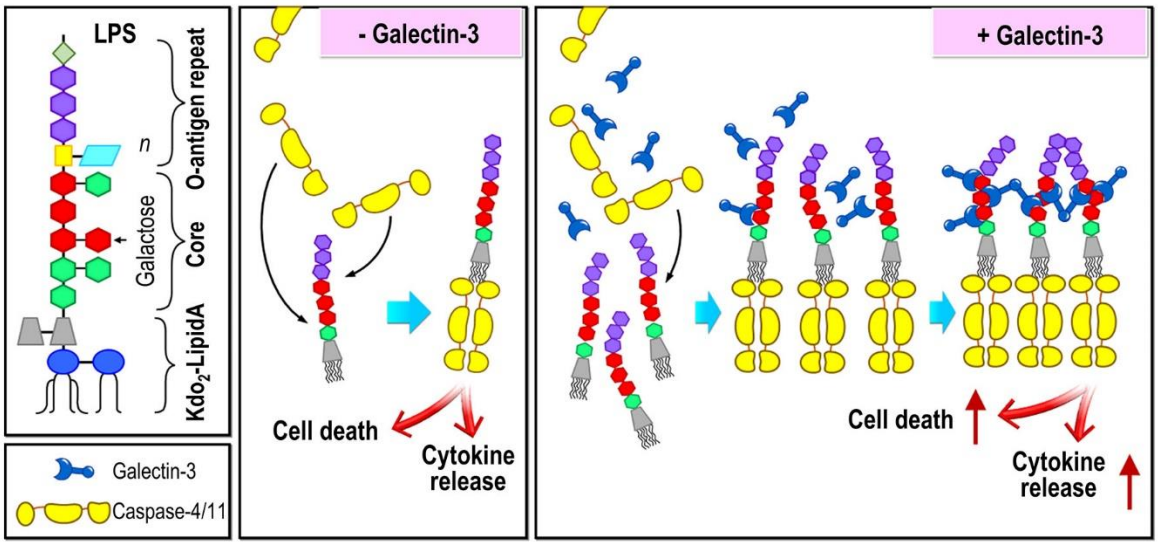
A critical molecule for regulating inflammatory cell death through intracellular binding to microbial glycans

Lipopolysaccharides (LPSs) are pathogen-associated molecular patterns released from bacteria that can elicit a host defense program through binding to the cell-surface receptor. Upon binding to the cell-surface receptor, LPSs initiate signal transduction events, thereby contributing to various inflammatory responses induced by bacterial infection. Inflammation is a biological response of the immune system and a critical host protection process against bacterial invasion. However, during severe infection, overstimulation of the innate immune response via LPSs may cause the uncontrolled release of pro-inflammatory cytokines, known as cytokine storm. Cytokine storm has been implicated in systemic inflammatory response syndrome (SIRS), causing severe multiple organ failure and sepsis. This is the leading cause of death worldwide in intensive care units.

Recently, a cytosolic LPS-sensing pathway involving caspase-4/5 in humans and caspase-11 in mice was discovered. Outer membrane vesicles from extracellular bacteria are known to be taken up by cells and release LPSs intracellularly. Cytosolic LPSs can bind directly to caspase-4/5/11 and induce their oligomerization and activation. Compared with the cell-surface receptor for LPS, the binding affinity of caspases for LPS is a thousand-fold higher. Thus, the cytosolic LPS-sensing pathway is regarded as the final line of host defense against bacterial invading. However, when this defensive line is triggered, the host immune system may respond in extreme ways, including cytokine storm and inflammatory cell death. Although this contributes to the pathogen elimination, the uncontrolled inflammatory responses may also cause multiple organ failure leading to high mortality rates of the infected individuals.

Galectins, a family of β-galactoside–binding proteins, contain a carbohydrate recognition domain (CRD) that binds β-galactosides. These proteins can decode host-derived complex glycans and are involved in various biological responses. Different galectins play essential functions in various diseases, and different galectins have the potential to become targets for the treatment of these diseases. Academia Sinica Vice President Dr. Fu-Tong Liu is a pioneer and leader in the field of galectin research and is also the discoverer of now well-known galectin-3. Galectin-3 can recognize microbial glycans, particularly LPSs, through its CRD and form oligomers when it binds to multivalent carbohydrates. However, these proteins are mainly present intracellularly, but little is known regarding their functions associated with binding to components of microorganisms, including LPSs, in the cytosol. We report that in cell-free systems, galectin-3 augments the LPS-induced assembly and activation of caspase-4/11. Moreover, our findings using cell-based system indicate that galectin-3 enhances intracellular LPS-induced caspase-4/11 oligomerization and activation, resulting in increased cytokine production and cell death. By intracellularly recognizing LPS glycan moieties, galectin-3 may act as a critical regulator of LPS-mediated cytokine storm and sepsis. Our study unravels a critical mechanism

of host response against bacterial infection that may provide opportunities for new therapeutic interventions, including improvement of the mortality rates and recovery in infected patients from sepsis. The results were published in Proceedings of the National Academy of Sciences of the United States of America (PNAS) on July 27, 2021.



A model for regulation of a cytosolic LPS-sensing pathway by galectin-3. Galectin-3 binds to cytosolic LPS glycans and enhances LPS-mediated caspase-4/11 oligomerization and activation, resulting in increased inflammatory cell death.

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