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.

Déclaration de conflit d'intérêt

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

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

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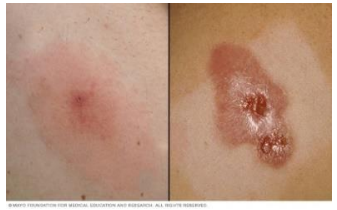
Staphylococcus aureus is responsible for a wide range of infections in human and animals

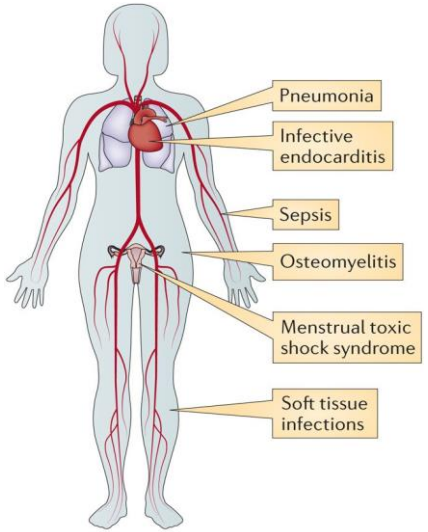
S. aureus-induced diseases represent serious problems, especially during chronic infections

Human

Mild skin infections



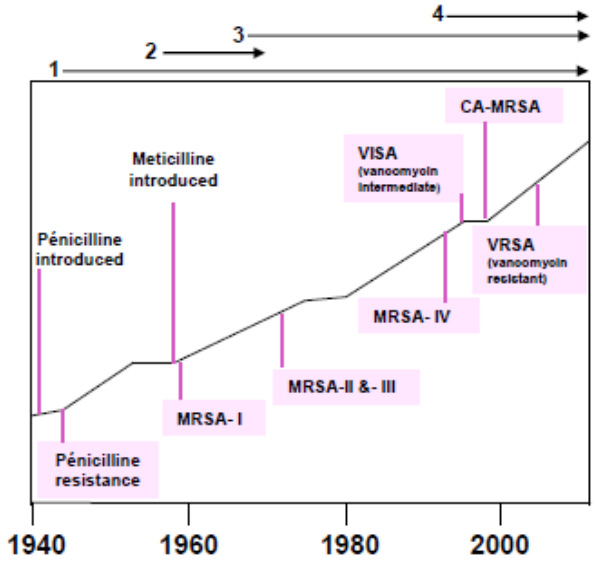
Life-threatening infections



Nature Reviews | Microbiology

Dairy cattle:
Chronic mastitis

Waves of *S. aureus* resistance



Chambers and DeLeo Nat Rev Microbiol 2010

Urgent Need

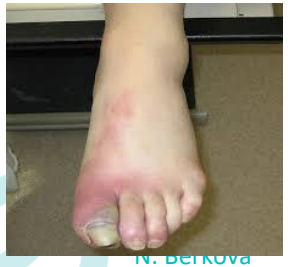
Unraveling Immunity to Strengthen the Host's Defense Against Recurrent *S. aureus* Infection

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



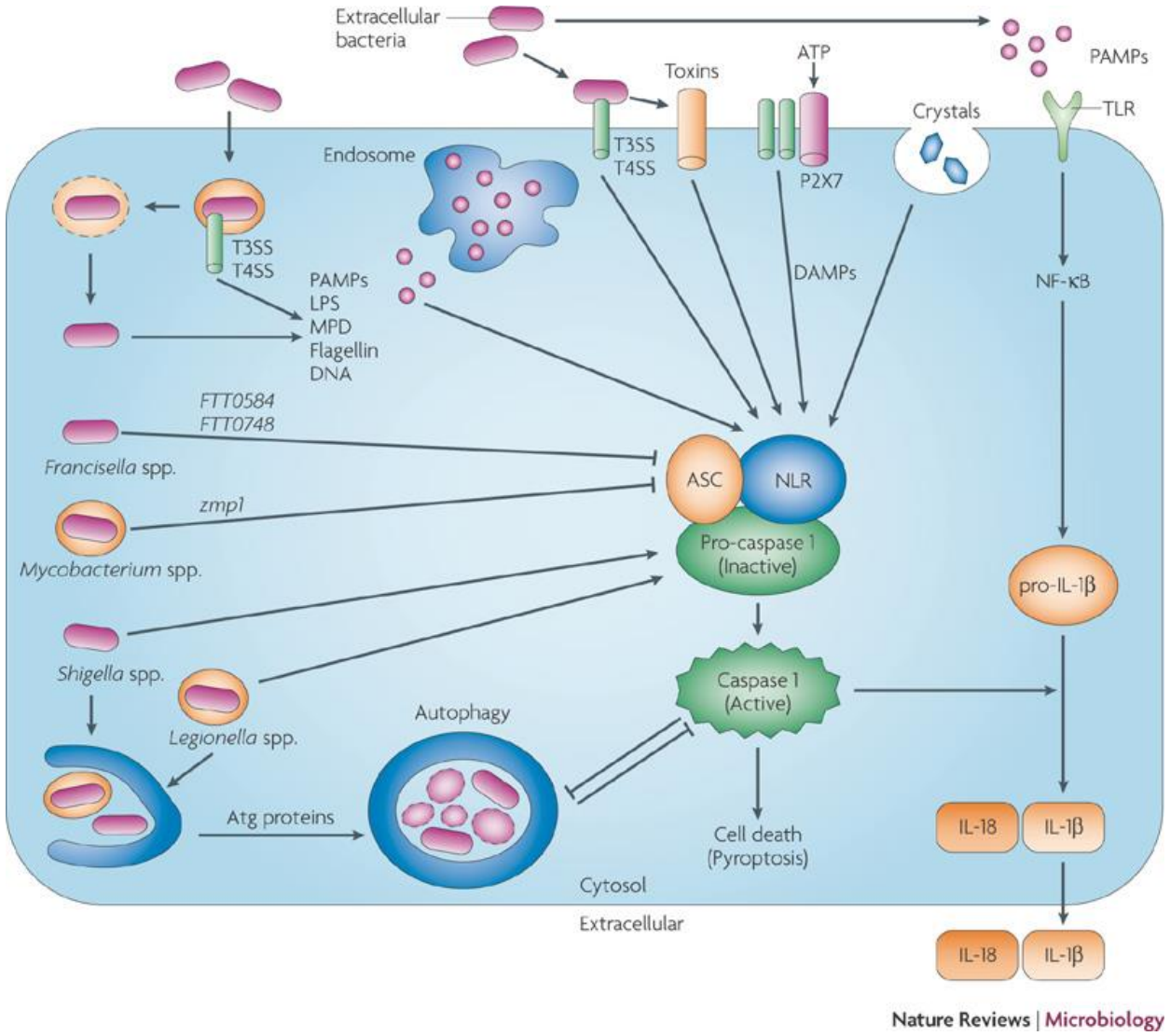
Osteomyelitis, often caused by *S. aureus* infections

