

# Inflammasome activation and an involvement of Caspase-1 in a bacterial clearance during S. aureus infection.

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# Inflammasome activation and an involvement of Caspase-1 in a bacterial clearance during *S. aureus* infection

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

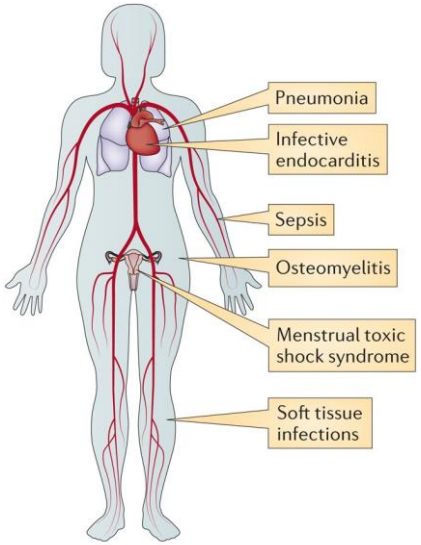
**Gram-positive bacterium that is carried by up to 50% of healthy people**

**Human:**

Mild skin infections



Life-threatening infections

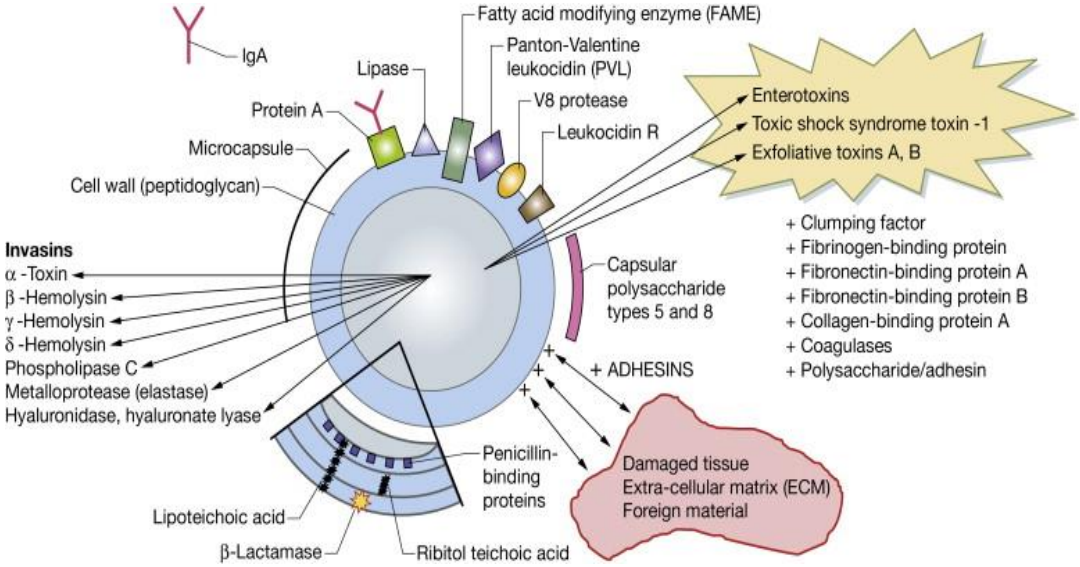



Nature Reviews | Microbiology

**Dairy_cattle**:

Chronic mastitis






***S. aureus* infections induce serious clinical problems. Despite antimicrobial therapy, there is a high percentage of relapse, leading to the chronicity**

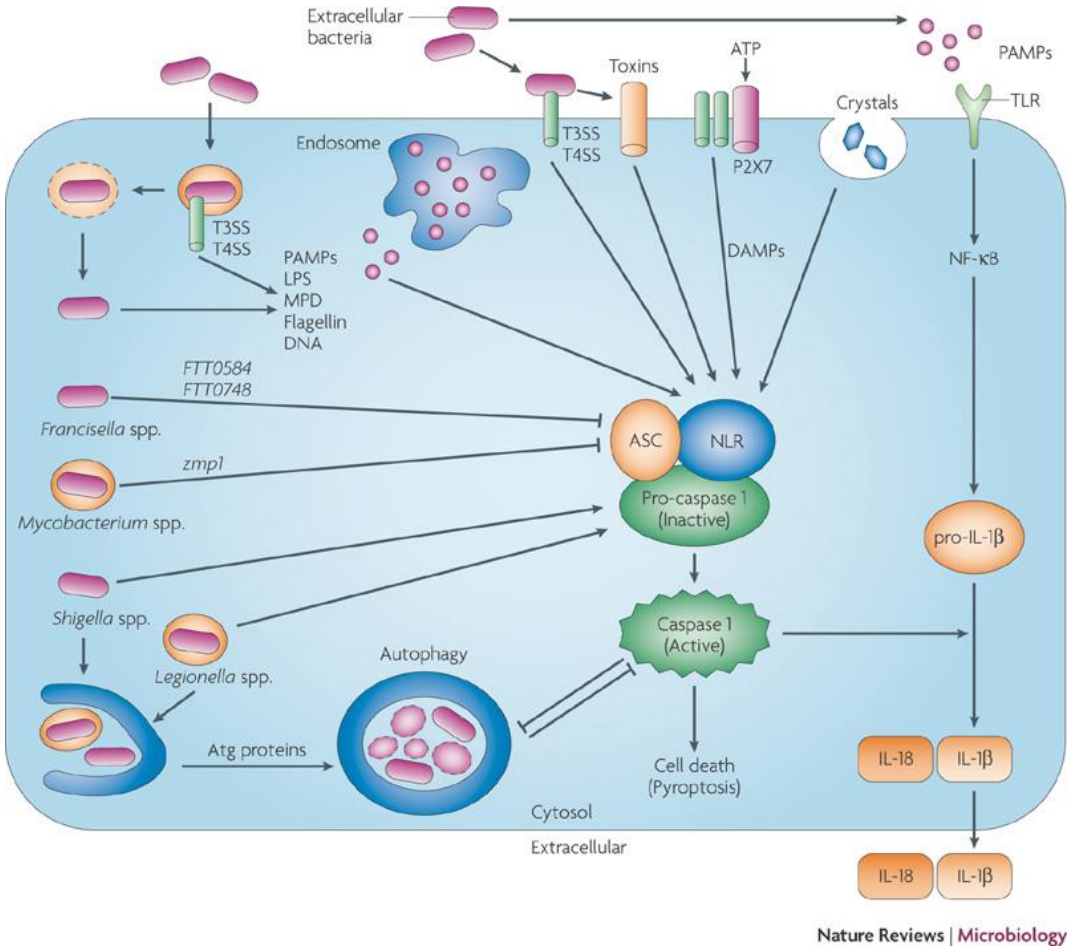
# INFLAMMATION
## as a defense mechanism against infection and injury

| Cause of inflammation | Physiological purpose | Outcomes |
|---|---|---|
| • **Microbial infection**<br>• Noxious substances<br>• Tissue stress<br>• Tissue injury | • **Defense from microbial infection**<br>• Expulsion of noxious substances<br>• Tissue repaire<br>• Adaptation to stress | • DNA damage<br>• Tissue damage<br>• Autoimmune diseases<br>• Disease of homeostasis<br>• Fibrosis, metaplasie, cancer |

