifier: R-HSA-8863678

Diseases: neurodegenerative disease



Neurodegenerative diseases manifest as the progressive dysfunction and loss of neurons, which is frequently accompanied by formation of misfolded protein deposits in the brain. Classification of neurodegenerative diseases is based on clinical symptoms, which depend on the anatomical region affected by neuronal dysfunction, the identity of misfolded proteins and cellular and subcellular pathology.

In Alzheimer's disease (AD), beta-amyloid protein (APP) deposits form in the extracellular space, where they can make plaques, while abnormally phosphorylated tau protein (MAPT) accumulates in neuronal cells.

Beside AD, neuronal and/or glial inclusions of hyperphosphorylated tau are also found in Pick disease (PiD), neurofibrillary tangle-dementia (NFT), primary age-related tauopathy (PART), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease (AGD) and globular glial tauopathies (GGT).

In prion disease, such as Creutzfeldt-Jakob disease, deposits of PrP protein are formed mostly in the extracellular and presynaptic space. PrP deposits in neuronal cell bodies are mainly confined to endosomes and lysosomes, which is attributed to neuronal uptake of pathological proteins and intercellular prion spreading.

In Parkinson disease (PD) and dementia with Lewy bodies (DLB), deposits of alpha-synuclein (SNCA) are formed in the cytoplasm of neuronal cell bodies and neurites. In multiple system atrophy (MSA), deposits of alpha-synuclein form in the cytoplasm of glial cells (Papp-Lantos bodies).

Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) are characterized by ubiquitin-positive cytoplasmic inclusions of TAR DNA-binding protein 43 (TARDBP, commonly known as TDP-43), a protein that normally localizes to the nucleus. Pathological TDP-43 inclusions have been associated with the TDP-43 gene mutations, as well as mutations in several other genes, including C9orf72, GRN, VCP, SQSTM1, DCTN1 and OPTN. TDP-43 inclusions have also been reported in AD, DLB, hippocampal sclerosis (HS) and chronic traumatic encephalopathy.

FUS protein-positive inclusion bodies are found in familial ALS, caused by mutations in the FUS gene, as well as in a small subgroup of FTLD-related diseases. FUS-positive inclusions may be accompanied by FET protein-positive inclusions.

For a detailed review of molecular pathology of neurodegenerative diseases, please refer to Kovacs 2016.

Within this broad domain, the process by which APP-triggered deregulation of CDK5 (cyclin-dependent kinase 5) triggers multiple neurodegenerative pathways associated with Alzheimer's disease has been annotated.

Literature references

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Editions

2016-08-18	Reviewed	D'Eustachio, P.
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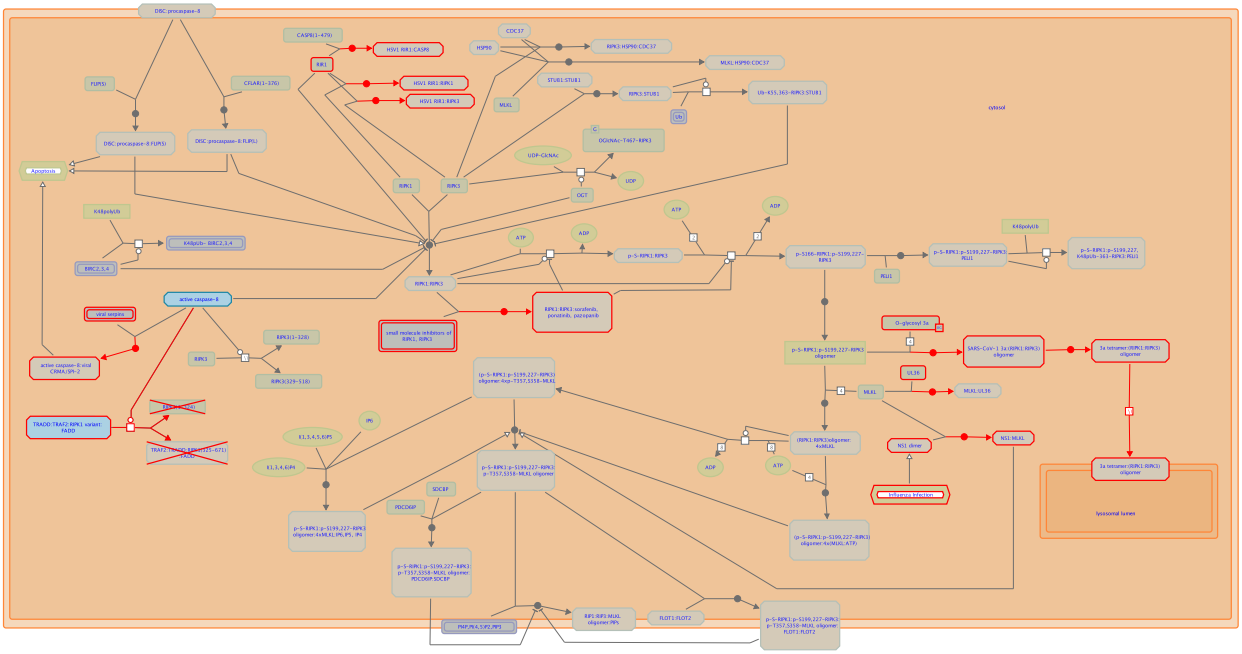
Defective RIPK1-mediated regulated necrosis ↗

Location: Diseases of programmed cell death

Stable identifier: R-HSA-9693928

Diseases: genetic disease



Receptor Interacting Serine/Threonine Kinase 1 (RIPK1)-mediated regulated necrosis also called necroptosis is an important type of programmed cell death in addition to apoptosis. Necroptosis eventually leads to cell lysis and release of cytoplasmic content into the extracellular region. Necroptosis must be tightly controlled. Disregulated or defective necroptotic cell death is often associated with a tissue damage resulting in an intense inflammatory response. Defects of necroptosis may contribute to various pathological processes, including autoimmune disease, neurodegeneration, multiple cancers, and kidney injury.

Literature references

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Editions

2020-06-26	Reviewed	D'Eustachio, P.
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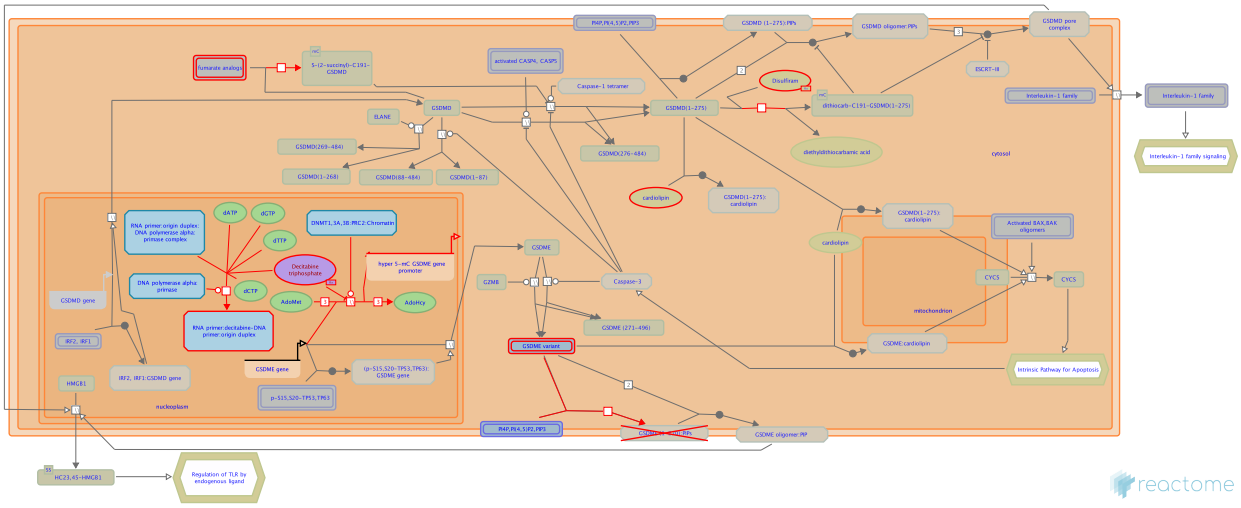
Defective pyroptosis ↗