How Osteoblasts Defend Against *S. aureus* Invasion?

INFLAMMASOMES activation as a defense mechanism against infection and injury

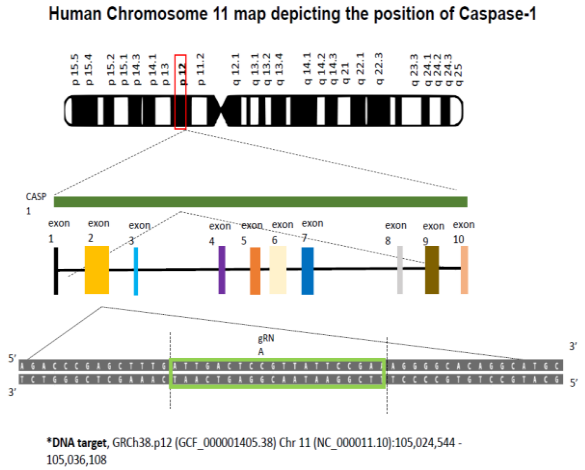
Persistent inflammation activates protein complexes, inflammasomes, that are composed of a sensor (NLR), an adaptor (ASC), and a zymogen procaspase-1

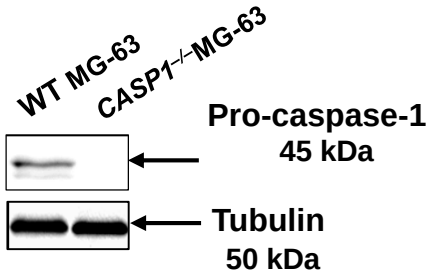
Inflammasomes activate Caspase-1, which proteolytically matures pro-IL-1β and pro-IL-18



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

a

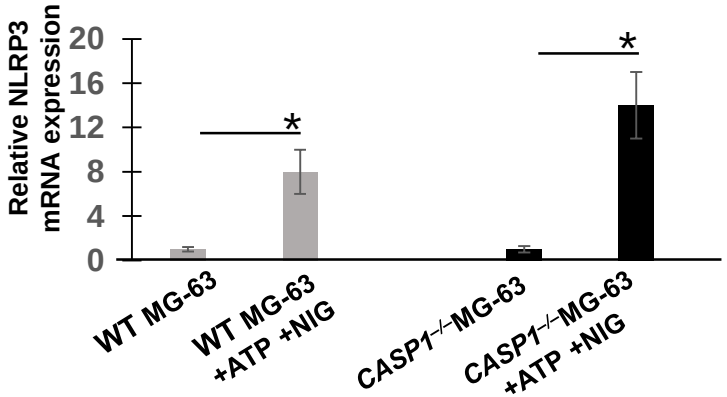


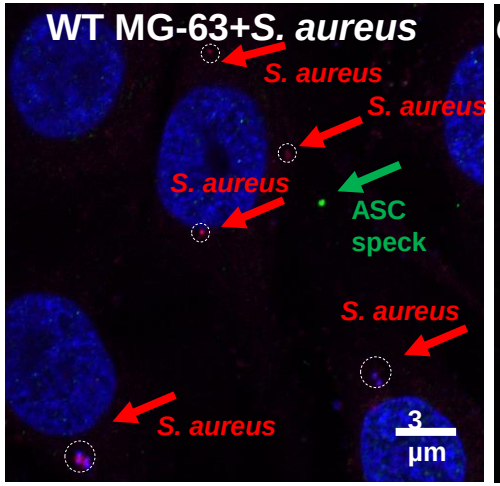


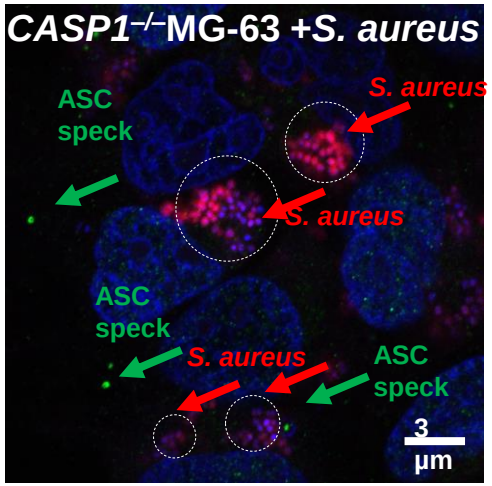
Lack of the 45-kDa band corresponding to pro-caspase-1 in CASP1$^{-/-}$ MG-63 cells

b

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

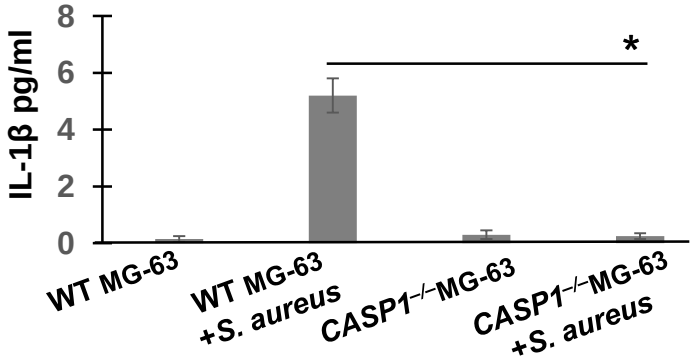






c

Lack of IL-1β production in CASP1−/−MG-63 in contrast to WT MG-63 cells (ELISA)



