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Development of trained immunity and activation of inflammasomes are promising strategies to combat *Staphylococcus aureus* infection

Emmanuel Chaumond, Elma Lima Leite, Sandrine Péron, Nathalie Daniel, Yann Le Gouar, Aurélie Nicolas, Jordane Ossemond, Arthur Gautron, David Gilot, Vasco Ariston de Carvalho Azevedo, et al.

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Société Française
de Microbiologie

MICROBES 2023

18^e CONGRÈS NATIONAL DE LA SFM

4-6
octobre

**LE COUVENT
DES JACOBINS**

CENTRE DES CONGRÈS DE
DE **RENNES** MÉTROPOLE



Déclaration de conflit d'intérêt

Pour cette présentation,
je déclare n'avoir aucun conflit d'intérêt.



INRAE

N. Berkova
SFM 2022

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Development of trained immunity and activation of inflammasomes are promising strategies to combat *Staphylococcus aureus* infection

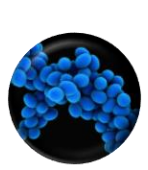
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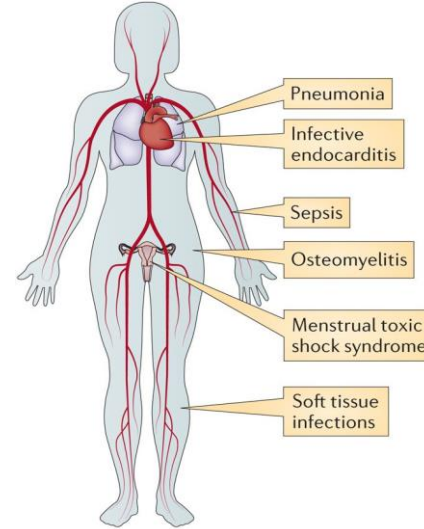
➤ *Staphylococcus aureus* is responsible for a wide range of infections in human and animals

S. aureus-induced diseases represent serious problems, especially during chronic infections

Human Mild skin infections



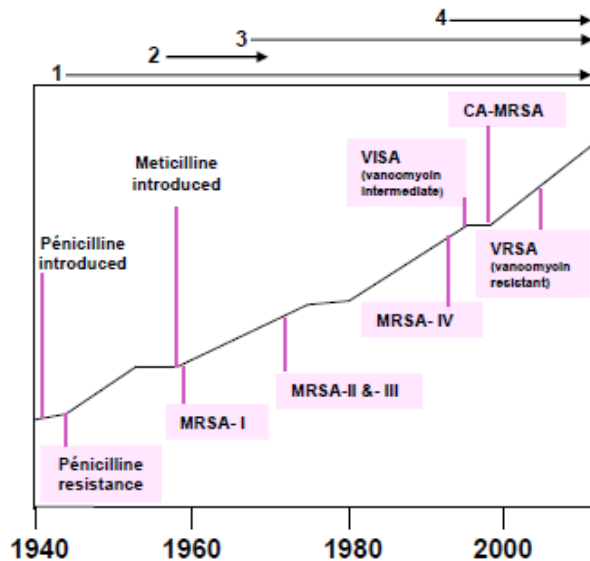
Life-threatening infections



Dairy_cattle: Chronic mastitis



Waves of *S. aureus* resistance



Nature Reviews | Microbiology

Urgent Need



Unraveling Immunity to Strengthen the Host's Defense Against Recurrent *S. aureus* Infection



➤ The compelling reasons to study non-immune cells in host-pathogen dynamics

Site-Specific Defense:

Non-immune cells with an extended lifespan are located in tissues prone to infections

Chronic Infections:

Tissue-residents non-immune cells, contribute to infection persistence by internalizing pathogens

Cellular Crosstalk:

Immune cells & non-immune cells communication shapes a coordinated defense response



