Defective pyroptosis

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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.

30/10/2022
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 1 pathway and 3 reactions (see Table of Contents)
Defective pyroptosis

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)β1β, ILβ18 (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’dC) 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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The GSDME gene promoter is hypermethylated

**Location:** Defective pyroptosis

**Stable identifier:** R-HSA-9710490

**Type:** omitted

**Compartments:** nucleoplasm

**Diseases:** colon cancer, melanoma, cancer, breast cancer

5-Methylation of cytosine residues in DNA is a heritable epigenetic mark that regulates gene expression. DNA methyltransferases (DNA MTase, (DNMTs)) catalyze the transfer of the CH3 group from Sadenosylmethionine (AdoMet) to DNA (Melanie E & Lacey M 2014; Laisne M et al. 2018). DNMTs associate with EZH2 of the Polycomb Repressive Complex 2 (PRC2) (Vire et al. 2006). 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). Epigenetic inactivation of GSDME due to hypermethylation of the GSDME promoter region has been linked to tumorigenesis (Akino K et al. 2007; Kim MS et al. 2008a,b; Croes L et al. 2017, 2018; Ibrahim J et al. 2019). Treatment with the DNA methyltransferase inhibitors such as FDAapproved 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**


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**Decitabine triphosphate incorporates into DNA**

**Location:** Defective pyroptosis

**Stable identifier:** R-HSA-9710480

**Type:** transition

**Compartments:** nucleoplasm

Cellular uptake of decitabine or 5-aza-2′-deoxycytidine is mediated by the equilibrative nucleoside transporters hENT1, hENT2, and hENT3, which also mediate cytosine uptake. Decitabine is a prodrug that has to be converted into a nucleoside triphosphate to become an active drug (reviewed in Raynal NJM & Issa JPJ 2016). The activation of the prodrug relies on three successive phosphorylation steps. The first phosphorylation is catalyzed by the deoxycytidine kinase (DCK) to produce the monophosphorylated form of decitabine or 5-aza-2′deoxycytidine-5′monophosphate (5-aza-2′dCMP). Subsequently, two additional phosphorylation reactions catalyzed by the deoxycytidine-5′monophosphate (dCMP) kinase and the nucleoside diphosphokinase will produce 5-aza-2′deoxycytidine-5′diphosphate (5-aza-2′dCDP) and 5-aza-2′deoxycytidine-5′triphosphate (5-aza-2′dCTP), respectively. Once in its triphosphate form, the active drug can be incorporated into the DNA of dividing cells by DNA polymerase, in the reaction annotated here. DNA polymerase has similar affinities for dCTP and 5-aza-2′dCTP (Raynal NJM & Issa JPJ 2016).

**Literature references**

GSDME variant does not bind PIPs

Location: Defective pyroptosis

Stable identifier: R-HSA-9710468

Type: transition

Compartments: plasma membrane, cytosol

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