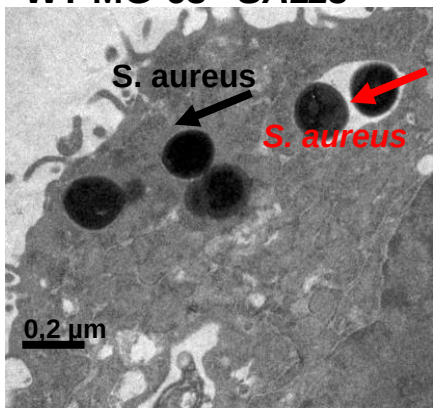
Only WT MG-63 cells produce IL-1β following exposure to *S. aureus*

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

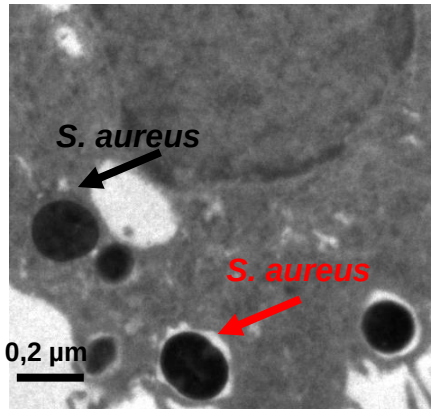
2h

Transmission electron micrographs

WT MG-63 +*SA113*

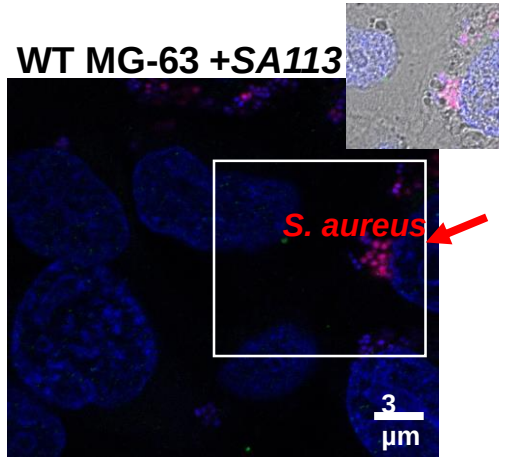


CASP1$^{-/-}$MG-63 +*SA113*

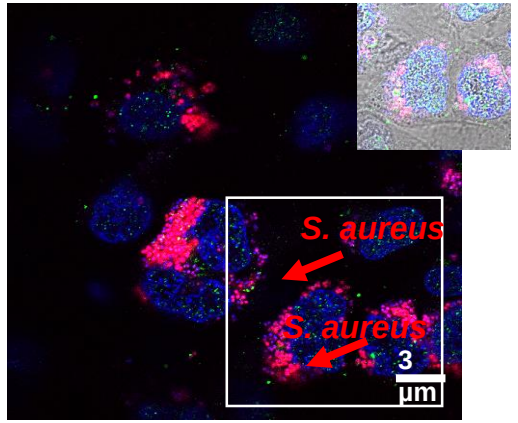


Most internalized bacteria are surrounded by phagosomal/lysosomal membranes, some bacteria are scattered freely in the cytosol