# Innate immune system instructs adaptive immune responses

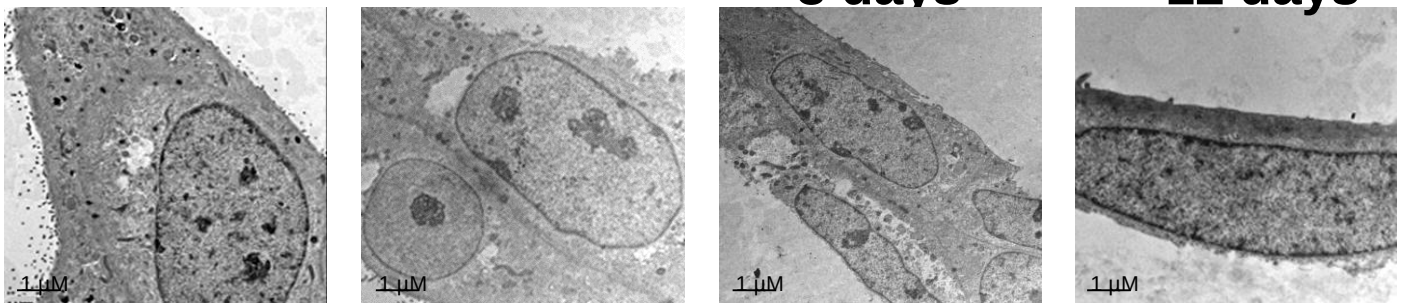
**Persistent inflammation induces the activation of inflammasomes that are central players of innate immunity to pathogens**

**Inflammasomes are multi-protein signaling complexes that are composed of a sensor (NLR), an adaptor (ASC), and a zymogen procaspase-1**

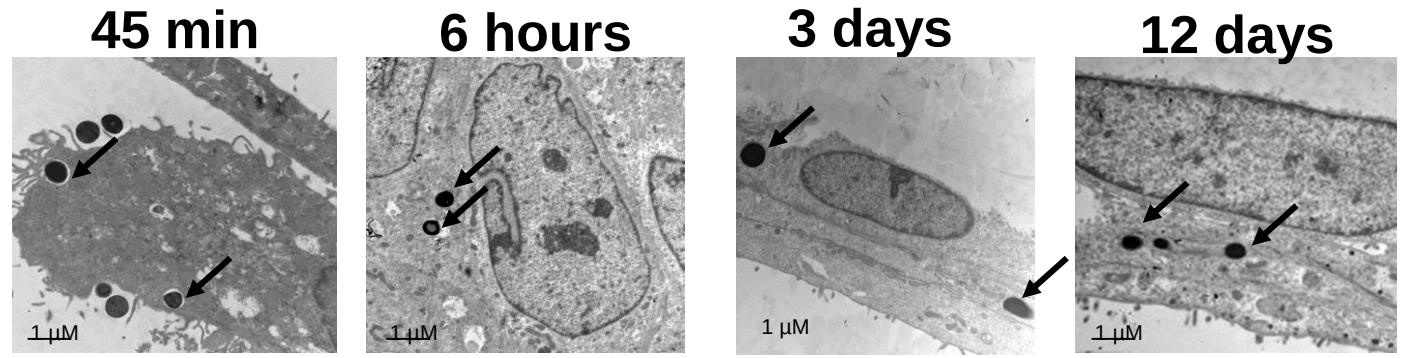


# *Staphylococcus aureus*, a facultative intracellular pathogen

**Control MG-63 cells**



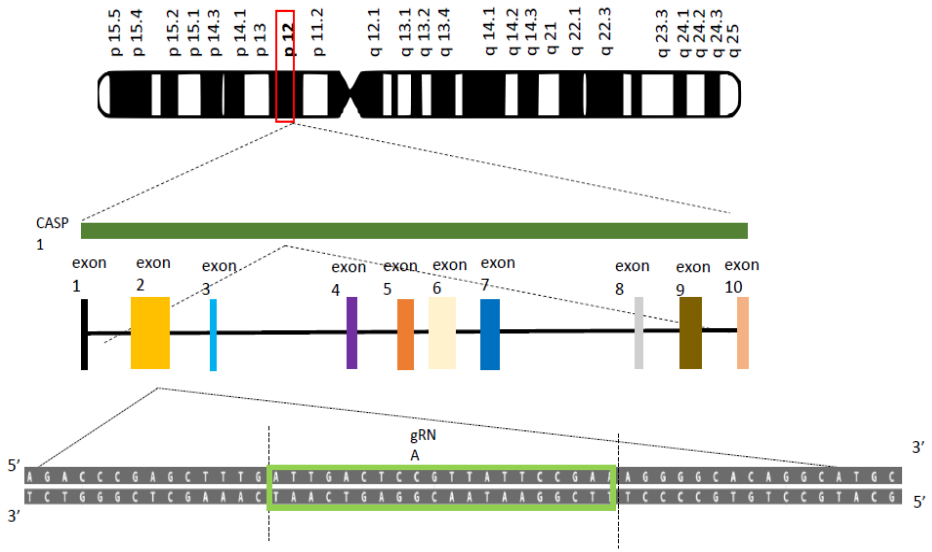

**MG-63 cells + *S. aureus***




**A long-term *S. aureus* infected cell culture as a model of chronic infection**

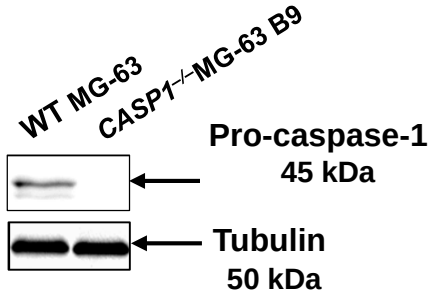
# Generation of *CASP1*$^{-/-}$ *MG*-63 cells using the CRISPR-Cas9 gene editing system

Human Chromosome 11 map depicting the position of Caspase-1

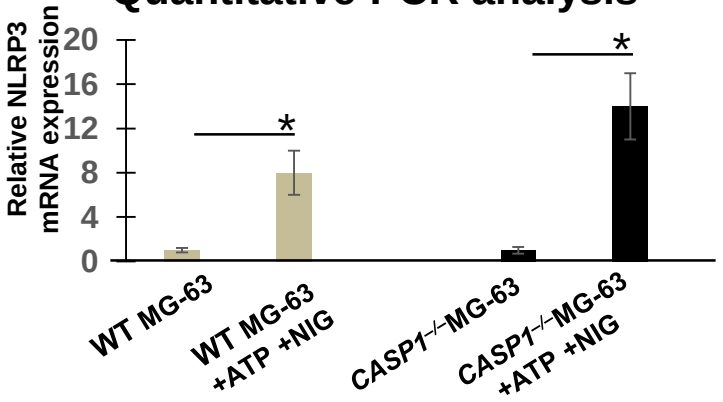



***DNA target**, GRCh38.p12 (GCF_000001405.38) Chr 11 (NC_000011.10):105,024,544 - 105,036,108

Western blot analysis



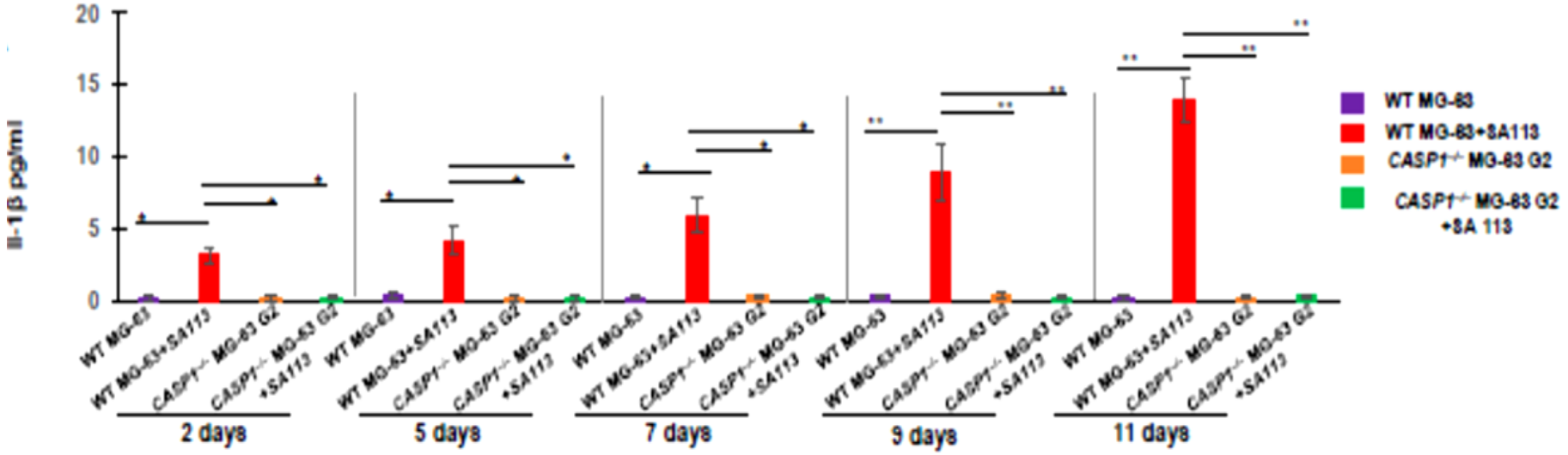

Quantitative PCR analysis




**CRISPR/Cas9 edits genes by precisely cutting DNA and then letting natural DNA repair processes to take over**

**Depletion of Caspase-1 does not impair upstream events of inflammasome formation**

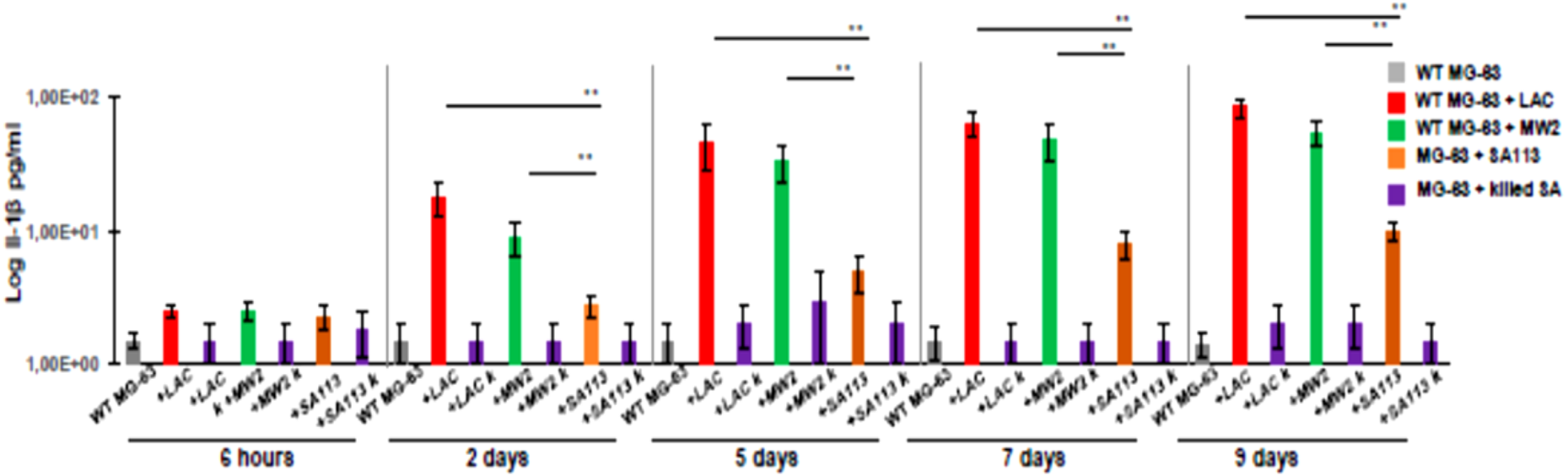
# *S. aureus*-induced release of IL-1β by infected WT MG-63 cells and CASP1$^{-/-}$MG-63 clone




**WT MG-63 cells and CASP1$^{-/-}$MG-63 clones express NLRP3 and form ASC specks**
**Only WT MG-63 cells produce IL-1β following the exposure *S. aureus***

**Monitoring of IL-1β produced by both cell lines are used for the analysis of inflammasomes activation**

# *S. aureus* strain-dependent release of IL-1β by infected MG-63 cells

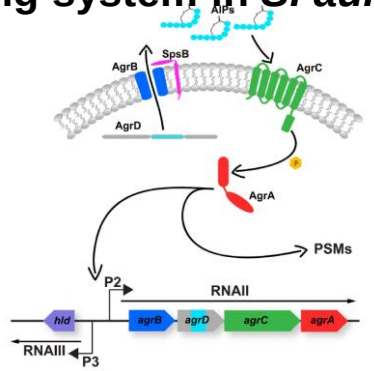



**Agr-defective SA113 strain induce a low levels of IL-1β**

**Strains MW2 and LAC (pTXΔ16), which harbor a functional Agr system induce a high level of IL-1β**

**Possible involvement of the Agr**

**The accessory gene regulator (Agr), the gene cluster that encodes the peptide quorum-sensing system in *S. aureus***



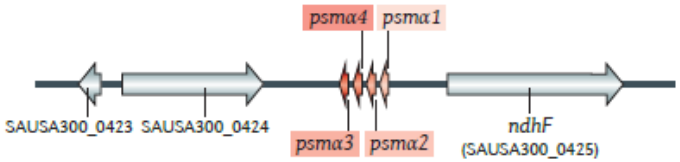
# Phenol-soluble modulins peptides (PSMs) define the virulence potential of *S. aureus*

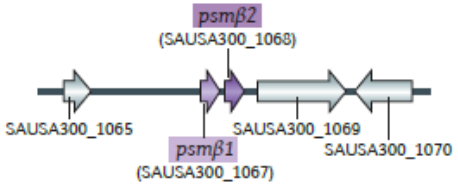
**PSMα1-PSMα4**
**δ-toxin**

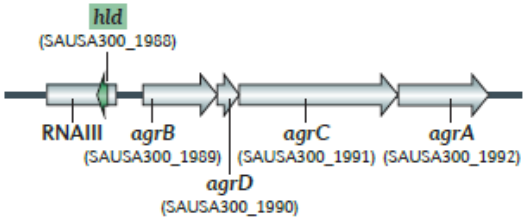
**20-25 amino acids**

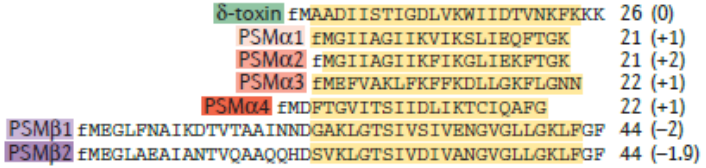
**PSMβ**

**44 amino acids**

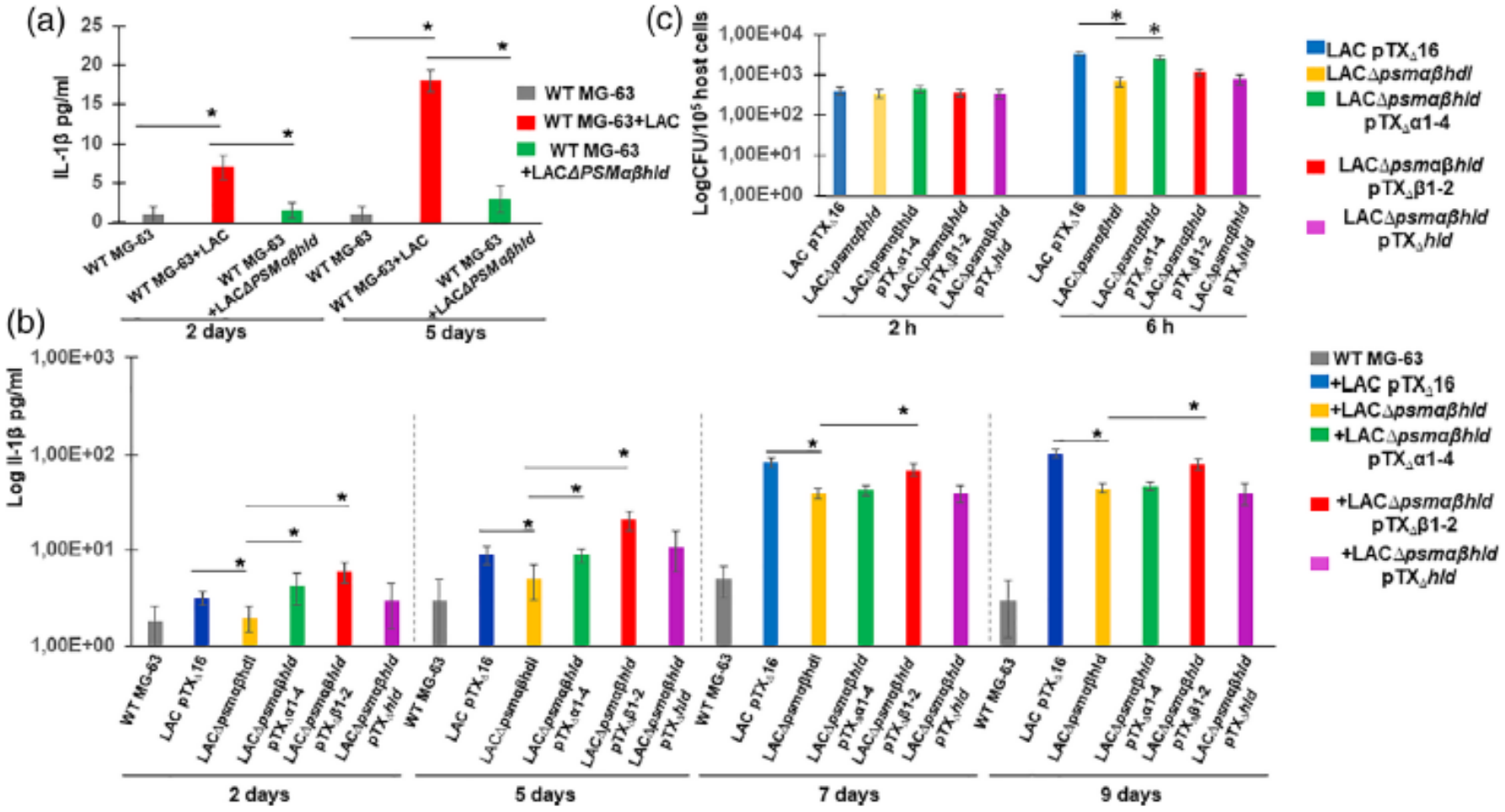


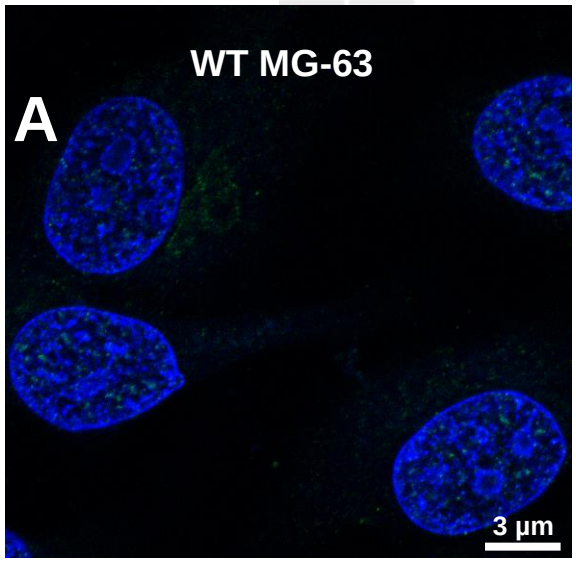



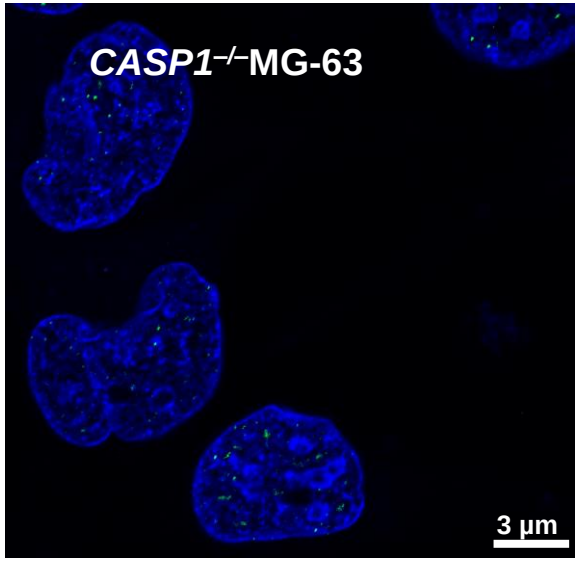



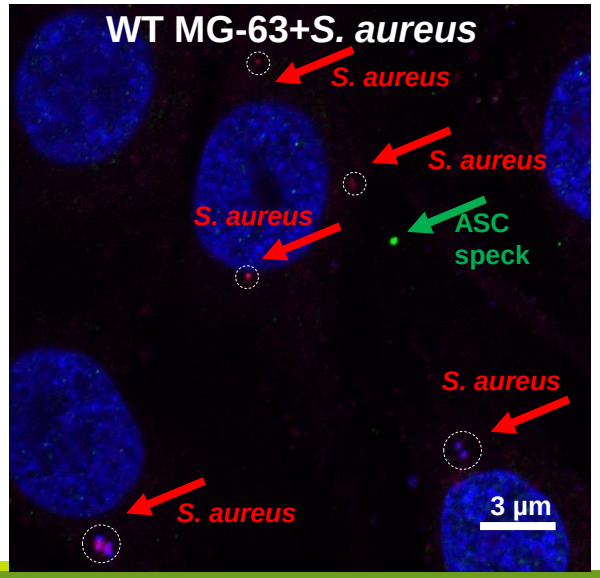
# S. aureus PSM toxins are involved in stimulation of IL-1β release by infected MG-63 cells

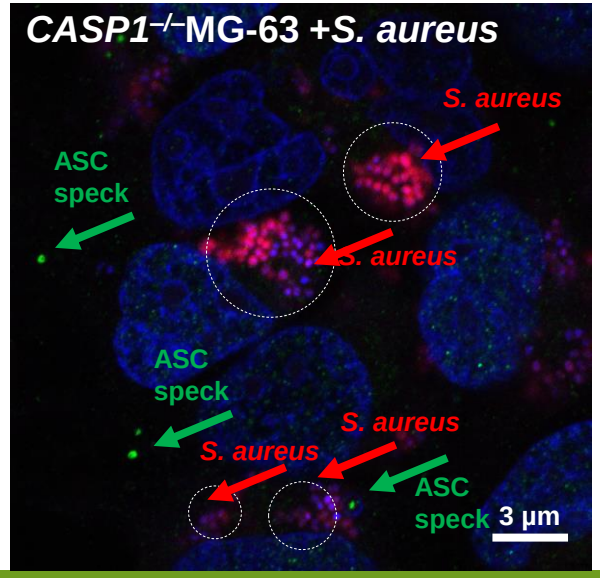


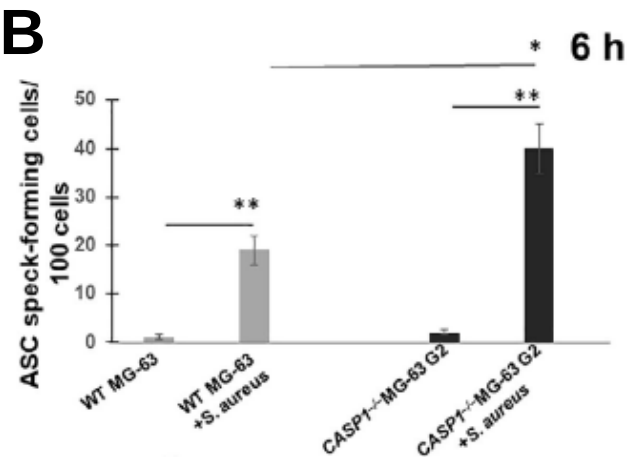
# Higher number of ASC specks in *S. aureus* infected CASP1$^{-/-}$ MG-63 cells compared to WT MG-63 cells

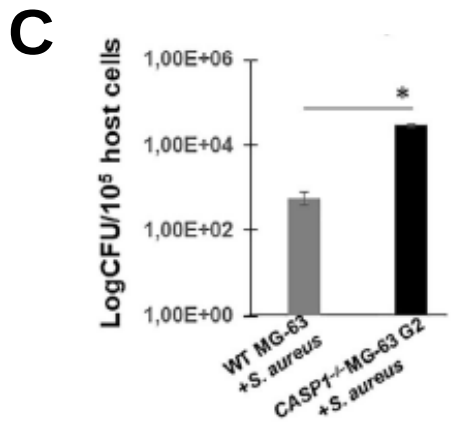


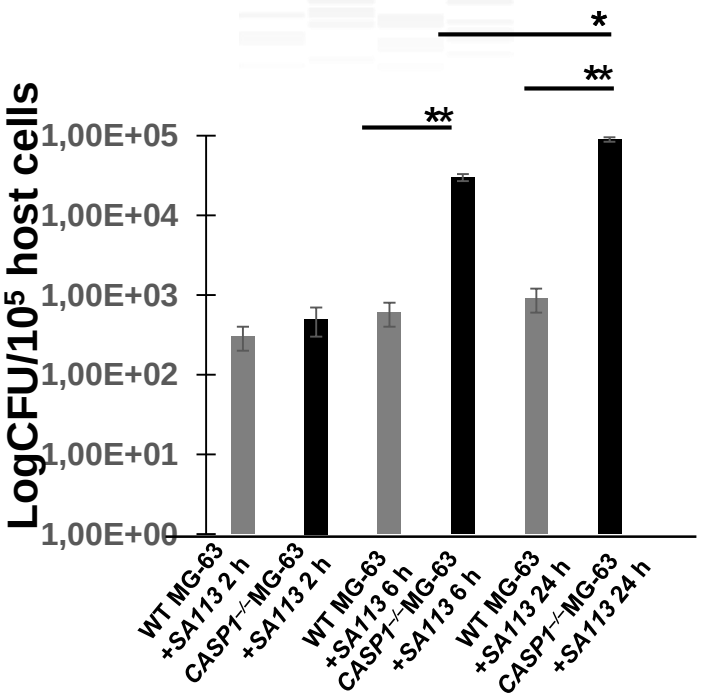



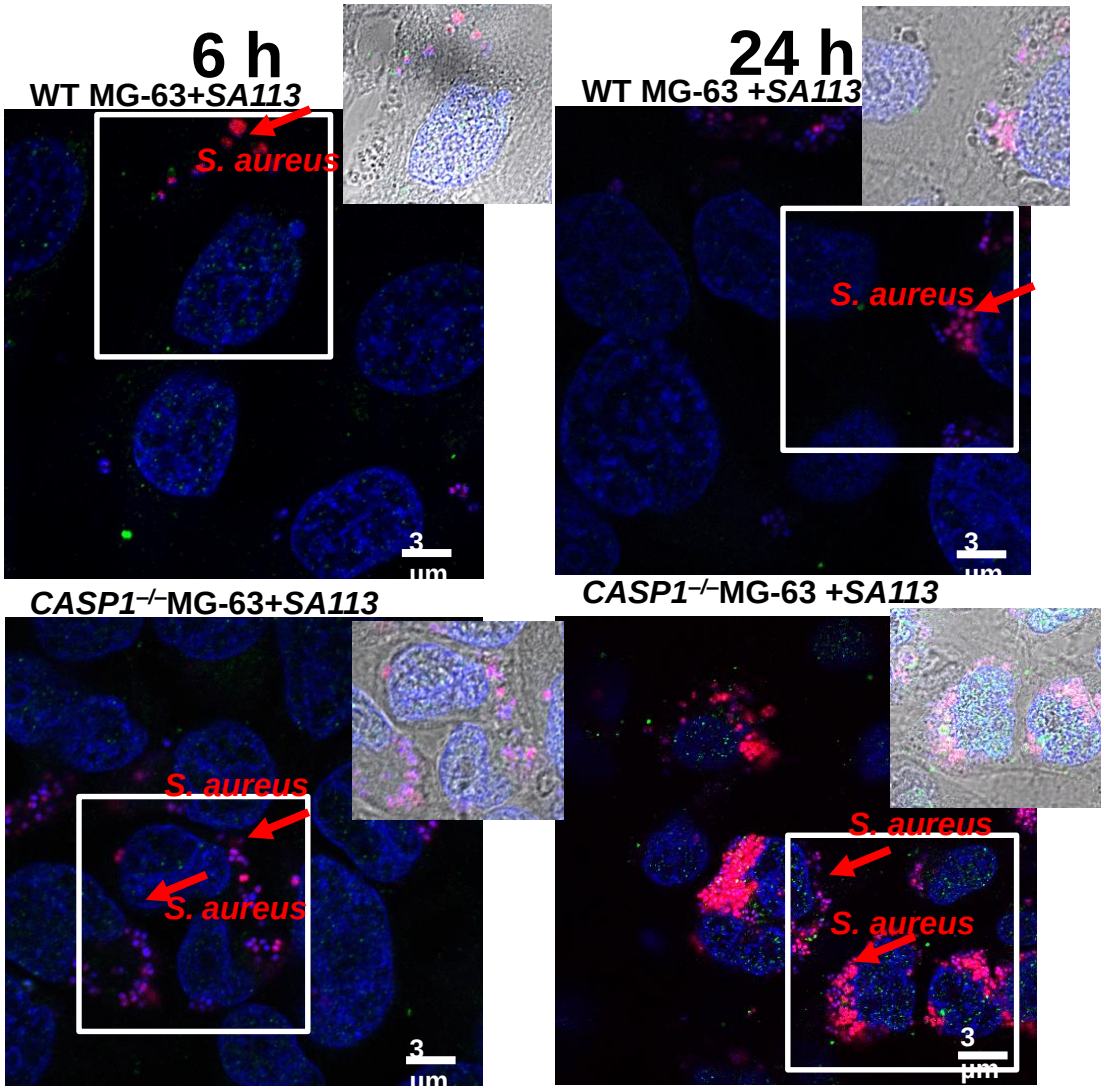



# *S. aureus* clearance by osteoblast-like MG-63 cells depends on caspase-1

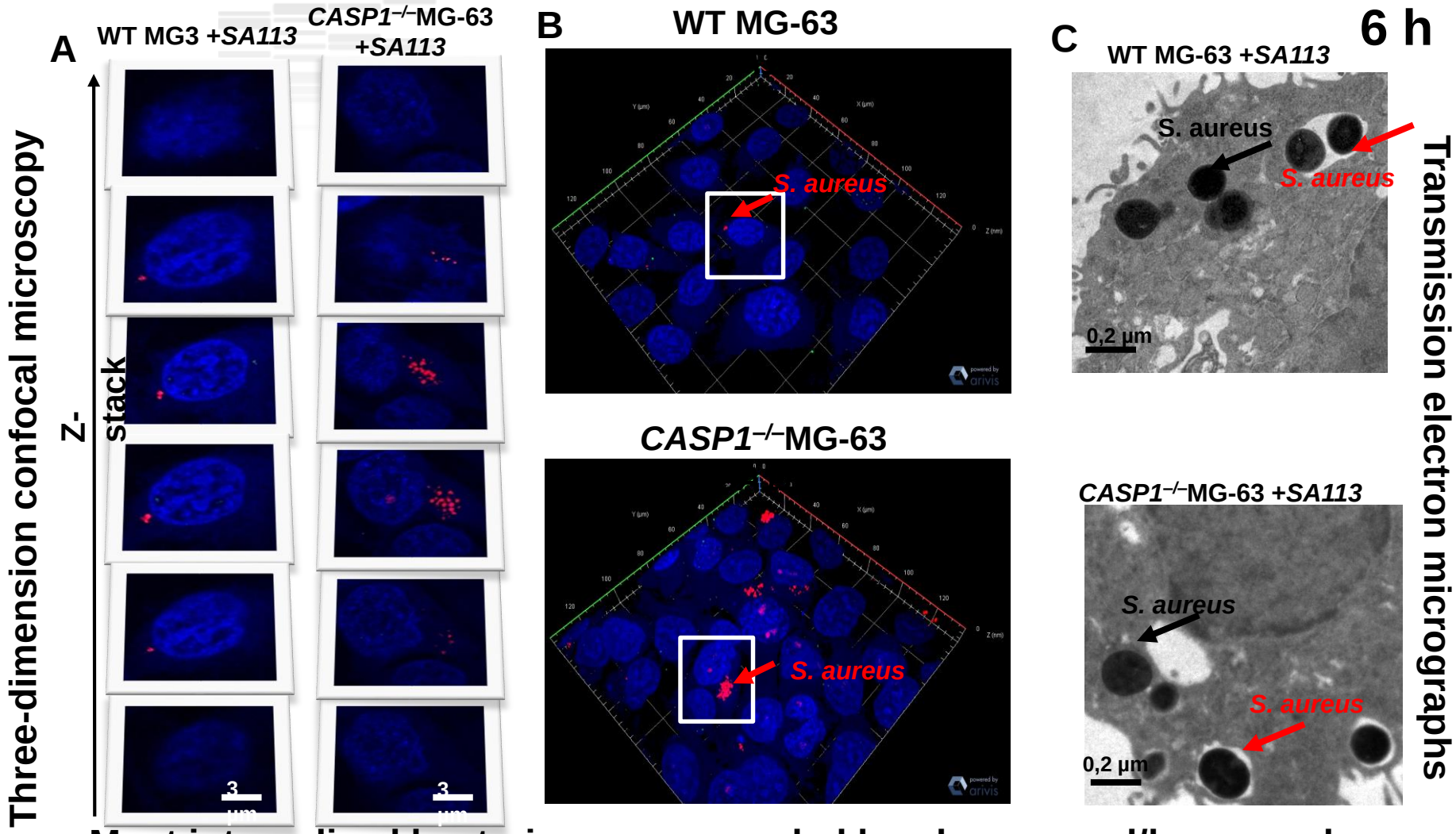



**Internalization of *S. aureus* (2h) was not impaired in CASP1$^{-/-}$MG-63 cells**

**Higher number of intracellular *S. aureus* was observed in CASP1$^{-/-}$ MG-63 cells compared to WT MG-63 cells 6h and 24h post-infection**

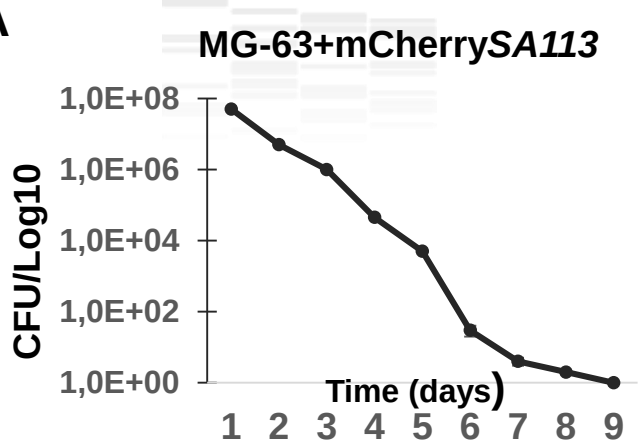
