Diseases of programmed cell death

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

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https://reactome.org
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: 82

This document contains 4 pathways (see Table of Contents)
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**


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**

Defective pyroptosis

Location: Diseases of programmed cell death

Stable identifier: R-HSA-9710421

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

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, IL18 (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 (5aza2'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


**Editions**

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Defective Intrinsic Pathway for Apoptosis

Location: Diseases of programmed cell death

Stable identifier: R-HSA-9734009

Diseases: neurodegenerative disease, cancer

Defects in the regulation of the intrinsic pathway for apoptosis are involved in diseases associated with increased cell loss, such as neurodegenerative diseases, as well as in diseases associated with impaired elimination of harmful cells, such as cancer and autoimmunity. For review, please refer to Reed 2001, Lavrik et al. 2009, and Tuzlak et al. 2016.

So far, Reactome has annotated apoptosis defects associated with the loss of function of the CDKN2A gene product p14ARF in cancer, loss of function of TP53 in cancer, and CDK5 dysregulation in neurodegenerative diseases.

Literature references


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