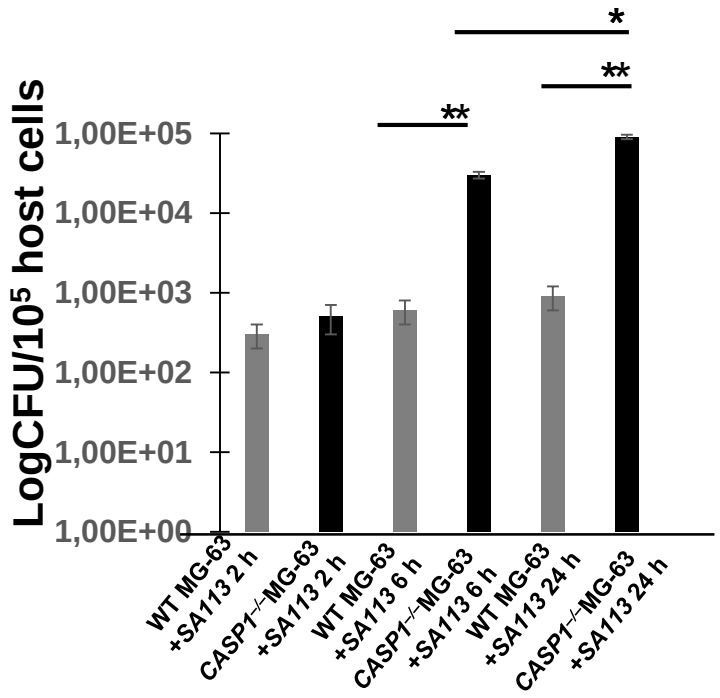
WT MG-63 +*SA113*



CASP1$^{-/-}$MG-63 +*SA113*



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

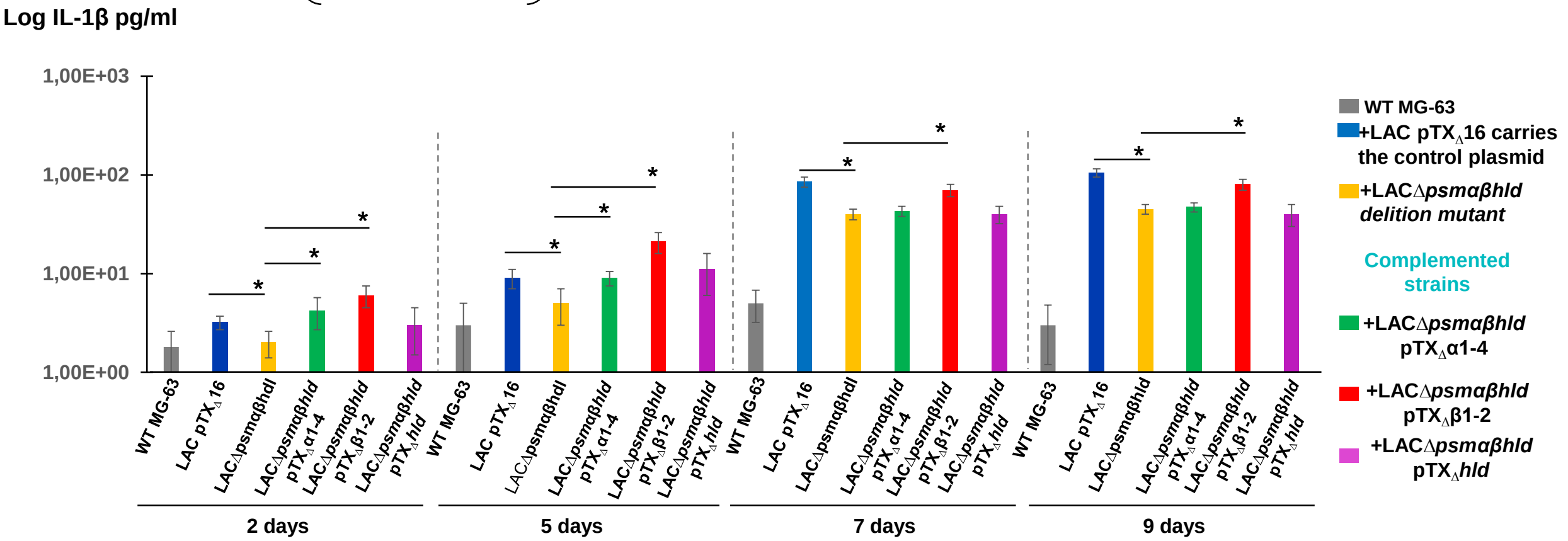


Internalization of *S. aureus* (2h) was not impaired in CASP1$^{-/-}$MG-63 cells

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

PSMα1-PSMα4
δ-toxin
20-25 amino acids

PSMβ
44 amino acids



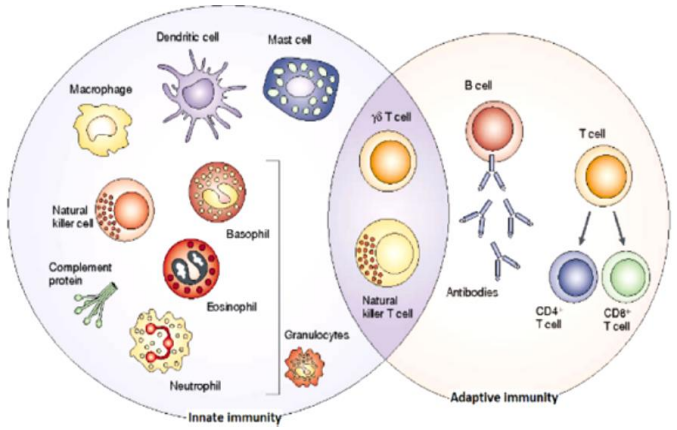
***S. aureus* phenol-soluble modulins stimulate IL-1β release from infected MG-63 cells**

Elma Lima Leite *et al*. Cell. Microbiol., 2020

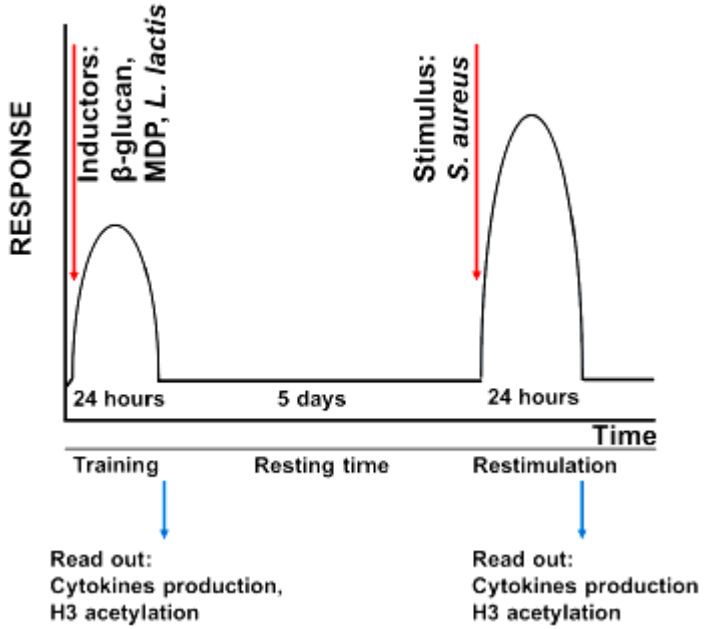
Trained Immunity: shaping host-pathogen interactions through a new paradigm

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

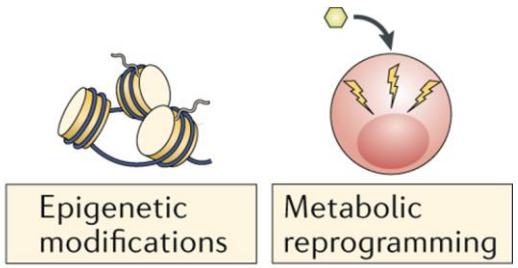
Innate immunity exhibits adaptive traits, termed innate immune memory or trained immunity, leading to an enhanced response after subsequent unrelated challenges



