Cologne Seminar Series on Ageing

Speaker: Feng Shao
National Institute of Biological Sciences, Beijing (CN)

Monday, 06 May, 2019, at 16:00

CECAD Research Center
Joseph-Stelzmann-Str. 26
Lecture hall, ground floor

Host: Manolis Pasparakis
(CECAD)

Scientific Background:

- 06/2014-present, Deputy Director for Academic Affairs, National Institute of Biological
- Sciences, Beijing
- 10/2012-present, Investigator, National Institute of Biological Sciences, Beijing
- 07/2005-09/2012, Assistant investigator, National Institute of Biological Sciences, Beijing
- 01/2004-06/2005, Damon Runyon Postdoctoral Fellow, Harvard Medical School, Boston, MA
- 04/2003-12/2003, Postdoctoral fellow, University of California, San Diego, CA, USA.
- 07/1999-03/2003 Ph.D., Biological Chemistry, University of Michigan, Ann Arbor, MI, USA.

Title: Innate immunity to cytosolic LPS: pyroptosis and beyond

About Prof Shao's talk:

Lipopolysaccharide (LPS), the major cell-wall component of Gram-negative bacteria, is long known to be sensed by the plasma membrane-bound TLR4 receptor. Ligation of TLR4 by the lipid A of LPS stimulates NF-κB and IRF-mediated inflammatory cytokine production. Recently, we showed that caspase-11, 4 and 5 are cytosolic immune receptors for LPS and activated by direct binding to its lipid A part. Like caspase-1 activation by the canonical inflammasome, caspase-11/4/5 activation induces pyroptosis, both of which are critical for antibacterial defense and development of immunological diseases. Caspase-11/4/5 and caspase-1 cleave Gasdermin D (GSDMD) to release the autoinhibition of its N-terminal domain that bears an intrinsic pore-forming activity for executing pyroptotic cell death. *Gsdmd*$^{-/-}$ mice are susceptible to various bacterial infections and also resist LPS-induced septic shock. GSDMD belongs to a large Gasdermin family sharing the pore-forming domain. Another family member GSDME whose expression is silenced in most cancer cells, is activated by caspase-3 cleavage; inflammatory damages caused by GSDME-mediated pyroptosis is the major determinant for the toxicity of those DNA-damaging chemotherapy drugs. Lastly, we discover that ADP-heptose, the precursor for LPS inner core oligosaccharide, is recognized in host cytosol by a novel kinase receptor ALPK1. Like lipid A-activated TLR4, ADP-heptose-activated ALPK1 potently stimulates NF-κB-dependent inflammatory responses both in cells and mice. These findings shift the paradigm of immune sensing of LPS and antibacterial defense, and open several new areas of research on innate immunity and pyroptosis-mediated inflammation. The cell-entry property of ADP-heptose also suggests a new way of modulating immune responses in mammals.

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