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CENTRO DE INVESTIGACION

THE FUTURE OF BIOMEDICAL RESEARCH CIPF Lecture Series

Sounding the Alarm and Putting Out the Fire: New Mechanistic Insights into Inflammatory Cell Death

Speaker: **Judy Lieberman, MD, PhD**

Boston Children's Hospital and Harvard Medical School, Boston, USA

Date: **10/05/19- 12:30 h**

Place: Sal6n de Actos CIPF

Abstract: Inflammasomes are multi-protein signaling scaffolds that assemble in response to invasive pathogens and sterile danger signals to activate inflammatory caspases, which trigger inflammatory death (pyroptosis) and processing and release of pro-inflammatory cytokines. Inflammasome activation contributes to many human diseases, including sepsis, the often-fatal response to systemic infection. We recently found that gasdermin D (GSDMD) causes pyroptosis by forming pores in the plasma membrane after it is cleaved by the inflammatory caspases. The N-terminal fragment binds to acidic phospholipids on the inner leaflet. GSDMD pores also assemble on bacterial membranes to kill the bacteria that trigger pyroptosis. Cryo-electron microscopy was used to solve the structure of the pore formed by 27 monomers of the related gasdermin, gasdermin A3. The N-terminal fragment undergoes radical conformational changes after it binds to lipids to assemble into a 108-stranded β -barrel that inserts into the membrane to form the pore. A small molecule screen identified several compounds that inhibit pore formation by covalently binding to a reactive cysteine in GSDMD and also inhibit other steps in inflammasome priming and assembly and caspase activation. One of the inhibitors, disulfiram, which is a drug used to treat alcohol dependence, promoted survival and reduced inflammatory cytokine secretion in LPS-induced sepsis in mice.

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