Dranoff, Nat Rev Cancer, 2004



The molecular basis of trained immunity involves metabolic and epigenetic changes



Adapted from Netea *at al.* Science, 2016

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

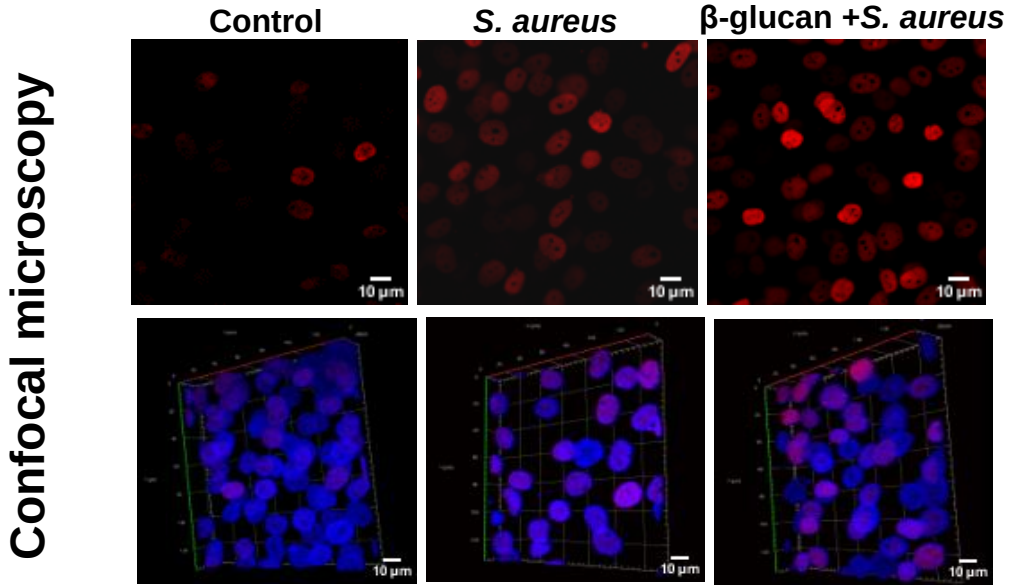
MG-63, osteoblast-like cells
A549, lung epithelial cells

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

MG-63

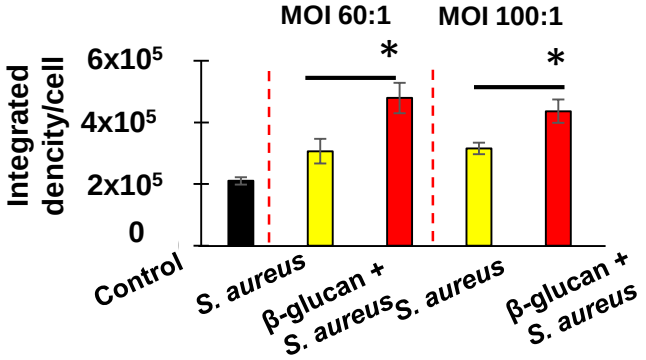
a

H3K27 acetylation



b

Normalized Integrated Density was monitored for comparing H3K27 acetylation



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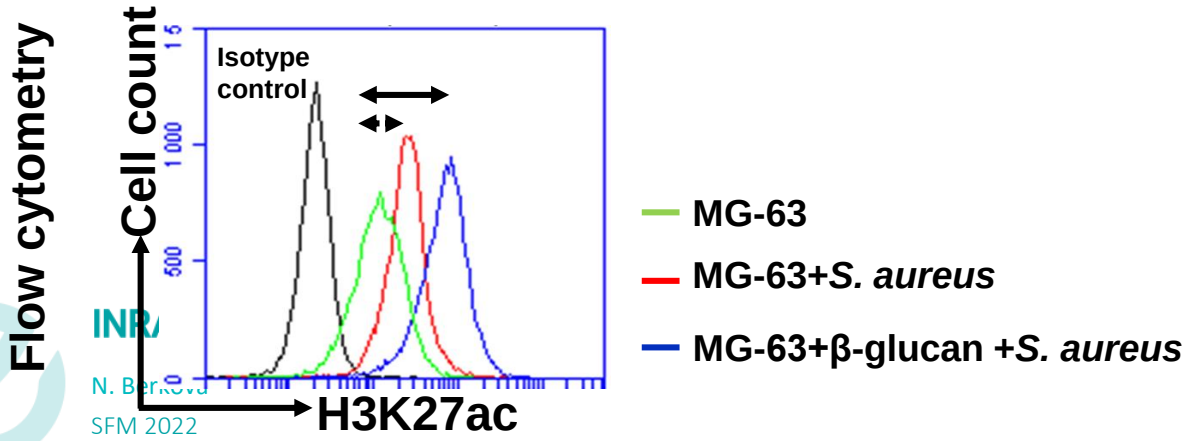
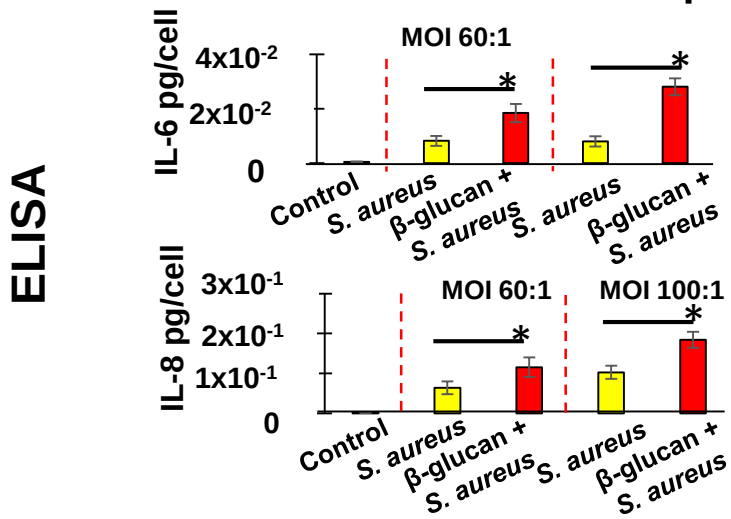