# Cytoplasmic localization of internalized *S. aureus*




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

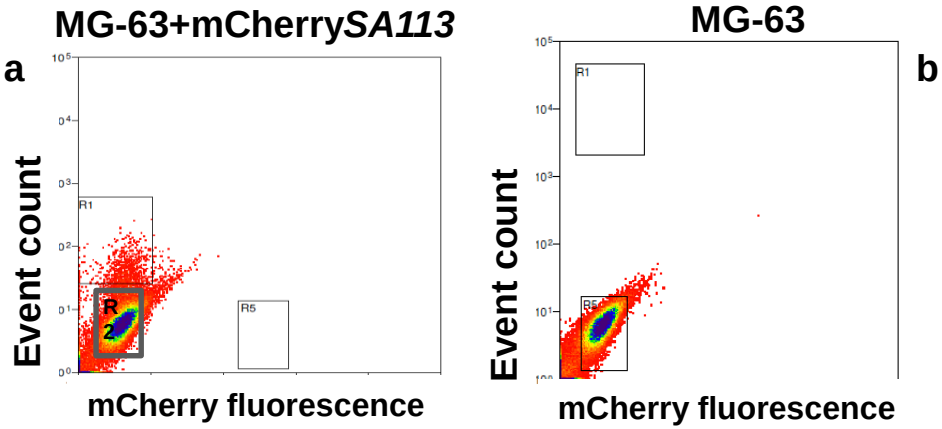
# Development of an infection model to isolate solely cells containing internalized *S. aureus*

A



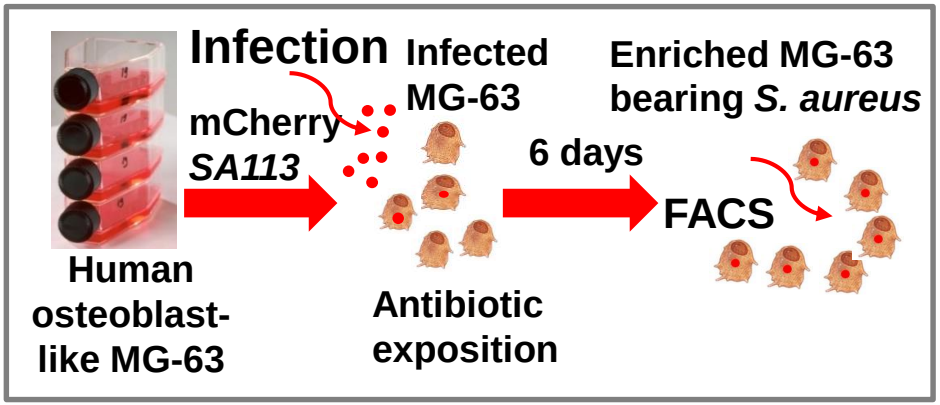

Survival curve of mCherrySA113 bacteria internalized into MG-63 cells

C



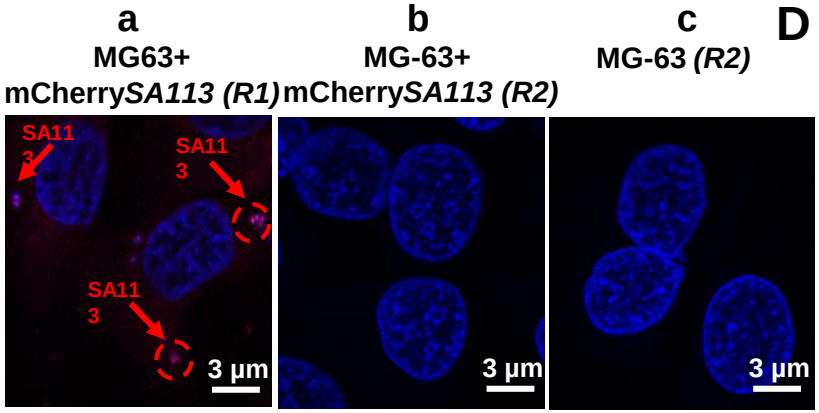

*S. aureus* infected cells (a) or uninfected control cells (b) were sorted using FACS