Osteomyelitis, often caused by *S. aureus* infections

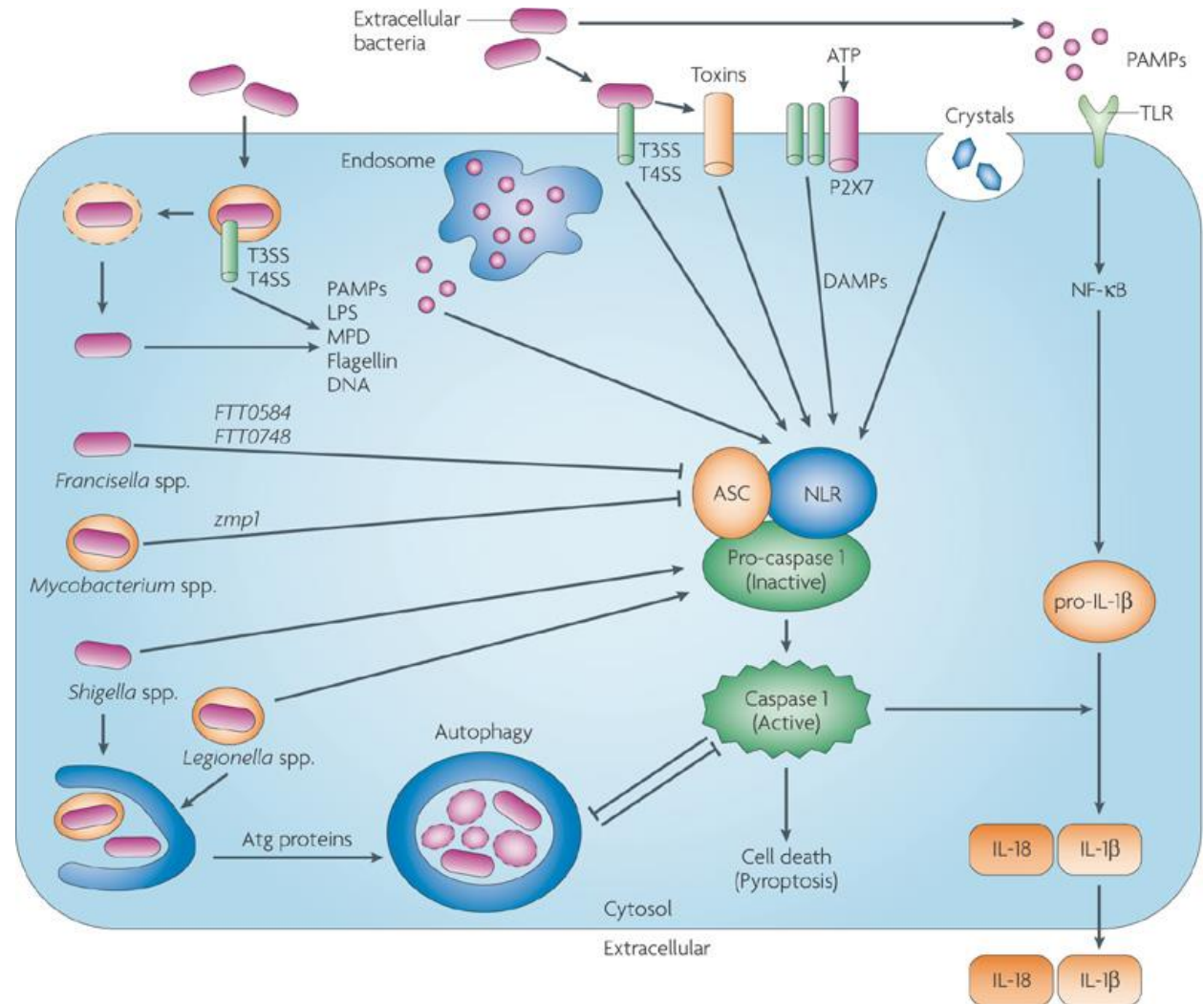


How Osteoblasts Defend Against *S. aureus* Invasion?

➤ INFLAMMASOMES activation as a defense mechanism against infection and injury

Persistent inflammation activates protein complexes, inflammasomes, that are composed of **a sensor (NLR)**, **an adaptor (ASC)**, and **a zymogen procaspase-1**

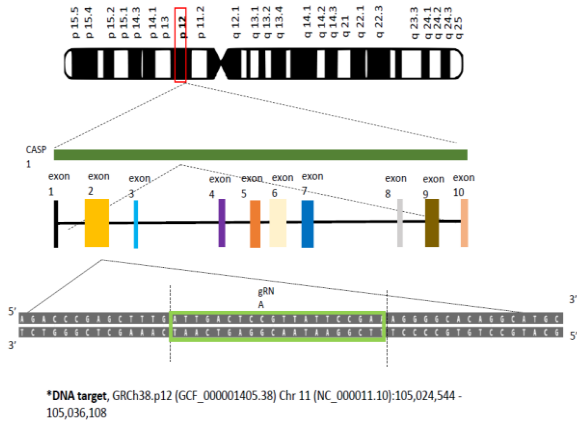
Inflammasomes activate Caspase-1, which proteolytically matures pro-IL-1 β and pro-IL-18



➤ Generation of *CASP1*^{-/-} MG-63 cells using the CRISPR-Cas9 gene editing system

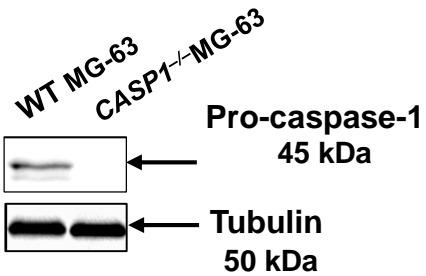
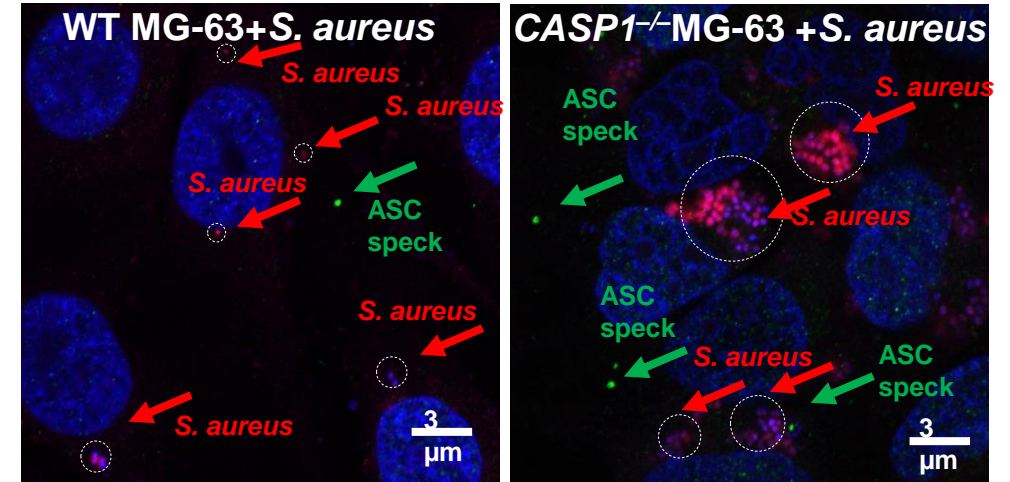
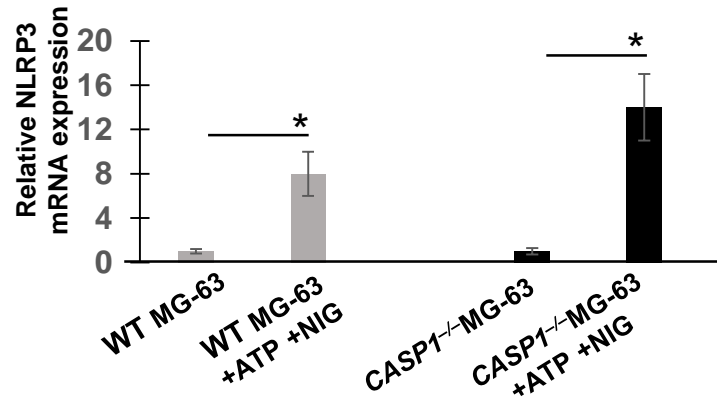
a

Human Chromosome 11 map depicting the position of Caspase-1



b

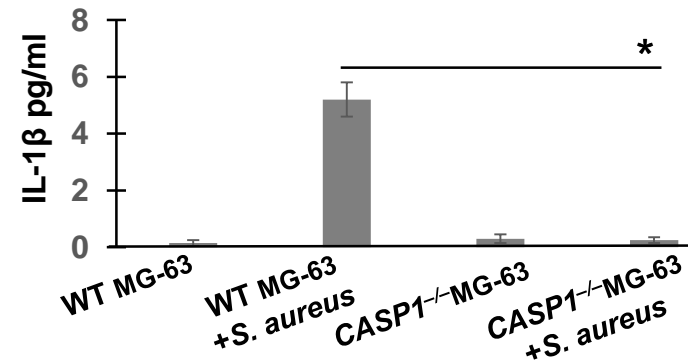
WT MG-63 cells and *CASP1*^{-/-} MG-63 clone express NLRP3 and form ASC specks.



