GASDERMIN AND ITS ROLE IN PYROPTOSIS

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The gasdermin family (GSDMs) contains a group of uncharacterized proteins that form membrane pores and serve as a major substrate for inflammatory caspases and the execution of pyroptosis, which is recognized as a novel type of programmed cell death [1]. Gasdermin (GSDM) family consists of Gasdermin A (GSDMA), Gasdermin B (GSDMB), Gasdermin C (GSDMC), Gasdermin D (GSDMD), Gasdermin E (GSDME) and Pejvakin (PJVK). With the exception of PJVK, all GSDMs consist of two conserved domains: the C-terminal inhibitory domain (RD) and the N-terminal effector domain (PFD), where the N-terminal domain is cytotoxic, while the full-length structure is not cytotoxic, indicating that the C-terminus of the GSDMs protein family (GSDMs-C) has auto-inhibitory and protective effects [2]. Because of the presence of the C-terminus, the GSDM protein does not cause cell death if it is not cleaved. Once RD is removed by hydrolysis, its PFD can combine with lipid components to form pores in the cell membrane [3]. Current studies have found that, except for PJVK, the N-terminal domains of almost all GSDMs have the ability to form pores in the plasma membrane. Among GSDMs, only the mechanism of GSDMD-induced pyroptosis is relatively clear.

The human genome encodes a single GSDMA, while the mouse genome encodes GSDMA, GSDMA2, and GSDMA3. Mice do not carry the gene for GSDMB. Humans have a single copy of the gene encoding GSDMC, while the mouse genome has four copies; both humans and mice have genes encoding GSDMD, GSDME, and PJVK.

The study found that the expression of GSDMA3 can up-regulate the expression of caspase-3, which means that GSDMA3 may induce apoptosis. In human embryonic kidney cells 293 cells and in mouse GSDMA3 carrying the same mutation, cell death can also be induced by autophagy, and GSDMA3 may also play a role in pyroptosis. However, the GSDMA protease that cleaves human or mouse has not been identified, and the mechanism of GSDMA3 pore formation in the plasma membrane is unclear [4]. GSDMB was previously known as GSDML
Gasdermin (gasdermin-like protein) and is found on chromosome 17q21. There are 411 amino acids in the GSDMB protein. GSDMB's preference for plasma membrane binding differs from that of other GSDMs. Both the full-length GSDMB and N-terminal domains bind to phosphatidylinositol 4, 5-diphosphate and glucolipid glucosinolate [5]. Recent studies have shown that GSDMB promotes caspase-4 activity by directly binding to the CARD domain of Caspase-4, which may uncover a novel GSDMB-mediated regulatory mechanism of non-classical induction pathway of cell pyroptosis and suggest a potential new strategy for the treatment of inflammatory diseases [6]. Little is known about the function of GSDMC. Studies have found that GSDMC is not expressed in normal epithelial cells, but the expression of GSDMC is increased in malignant melanoma and inhibited in esophageal cancer and gastric cancer. However, no studies have found that Gasdermin C plays a role in human and mouse diseases [7].

Gasdermin D (GSDMD), a caspase-1 substrate, has been identified as a key pyroptosis mediator [8]. Caspase-1 proteolytically activates GSDMD, which then creates pores in the plasma membrane, resulting in pyroptosis [9]. GSDMD is a cytoplasmic protein with a pore-forming domain on the N-terminus, a regulatory domain on the C-terminus, and a central linker region. In full-length GSDMD, the C-terminal domain inhibits the N-terminal domain's pore-forming function. The N-terminal domain of GSDMD is separated from the C-terminal domain by caspase-1 cleavage at the linker region. The N-terminal portion (GSDMD p30) binds to phosphatidylinositol phosphates, phosphatidic acid, and PS on the inner leaflet of the plasma membrane. The conformational alterations in GSDMD p30 molecules favor oligomerization and membrane insertion, resulting in transmembrane-barrel holes with an inner diameter of 10–15 nm [10]. Because both processed and unprocessed forms of active caspase-1 cleave GSDMD to produce GSDMD p30, both forms of active caspase-1 may cause pyroptosis [11]. Caspases-4, -5, and -11, in addition to caspase-1, cause pyroptosis by digesting GSDMD at the same location as caspase-1 in the presence of LPS [12]. In addition, caspase-8, neutrophil elastase (NE), and cathepsin G have been implicated in the proteolytic activation of GSDMD [13].

Lu et al. found that GSDME was expressed in a variety of lung cancer cell lines, and coke death and apoptosis were also found in lung cancer cells, proving that GSDME is closely related to coke death and apoptosis, and may be converted to each other under specific circumstances [14]. At the same time, Wang et al. found that the loss of caspase-3 function did not prevent cell apoptosis induced by caspase-7 activation, and also found that caspase-3 could also induce cell apoptosis by shearing GSDME, revealing GSDME for the first time Caspase-3-dependent apoptosis was transformed into pyroapoptosis in gastric cancer cells induced by chemotherapy drugs [15]. The role of gasdermins in pyroptosis is a fascinating new discovery. The discovery of six proteins with the ability to generate membrane pores and trigger lysis opens up a vast field of research. Caspase-1 can be activated by at least five inflammasomes, causing pyroptosis via gasdermin D. Gasdermin D is likewise cleaved by caspase-11/4/5, resulting in pyroptosis.

Reference: