Programmed cell death: The roles of caspase-1 and gasdermin D in apoptosis and pyroptosis
5 July 2019

Recently, it has been demonstrated that activated caspase-1 induces pyroptosis, inflammatory and necrosis-like programmed cell death, although it was previously thought to induce apoptosis. It was not known why caspase-1 induces two different modes of programmed cell death with distinctive characteristics depending on the biological context. Credit: Kanazawa University

Most unnecessary or dangerous cells, such as virus-infected cells, commit suicide by activating an in-built suicide program called apoptosis. This type of cell death is referred to as "programmed cell death." Until about year 2000, apoptosis was believed to be the sole mode of programmed cell death, at least in mammals. However, in recent years, various modes of "non-apoptotic" programmed cell death, called pyroptosis and necroptosis, have been defined based on the molecular mechanisms and morphological characteristics.

In the process of apoptosis, the group of proteases called caspases, about 10 species of which are found in humans, function as suicide enzymes. Caspase-1, the first caspase found in mammals, has been reported to induce apoptosis in neurons in animal models of neurological disorders such as cerebral infarction, Alzheimer's disease and amyotrophic lateral sclerosis (ALS). However, subsequent studies revealed that in macrophages infected by bacteria, caspase-1 induces necrosis-like and inflammatory programmed cell death, which was thereafter named pyroptosis. Thus, caspase-1 has been reported to induce apoptosis or pyroptosis depending on the biological context (Figure 1). The reason for this apparent discrepancy has not been clarified.

Caspase-1 triggers programmed necrosis called pyroptosis by gasdermin-D (GSDMD) cleavage. GSDMD-deficient cells are, however, susceptible to caspase-1-mediated cell death. Researchers at Kanazawa University and others discovered that caspase-1 proteolytically activates Bid and initiates apoptosis in GSDMD-deficient cells. Furthermore, cortical neurons and mast cells, exhibiting little GSDMD expression, undergo apoptosis after appropriate stimulation in a caspase-1- and Bid-dependent manner. This study clarifies molecular mechanisms and biological roles of caspase-1-induced apoptosis in GSDMD-low/null cells.

Recently, it was revealed that pyroptosis is induced by proteolysis of a protein called gasdermin D (GSDMD) by caspase-1. Nonetheless, macrophages whose GSDMD gene was destroyed exhibited cell death upon activation of caspase-1, although more slowly than wild-type macrophages. Therefore, it seemed that there should be a mechanism of caspase-1-mediated cell death independent of GSDMD. However, the form and molecular mechanism of such cell death remained unknown.
The present research team led by scientists of Kanazawa University together with scientists from Hokkaido University, the University of Tokyo and National Institute of Genetics, Japan, investigated the caspase-1-mediated programmed cell death of macrophages. First, they found that GMDSD-deficient macrophages underwent apoptosis when they were infected with *Salmonella*, although wild-type macrophages underwent pyroptosis under the same conditions. Since caspase-1-deficient macrophages exhibited little cell death under the same conditions, it was clear that both modes of programmed cell death, pyroptosis and apoptosis, were mediated by caspase-1.

Caspase-1 induces pyroptosis in those cells that express gasdermin D such as macrophages. On the other hand, in the case of those cells like neurons that do not express gasdermin D, it induces apoptosis though Bid activation. Credit: Kanazawa University

Next, the team investigated caspase family members required for caspase-1-mediated apoptosis in GSDMD-deficient cells. As a result, caspase-3 and caspase-9 were found to be involved; caspase-3 is known to be necessary for induction of a broad spectrum of apoptosis, while caspase-9 is activated in response to cytochrome c release from mitochondria. Then, Bid, a pro-apoptotic cytoplasmic protein, emerged as a candidate for a mediator of caspase-1-induced apoptosis for the following reasons: Bid is a well-known substrate of caspase-8, and its cleaved product, tBid, induces cytochrome c release from mitochondria and subsequent caspase-9 activation. Furthermore, it has been reported that Bid can also be cleaved by caspase-1. Thus, the team generated GSDMD/Bid double deficient cells; on activation of caspase-1, it was found that apoptosis was suppressed in these cells compared to the GSDMD-deficient cells. Furthermore, GSDMD/Bid double deficient macrophages were found to be more resistant to *Salmonella* infection than GSDMD deficient macrophages. These results indicated that in GSDMD-deficient cells, caspase-1 activated Bid instead, which induced apoptosis.

In previous studies, caspase-1 was reported to be involved in the apoptosis of spinal cord neurons in mouse models of familial amyotrophic lateral sclerosis and of cortical neurons after oxygen/glucose deprivation. It was also demonstrated that such apoptosis was accompanied by Bid cleavage (activation) in a caspase-1-dependent manner. However, it was not clear whether Bid was necessary for the programmed death of those neurons or whether cortical and spinal cord neurons expressed GSDMD. Thus, the team investigated the expression of GSDMD mRNA and protein in the cerebral cortex and the spinal cord, and found that little GSDMD is expressed in these tissues. Moreover, cultured cortical neurons from caspase-1-deficient mice and those from Bid-deficient mice under oxygen/glucose deprivation were less susceptible to apoptosis in comparison with wild-type neurons. In addition, by consulting BioGPS (http://biogps.org/, a public database of protein expression), mast cells, a kind of immune cell, were found to express caspase-1 and Bid, but little GSDMD. Accordingly, when mast cells were stimulated by nigericin, a bacterial toxin, which is known to induce pyroptosis in macrophages, mast cells exhibited caspase-1- and Bid-dependent apoptosis.

The results of the present study revealed that apoptosis was induced even with neurons and mast cells that express little GSDMD by activation of Bid through caspase-1 action.
Caspase-1 is expressed in various cell-types and tissues besides macrophages and neurons, and has been suggested to be involved in myocardial infarction and renal disorders in addition to neurodegenerative diseases. It is necessary to elucidate whether in these cases, caspase-1-dependent cell death is GSDMD-dependent pyroptosis or Bid-dependent apoptosis or even due to other programmed cell death mechanisms.

In the future, by developing selective inhibitors for individual modes of programmed cell death in specific cells based on their underlying mechanisms, improvements may be expected in the prevention and treatment of diseases caused by programmed cell death.


Provided by Kanazawa University

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