d

Assessment of IL-6 and IL-8 production

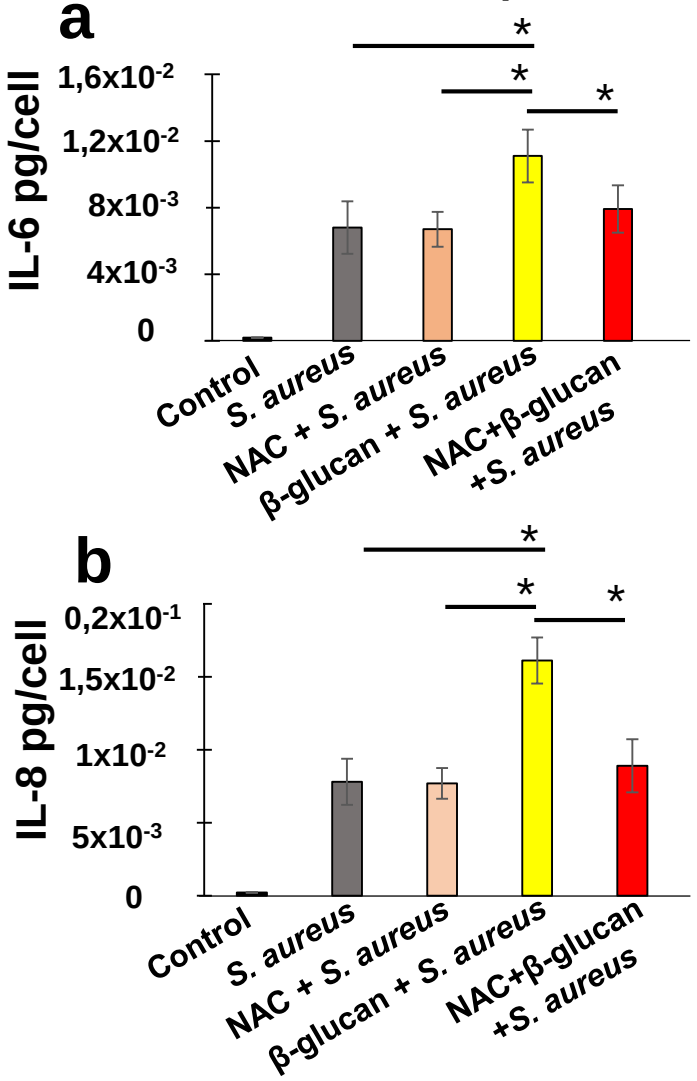


Development of the innate immune memory depends on reactive oxygen species

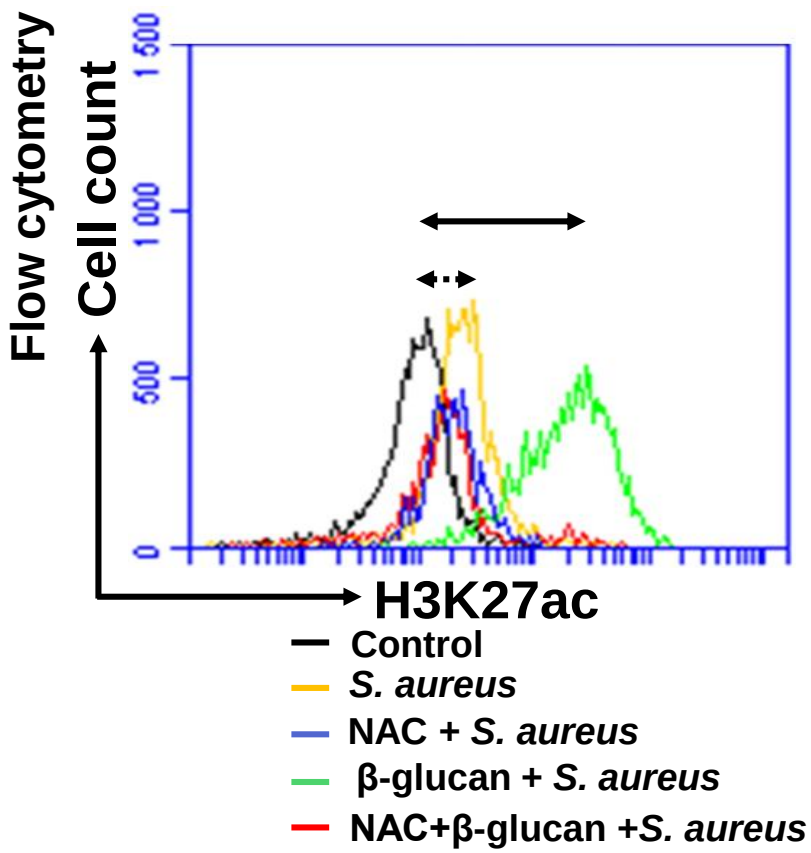
Pre-treatment of cells with the ROS inhibitor NAC, prior to β-glucan treatment