Lack of the 45-kDa band corresponding to pro-caspase-1 in *CASP1*^{-/-} MG-63 cells

c

Lack of IL-1 β production in *CASP1*^{-/-}MG-63 in contrast to WT MG-63 cells (ELISA)

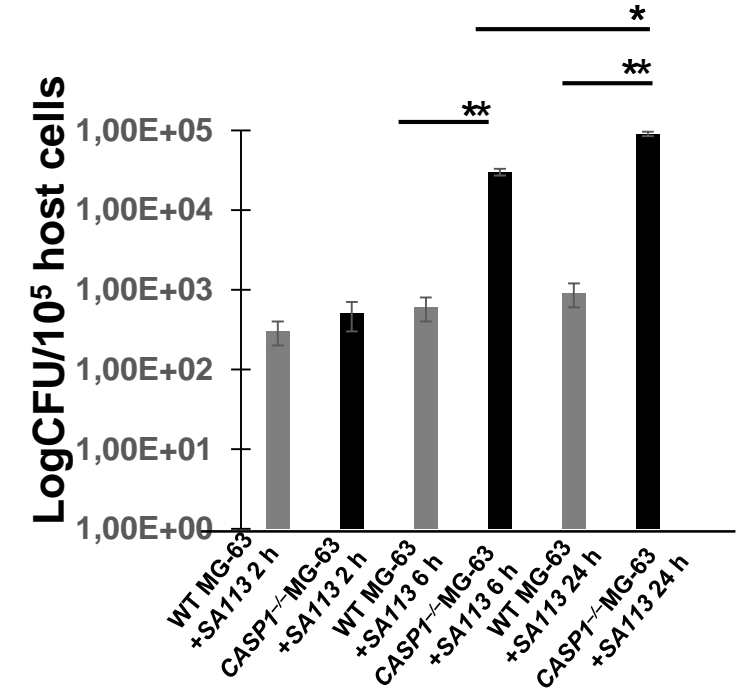
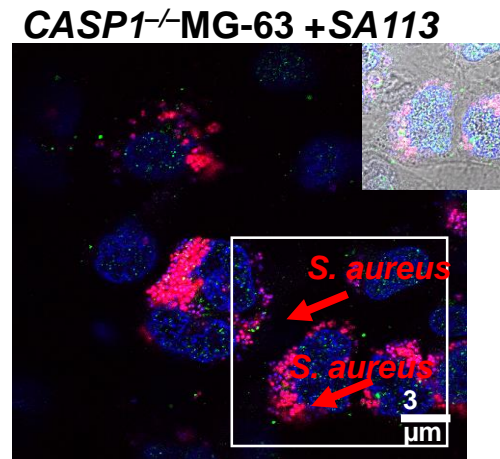
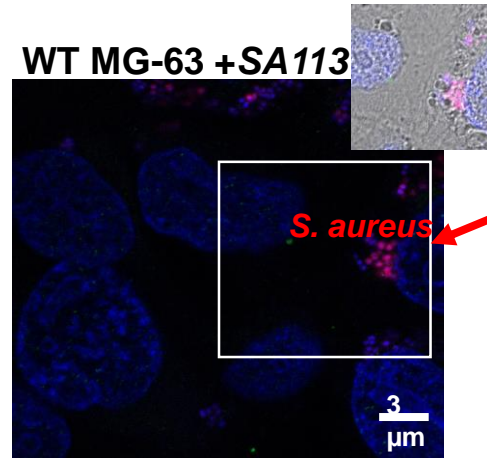
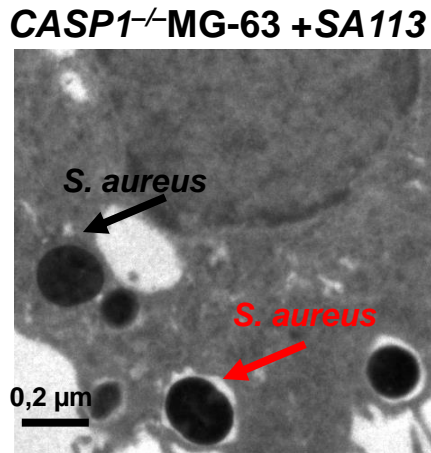
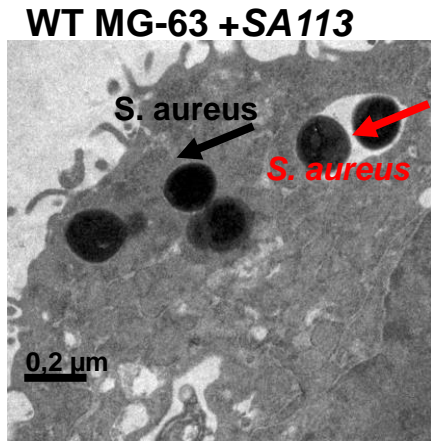


Only WT MG-63 cells produce IL-1 β following exposure to *S. aureus*

➤ *S. aureus* clearance by osteoblast-like MG-63 cells depends on caspase-1

2h

Transmission electron micrographs

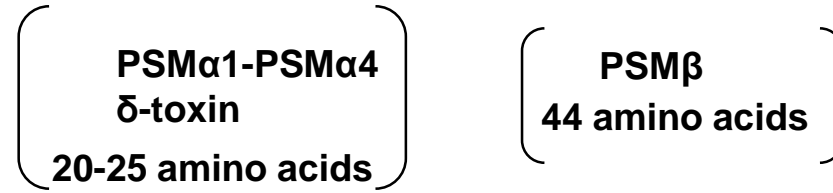


Internalization of *S. aureus* (2h) was not impaired in CASP1^{-/-}MG-63 cells

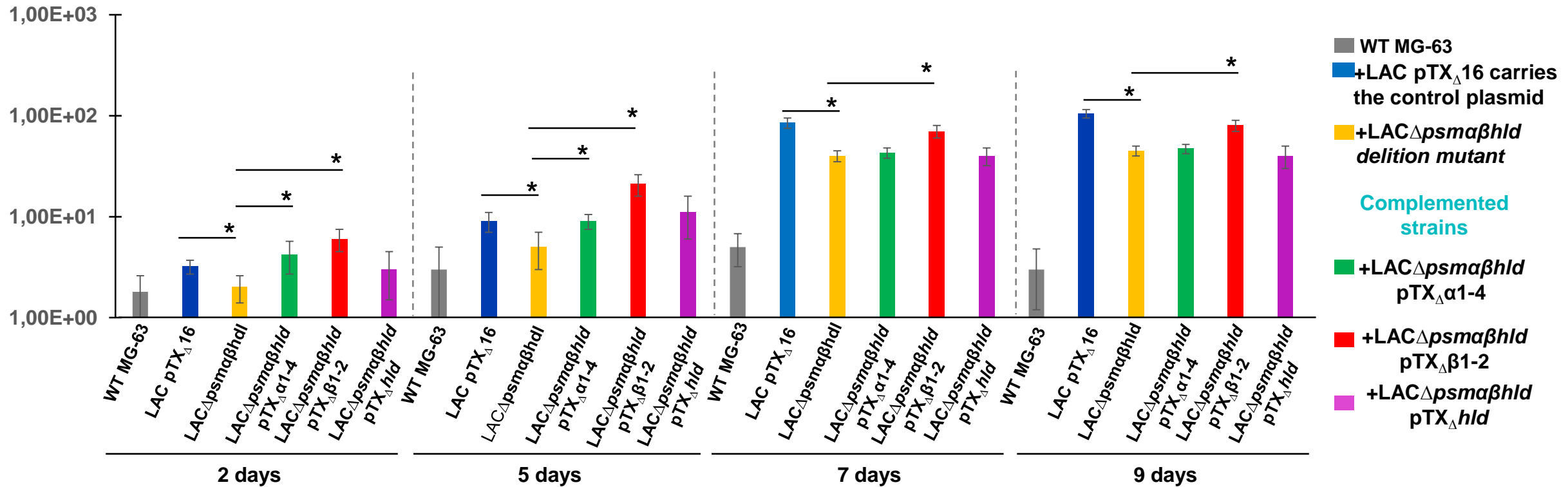
Most internalized bacteria are surrounded by phagosomal/lysosomal membranes, some bacteria are scattered freely in the cytosol

Higher number of intracellular *S. aureus* cells was observed in CASP1^{-/-} MG-63 cells compared to WT MG-63 cells

➤ Phenol-soluble modulins peptides (PSMs) define the virulence potential of *S. aureus*



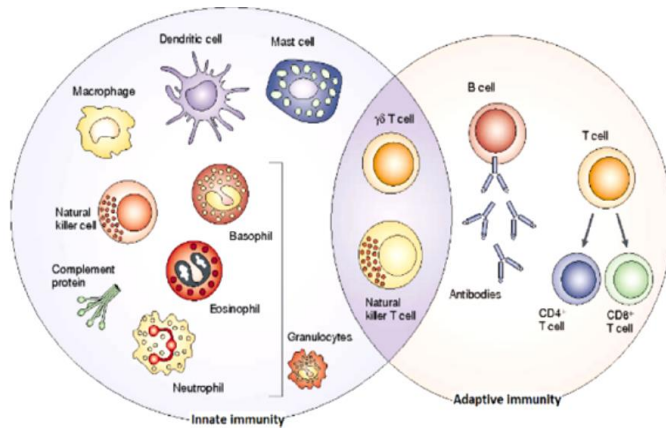
Log IL-1 β pg/ml



S. aureus phenol-soluble modulins stimulate IL-1 β release from infected MG-63 cells

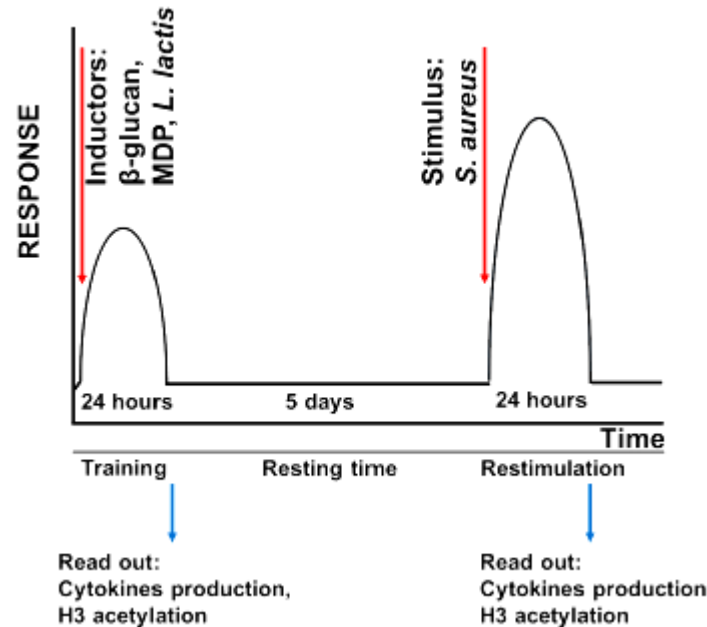
➤ Trained Immunity: shaping host-pathogen interactions through a new paradigm

Traditionally, the immune system has been divided into innate and adaptive components



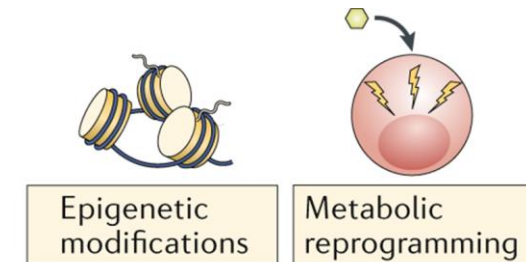
Dranoff, Nat Rev Cancer, 2004

Innate immunity exhibits adaptive traits, termed **innate immune memory** or **trained immunity**, leading to an **enhanced response** after subsequent unrelated challenges



