CASP3 cleaves GSDME

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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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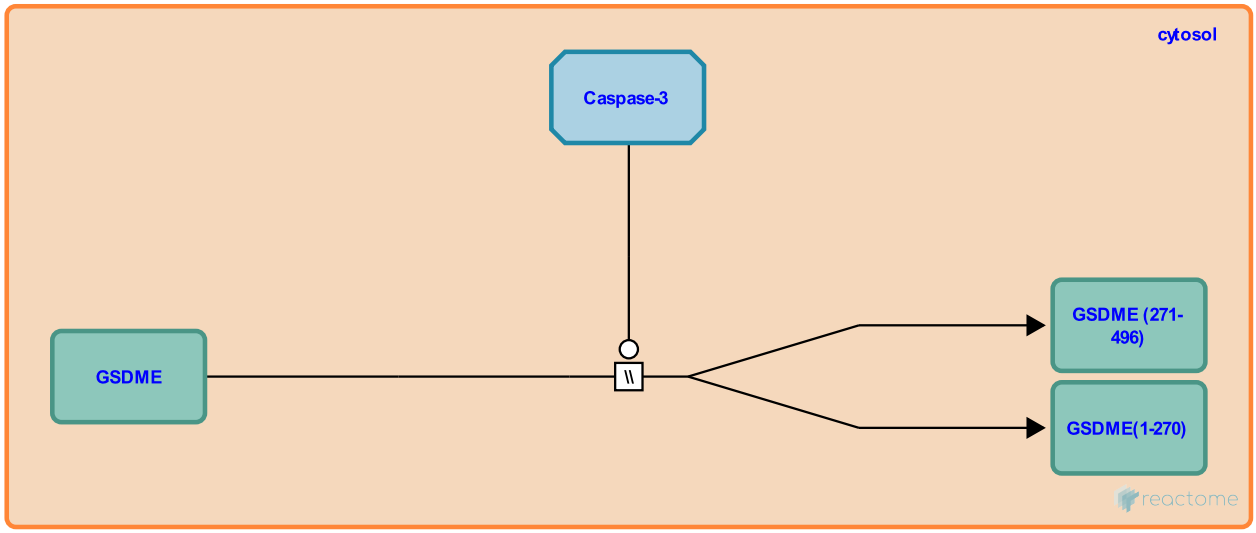
Stable identifier: R-HSA-9647632

Type: omitted

Compartments: cytosol



Gasdermin E (GSDME, also known as DFNA5) was identified as a substrate of activated caspase-3 (CASP3), the executioner caspase of apoptotic cell death (Wang Y et al. 2017; Rogers C et al. 2017). GSDME can switch TNF- or chemotherapy drug-induced CASP3-mediated apoptosis to secondary necrosis/pyroptosis (Wang Y et al. 2017; Rogers C et al. 2017; Zhang CC et al. 2019; Zhang J et al. 2020; Zhang Z et al. 2020; reviewed in Jiang M et al. 2020). The expression level of GSDME determines the type of cell death (Wang Y et al. 2017). CASP3-mediated cleavage of GSDME drives pyroptosis in GSDME-expressing cells, including normal and certain types of cancer cells, while cells lacking sufficient levels of GSDME undergo apoptosis without progression into pyroptosis or secondary necrosis (Wang Y et al. 2017; reviewed in Jiang M et al. 2020). CASP3 cleaves GSDME in the linker after Asp270, generating the GSDME N-terminal fragment GSDME(1-270) that disrupts cell membranes and induces secondary necrotic/pyroptotic cell death (Wang Y et al. 2017; Rogers C et al. 2017). GSDME D267A and GSDME D270A mutations resisted cleavage in TNF-stimulated HeLa cells and showed no death-switching activity (Wang Y et al. 2017). The processing of GSDME was inhibited by the specific CASP3 inhibitor (zDEVD) in GSDME-expressing human neuroblastoma SH-SY5Y (Zhang J et al. 2020) and colon cancer HT-29 and HCT116 cells (Yu J et al. 2019) upon treatment with a chemotherapeutic drug. Similarly, a specific CASP3 inhibitor and a pan-caspase inhibitor (zVAD) suppressed drug-induced GSDME(1-270) generation and reduced pyroptosis in human lung cancer A549 cells (Zhang CC et al. 2019; Zhang J et al. 2020). In addition, GSDME(1-270) was shown to permeabilize the mitochondrial membrane, releasing cytochrome c and activating the apoptosome in GSDME-expressing human embryonic kidney (HEK293) cells (Rogers C et al. 2019). The release of cytochrome c and CASP3 activation in response to apoptotic stimuli were significantly reduced in GSDME-deficient human T-lymphoblastic (CEM-C7) cells (Rogers C et al. 2019). Moreover, GSDME deficiency accelerated cell growth in human melanoma cell line (MeWo) and in mouse models of melanoma, colon (CT26) and breast (EMT6) tumors (Lage H et al. 2001; Zhang Z et al. 2020). Gsdme-/- mice were protected from chemotherapy-induced tissue damage (Wang Y et al. 2017). These data suggest that GSDME may have cytotoxic effects in tumor cells by triggering pyroptotic cell death. GSDME-induced pyroptosis was shown to suppress tumor growth by increasing anti-tumor functions of tumor-infiltrating NK and CD8+ T killer lymphocytes (Zhang Z et al. 2020). Cancer-related GSDME mutations significantly reduced lactate dehydrogenase (LDH) release, a hallmark of lytic cell death (Zhang Z et al. 2020). The tumor suppressor role of GSDME is further supported by studies showing reduced expression of GSDME due to increased methylation of the GSDME gene promoter in primary gastric tumors, colorectal adenocarcinomas and breast

tumors (Akino K et al. 2006; Kim MS et al. 2008; Yokomizo K et al. 2012; Croes L et al. 2017; Ibrahim J et al. 2019). GSDME-deficient tumors are associated with reduced survival in patients (reviewed in Xia X et al. 2019). Thus, CASP3 can induce pyroptosis and apoptosis in a manner that is dependent on the expression level of GSDME. GSDME was dispensable for the regulation of pyroptosis in human Jurkat T cells and THP-1 monocytes (Tixeira R et al. 2018). In line with this study, GSDME was not required for pyroptosis in mouse Casp1-and Casp11-deficient bone marrow-derived macrophages (BMDMs) treated with flagellin, cytochrome c or Fas ligand (Lee BL et al. 2018). Together, these findings suggest that factors in addition to the ones annotated here play a role in connecting apoptosis and pyroptosis, which has been shown in the context of PANoptosis (Karki R et al. 2021).

This Reactome event shows CASP3-mediated cleavage of GSDME at D270.

Literature references

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Editions

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