reduces IL-6/IL-8 production

ELISA



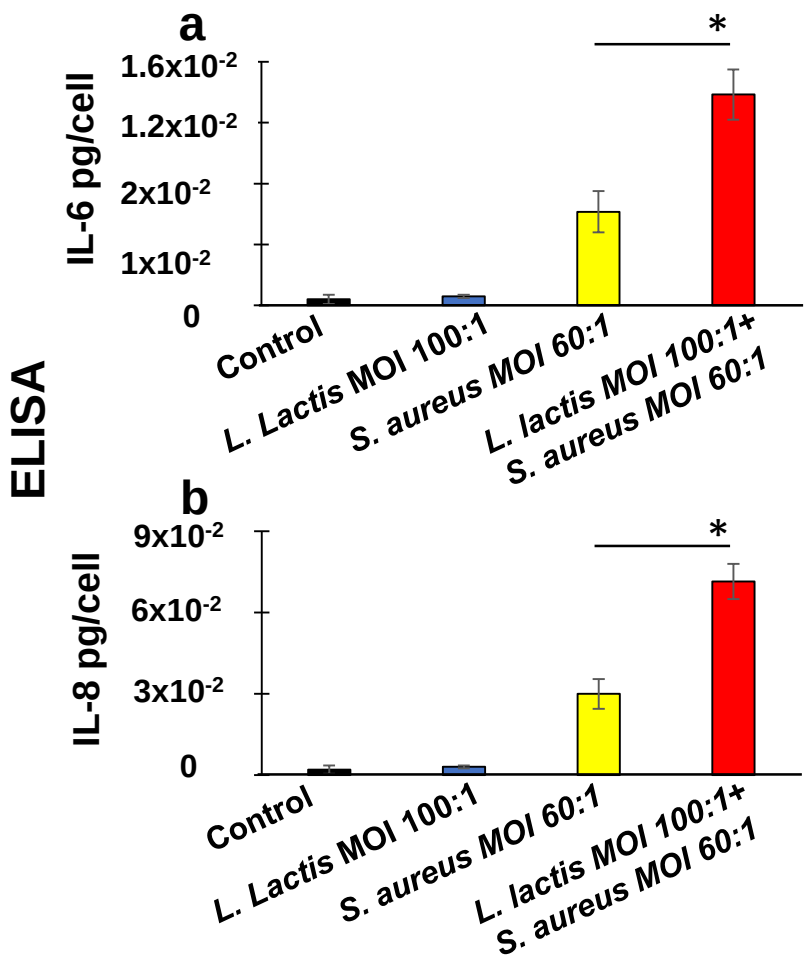
reduces H3K27 acetylation



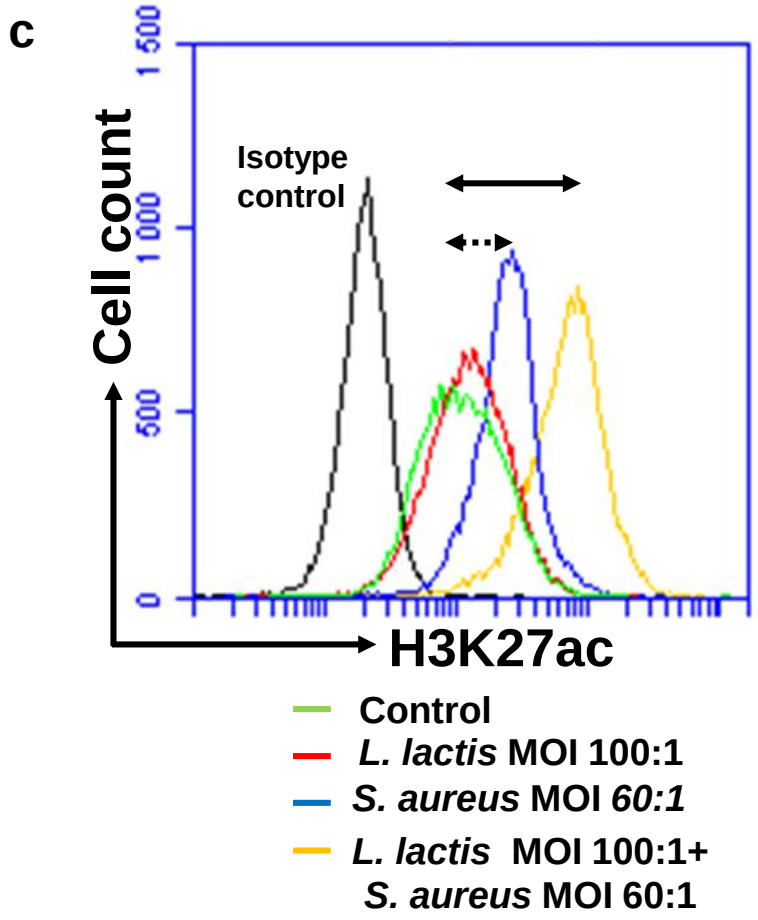
The decrease in IL-6/IL-8 production correlates to the decline in H3K27 acetylation in NAC-pre-treated cells