Adapted from Netea *at al.* Science, 2016

The molecular basis of trained immunity involves metabolic and epigenetic changes



Exploring Trained Immunity Potential in Non-Immune Cells against *S. aureus* Infection

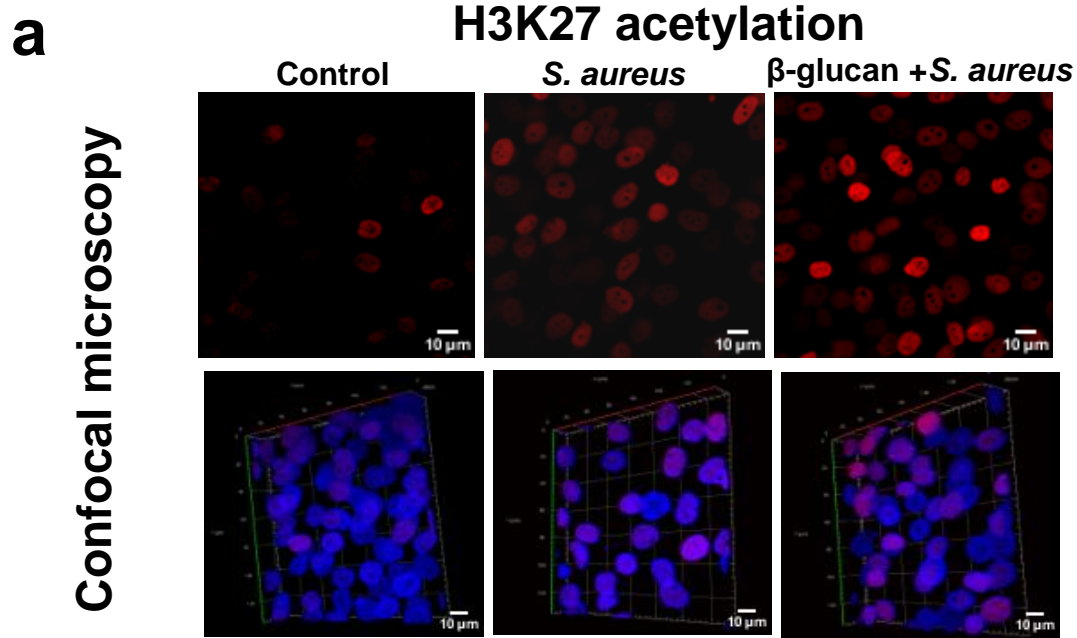
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MG-63, osteoblast-like cells
A549, lung epithelial cells

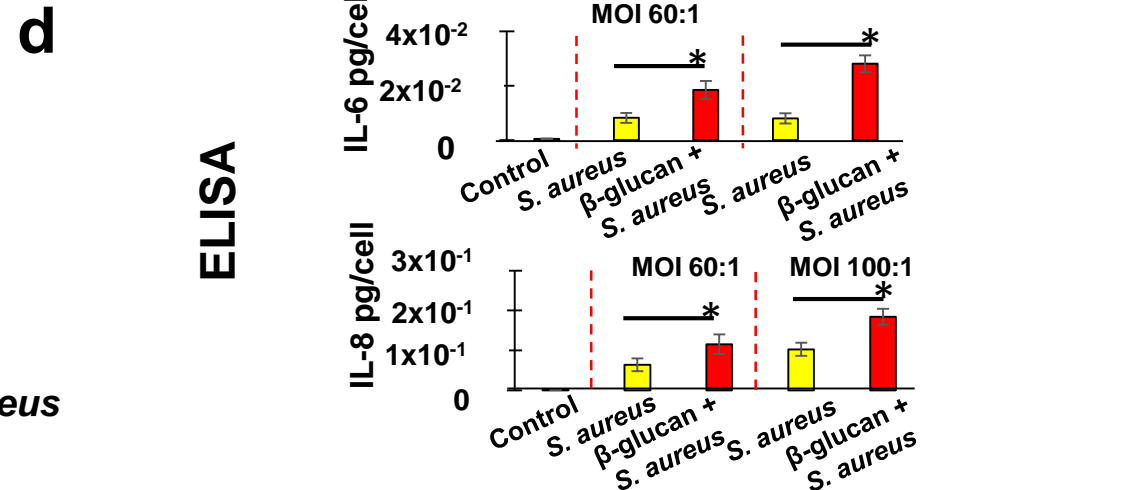
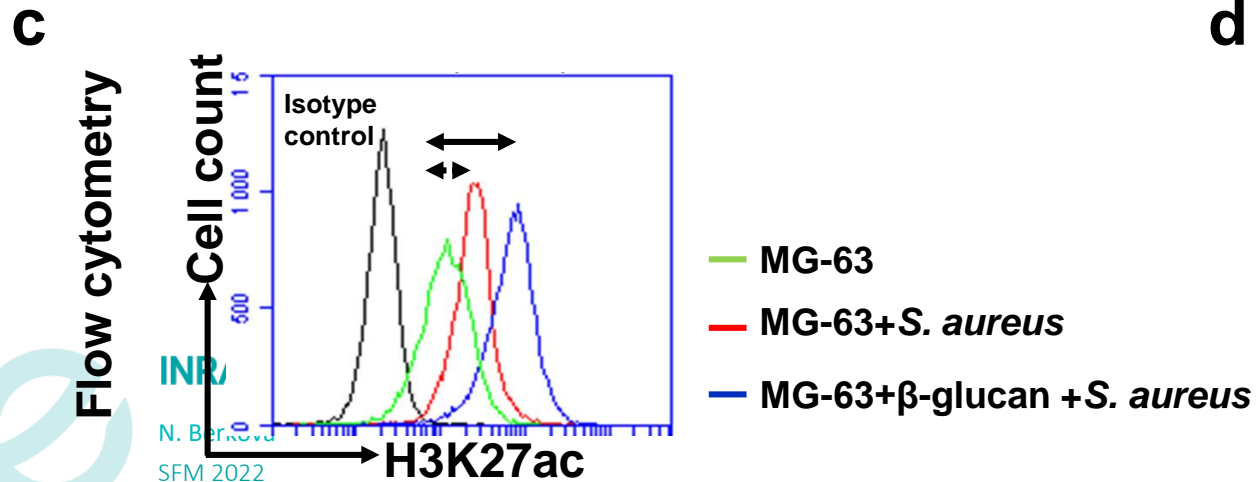
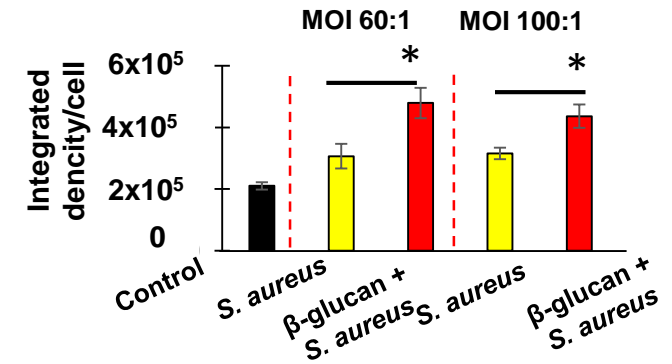
Enhanced H3K27 acetylation in β -glucan-trained cells upon *S. aureus* stimulation, positively correlating with IL-6/IL-8 production