Location: Diseases of programmed cell death

Stable identifier: R-HSA-9710421

Diseases: cancer, breast carcinoma, colon adenocarcinoma, gastric adenocarcinoma, head and neck squamous cell carcinoma, lung adenocarcinoma, melanoma



Pyroptosis is a form of lytic inflammatory programmed cell death that is mediated by the pore‐forming gasdermins (GSDMs) (Shi J et al. 2017) to stimulate immune responses through the release of pro‐inflammatory interleukin (IL)‐1β, IL‐18 (mainly in GSDMD-mediated pyroptosis) as well as danger signals such as adenosine triphosphate (ATP) or high mobility group protein B1 (HMGB1) (reviewed in Shi J et al. 2017; Man SM et al. 2017; Tang D et al. 2019; Lieberman J et al. 2019). Pyroptosis protects the host from microbial infection but can also lead to pathological inflammation if overactivated or dysregulated (reviewed in Orning P et al. 2019; Tang L et al. 2020). During infections, the excessive production of cytokines can lead to a cytokine storm, which is associated with acute respiratory distress syndrome (ARDS) and systemic inflammatory response syndrome (SIRS) (reviewed in Tisoncik JR et al. 2012; Karki R et al. 2020; Ragab D et al. 2020). Pyroptosis has a close but complicated relationship to tumorigenesis, affected by tissue type and genetic background. Pyroptosis can trigger potent antitumor immune responses or serve as an effector mechanism in antitumor immunity (Wang Q et al. 2020; Zhou Z et al. 2020; Zhang Z et al. 2020), while in other cases, as a type of proinflammatory death, pyroptosis can contribute to the formation of a microenvironment suitable for tumor cell growth (reviewed in Xia X et al. 2019; Jiang M et al. 2020; Zhang Z et al. 2021).

This Reactome module describes the defective GSDME function caused by cancer‐related GSDME mutations (Zhang Z et al. 2020). It also shows epigenetic inactivation of GSDME due to hypermethylation of the GSDME promoter region (Akino K et al. 2007; Kim MS et al. 2008a,b; Croes L et al. 2017, 2018; Ibrahim J et al. 2019). Aberrant promoter methylation is considered to be a hallmark of cancer (Ehrlich M et al. 2002; Dong Y et al. 2014; Lam K et al. 2016; Croes L et al. 2018). Treatment with the DNA methyltransferase inhibitor decitabine (5‐aza‐2'‐deoxycytidine or DAC) may elevate GSDME expression in certain cancer cells (Akino K et al. 2007; Fujikane T et al. 2009; Wang Y et al. 2017).

Literature references

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Editions

2020-11-09	Authored	Shamovsky, V.
2021-02-17	Reviewed	D'Eustachio, P., Kanneganti, TD.
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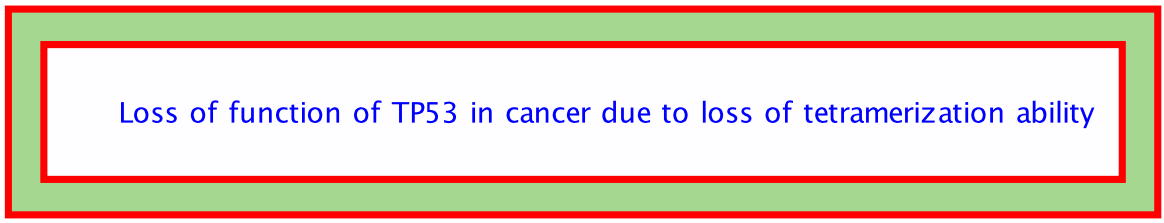
2021-04-22	Reviewed	Shao, F.

Loss of Function of TP53 in Cancer ↗

Location: Diseases of programmed cell death

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

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Editions

2021-04-07	Authored	Orlic-Milacic, M.
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