Diseases of programmed cell death

Defective Intrinsic Pathway for Apoptosis Due to p14ARF Loss of Function

Neurodegenerative Diseases

Defective RIPK1-mediated regulated necrosis

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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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Literature references


Reactome database release: 75

This document contains 4 pathways (see Table of Contents)

https://reactome.org
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**


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


Editions

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Neurodegenerative Diseases

**Location:** Diseases of programmed cell death

**Stable identifier:** R-HSA-8863678

**Diseases:** neurodegenerative disease

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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**


**Editions**

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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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