MG-63



b

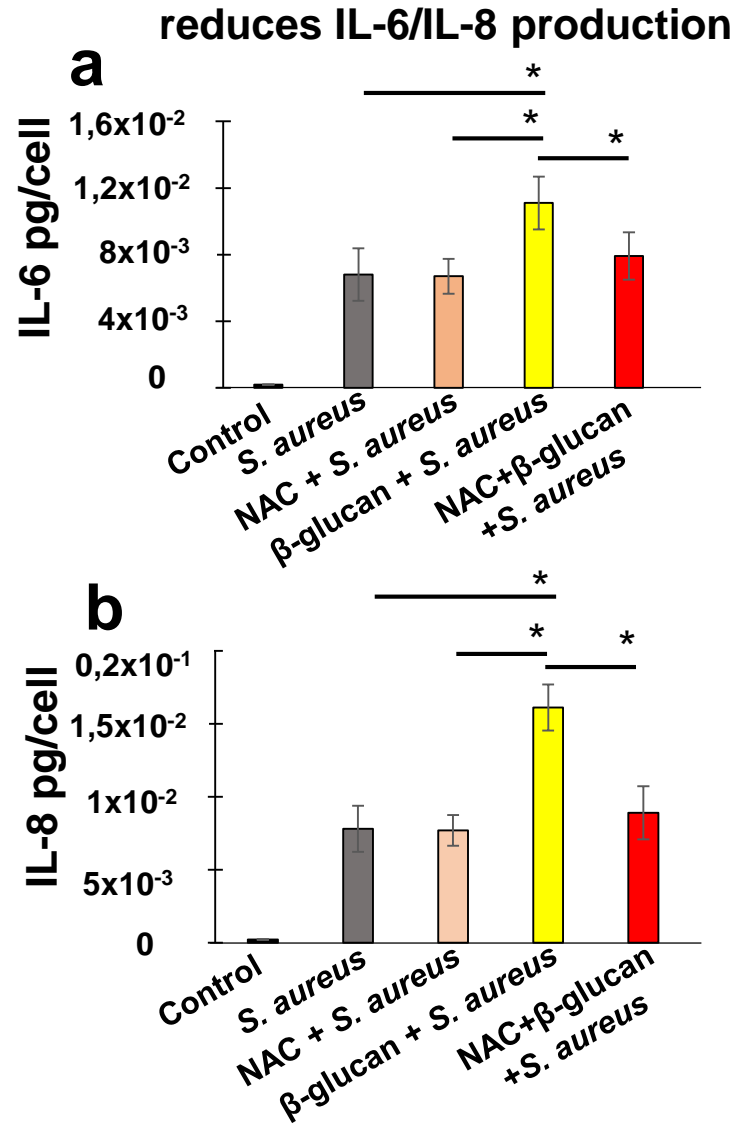
Normalized Integrated Density was monitored for comparing H3K27 acetylation



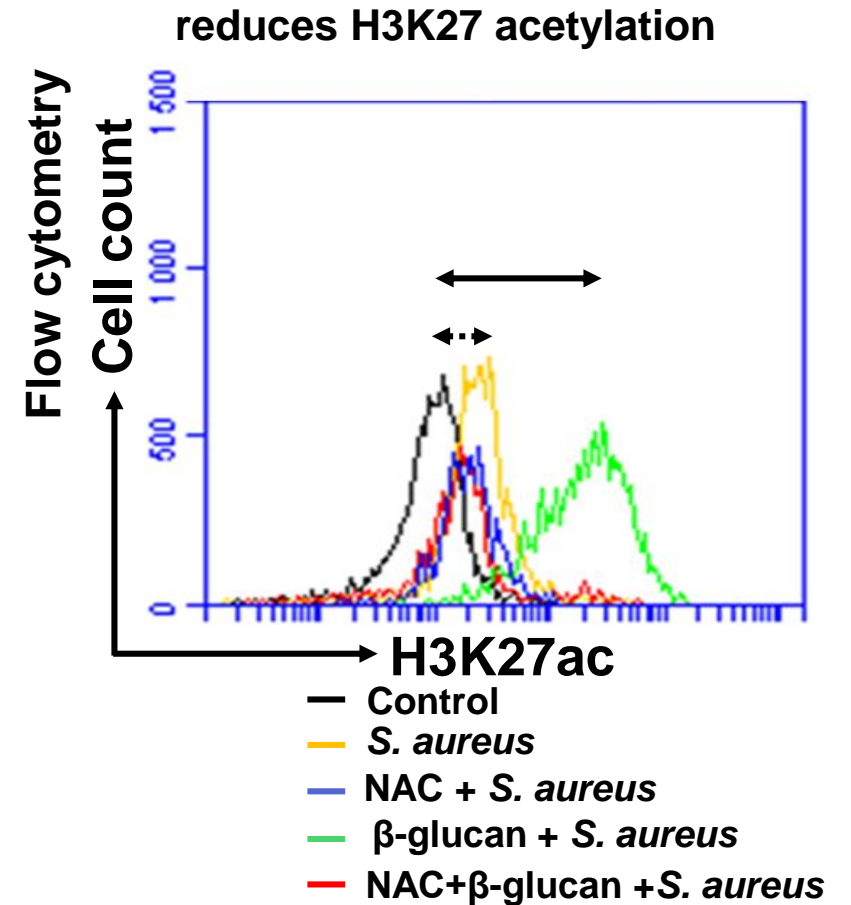
➤ Development of the innate immune memory depends on reactive oxygen species

