LUXEMBOURG INSTITUTE OF HEALTH
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LECTURE SERIES & WORKSHOPS

INFECTION & IMMUNITY

12
OCT. 2017
Thursday

LECTURE
Lycée Technique
d'Esch/Alzette
Salle de Projection *
11.30 am - 12.30 pm

MEET & EAT *
light lunch provided
House of BioHealth,
Room Françoise
Barré-Sinoussi
1.00 - 2.30 pm

9 10 11 12 1 2 3 4

*Please register sending a mail to florence.henry@lih.lu

SPEAKER

Prof. Veit HORNUNG

Chair of Immunobiochemistry (W3)
Gene Center, Department of Chemistry and Biochemistry, University of Munich, LMU, Germany

HOST:
Department of Infection and Immunity

RESPONSIBLE LIH SCIENTIST:
Prof. Dirk Brenner (dirk.brenner@lih.lu)

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MOUSE IS NOT MAN - INFLAMMASOME SIGNALING IN THE HUMAN SYSTEM

ABSTRACT

The past years have seen a tremendous increase in our knowledge on the mechanisms that regulate the biological activity of cytokines of IL-1 family, such as IL-1β and IL-18. It is now well established that so-called inflammasome complexes regulate the activity of caspase-1, the enzyme that matures these central pro-cytokines by proteolytic cleavage. Since their initial description as large cytosolic protein complexes, inflammasomes have been extensively studied with regards to their ligand specificity, their signaling cascades and their effector functions in both microbial infection as well as sterile inflammatory conditions. In this regard, much attention has focused on NLRP3, which appears to be a universal sensor of cell stress or damage. Despite enormous research efforts, a defined mechanism of NLRP3 inflammasome activation has not been identified so far. Nevertheless, it is well accepted that NLRP3 inflammasome activation leading to IL-1β maturation requires two steps: A so-called signal 1 that primes the expression of pro-IL-1β and NLRP3 and a signal 2 that leads to NLRP3 activation. The latter mechanism involves the induction of potassium efflux, a phenomenon that appears to be required and sufficient to trigger NLRP3 activation. NLRP3 inflammasome activation does not only lead to the activation of caspase-1 and subsequent IL-1β processing, but it also results in the formation of a large, helically structured complexes of ASC (pyroptosomes) that serve as a scaffold to recruit and activate caspase-1 (hence the name inflammasome). Another feature of inflammasome activation is the induction of a special type of caspase-1 dependent cell death, known as pyroptosis. Most of these hallmarks of NLRP3 inflammasome activation have been described and characterized in murine macrophages or human monocytic cell lines (e.g. THP1 cells) and based on these findings extrapolations to the human system have been made. To dissect inflammasome signaling in human cells, we have established a B-cell transdifferentiation system, by which human monocyte like cells can be obtained from immortalized B-cells. Applying CRISPR/Cas9 gene targeting within the B-cell stage, this transdifferentiation system allows us to genetically dissect inflammasome signaling in human monocytes. Using this approach, we have revisited the role of signal 1 and 2 in NLRP3 activation in human monocytes and uncovered a novel entity of inflammasome signaling that greatly differs from the classical model of NLRP3 activation, as it is known from the murine system. In my talk I will discuss the mechanisms of this signaling cascade and outline its relevance for human sterile inflammatory diseases.

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