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*

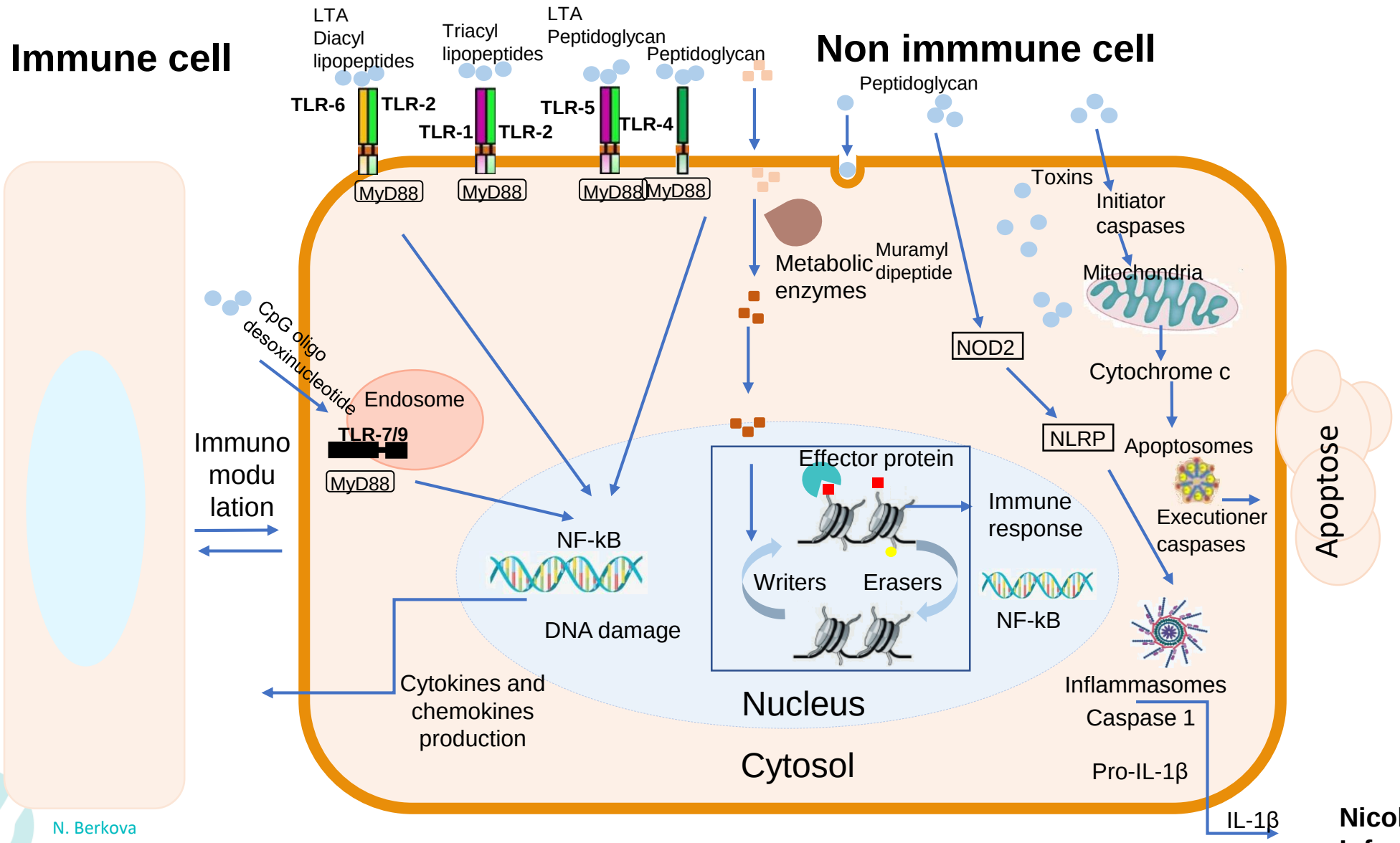


The increase in IL-6/IL-8 production correlates with the rise in H3K27 acetylation in cells pre-treated with *L. lactis*

***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



Nicolas *et al*. Front Cell Infect Microbiol., 2022

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**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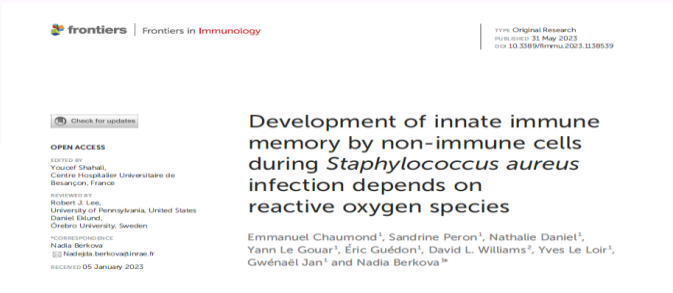
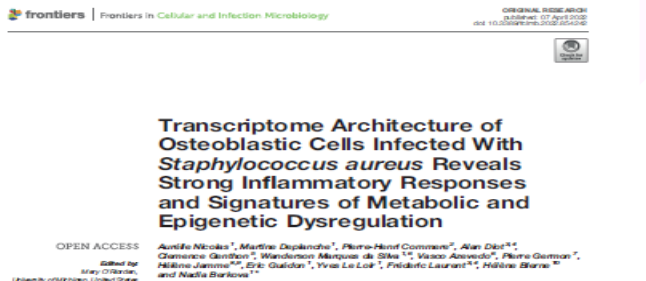
DOI: 10.1111/cmi.13204
RESEARCH ARTICLE
WILEY
Involvement of caspase-1 in inflammasomes activation and bacterial clearance in *S. aureus*-infected osteoblast-like MG-63 cells
Elma Lima Leite[1,2] | Arthur Gautron[3] | Martine Deplanche[1] | Aurélie Nicolas[1] | Jordane Ossemond[1] | Minh-Thu Nguyen[4] | Fillipe L. R. do Carmo[1,2] | David Gilot[3] | Vasco Azevedo[2] | Friedrich Götz[5] | Yves Le Loir[1] | Michael Otto[6] | Nadia Berkova[1]


frontiers | Frontiers in Immunology
TYPE Original Research
PUBLISHED 31 May 2023
DOI 10.3389/fimmu.2023.1138539
OPEN ACCESS
Development of innate immune memory by non-immune cells during *Staphylococcus aureus* infection depends on reactive oxygen species
Emmanuel Chaumond[1], Sandrine Peron[1], Nathalie Daniel[1], Yann Le Gouar[1], Éric Guédon[1], David L. Williams[2], Yves Le Loir[1], Gwénaël Jan[1] and Nadia Berkova[1]*


frontiers | Frontiers in Cellular and Infection Microbiology
OPEN ACCESS
Transcriptome Architecture of Osteoblastic Cells Infected With *Staphylococcus aureus* Reveals Strong Inflammatory Responses and Signatures of Metabolic and Epigenetic Dysregulation

COLLABORATIONS

THANK YOU FOR YOUR ATTENTION

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