Pre-treatment of cells with the ROS inhibitor NAC, prior to β -glucan treatment

ELISA



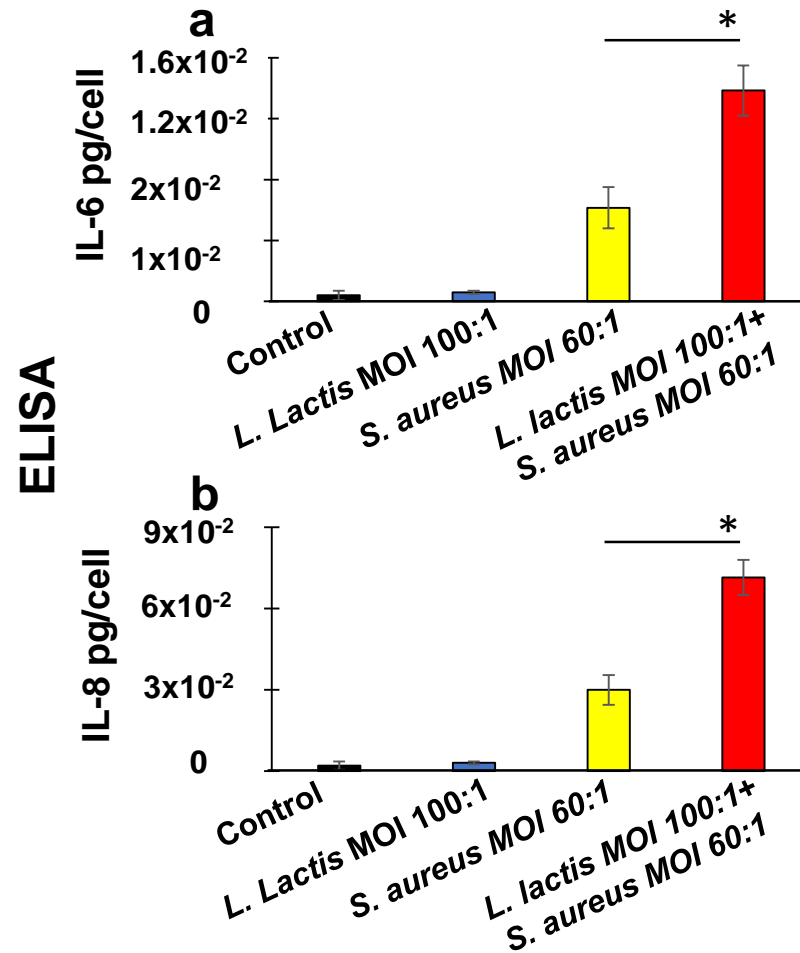
c



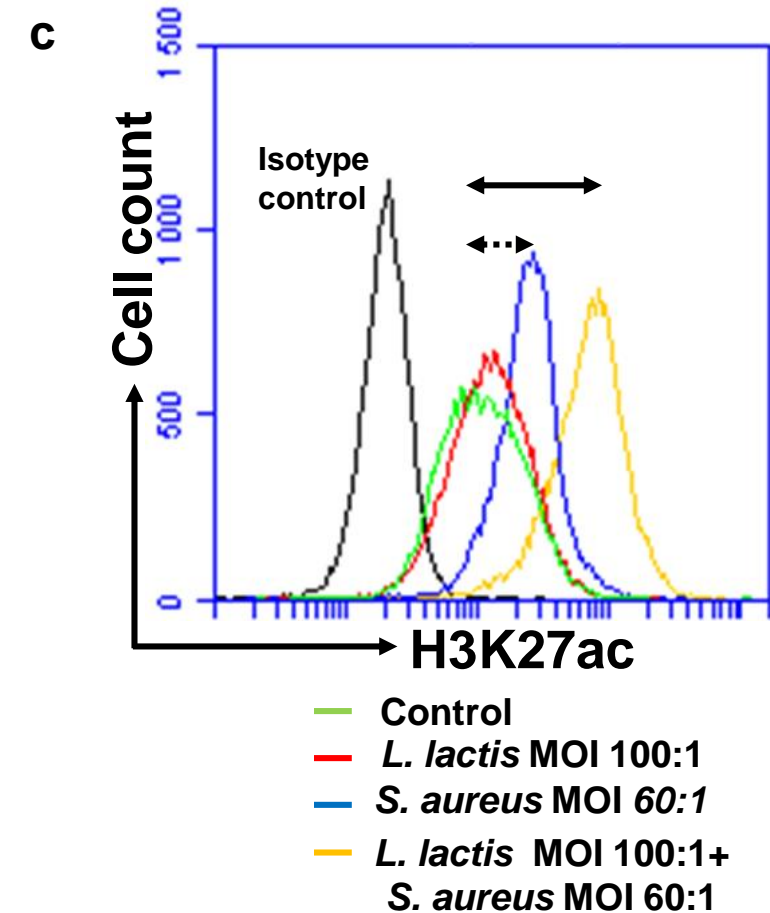
The decrease in IL-6/IL-8 production correlates to the decline in H3K27 acetylation in NAC-pre-treated cells

➤ Cells exposed to *L. lactis* increase IL-6/IL-8 production upon *S. aureus* stimulation, correlating with H3K27 acetylation

Pre-exposure of cells to *L. lactis* increases IL-6 /IL-8 production upon a stimulation with *S. aureus*



Pre-exposure of cells to *L. lactis* increases H3K27 acetylation upon a stimulation with *S. aureus*

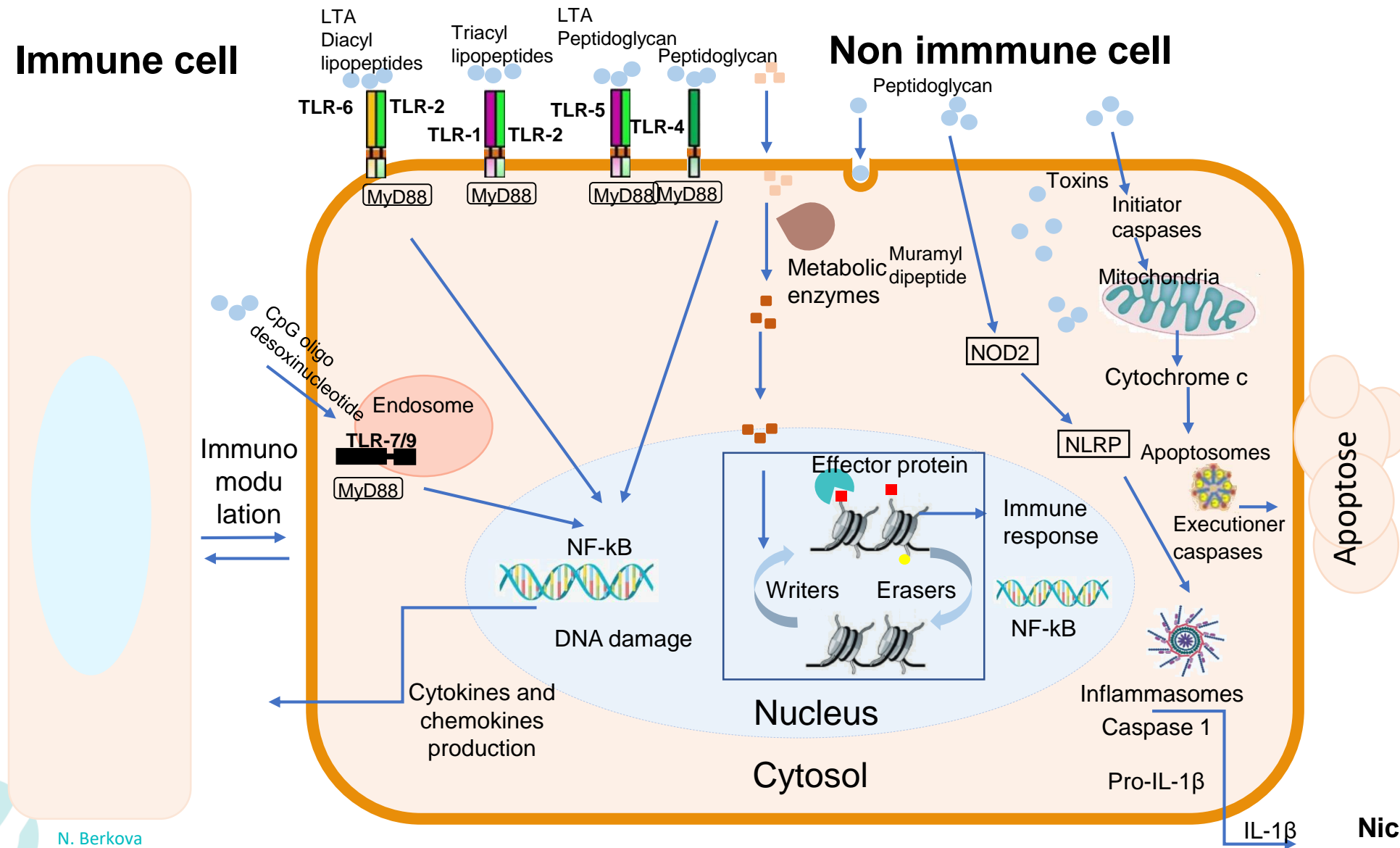


The increase in IL-6/IL-8 production correlates with the rise in H3K27 acetylation in cells pre-treated with *L. lactis*

Lactococcus lactis may be a potential inducer of trained immunity

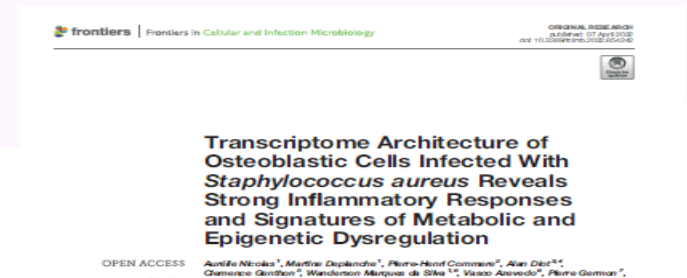
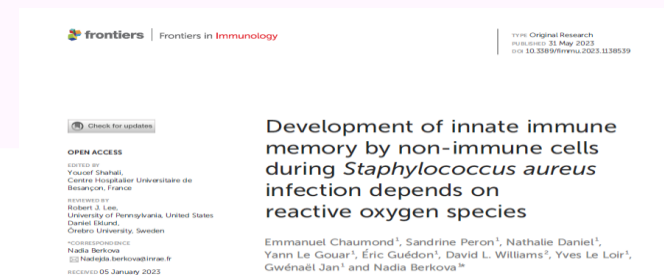
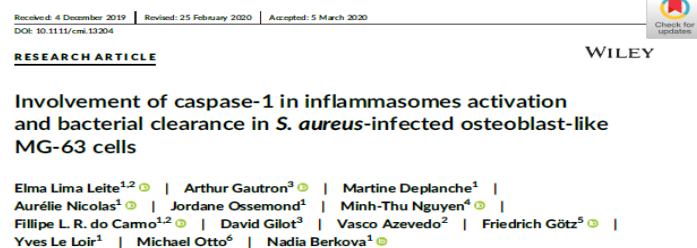
Chaumond et al. Front. Immunol. 2023

➤ Model of the immune, metabolic and epigenetic dysregulated signatures induced by long-term *S. aureus* infection



➤ CONCLUSION

- ❖ Besides structural functions, non-immune cells contribute to the defense response against *S. aureus* through inflammasomes activation
- ❖ The active caspase-1 restricts intracellular replication of *S. aureus* in non-professional phagocytes
- ❖ Non-immune cells develop trained immunity that is at least partially dependent on ROS
- ❖ *L. lactis* may be a potential inducer of trained immunity, suggesting the possibility of using this bacterium as a preventive measure against staphylococcal infections



COLLABORATIONS

THANK YOU FOR YOUR ATTENTION



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