B




Scheme of the selection of mCherrySA113-containing MG-63 cells

D




Fluorescence microscopy

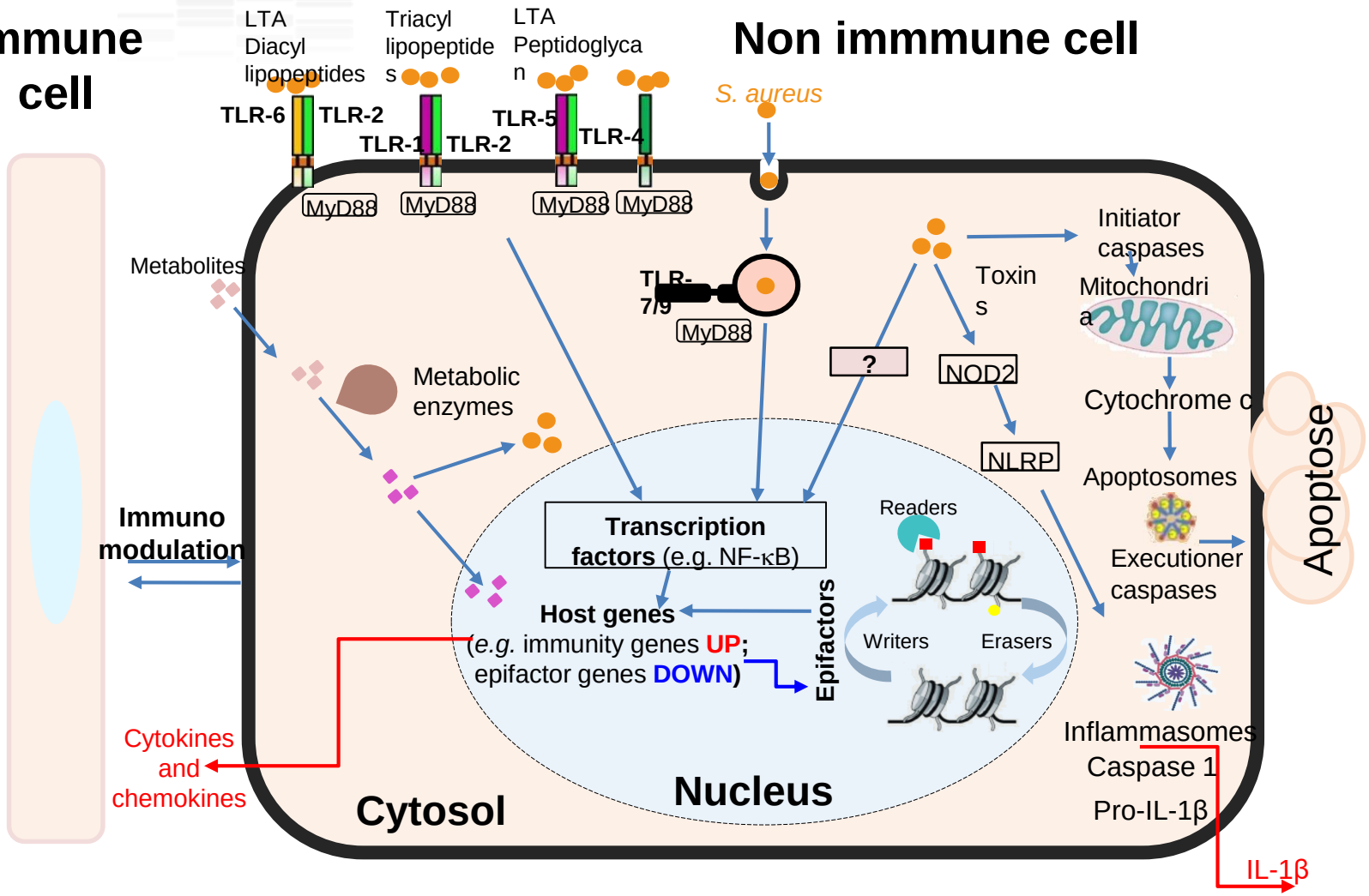
# Immune system and signal transduction genes are among the top highly induced DEGs




**Enriched Reactome pathways in infected cells.**

**Enriched Reactome pathways in infected cells. Gene-set enrichment analysis was performed in *S. aureus*-bearing cells compared to uninfected control cells by ReactomePA software.**

# Schematic model of the immune, metabolic and epigenetic dysregulated signatures induced *S. aureus* infection



# CONCLUSIONS

**Non-professional phagocytes induce an immune response against *S. aureus* through inflammasomes activation and processing of IL-1β**

**The outcome of the infection depends on the balance between the host immune response and the action of main *S. aureus* virulence factors, such as PSMs, whose production differ among the *S. aureus* strains**

**The active caspase-1 prevents exacerbated intracellular replication of *S. aureus* in non-professional phagocyte**

**Our findings suggest that pathogens, which inhibit caspase-1 activation, do so not only to govern the generation of inflammatory cytokines but also to permit bacterial replication**

**Our results provide an atlas of deregulated host genes and biological pathways and identify novel markers and potential candidates for prophylactic and therapeutic approaches**

# 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]

*Cellular Microbiology*. 2020;22:e13204.

SCIENTIFIC REPORTS

# Transcriptome Architecture of Osteoblastic Cells Infected With *Staphylococcus aureus* Reveals Strong Inflammatory Responses and Signatures of Metabolic and Epigenetic Dysregulation

*Aurélie Nicolas[1], Martine Deplanche[1], Pierre-Henri Commere[2], Alan Diot[3,4], Clemence Genthon[5], Wanderson Marques da Silva[1,6], Vasco Azevedo[6], Pierre Germon[7], Hélène Jamme[8,9], Eric Guédon[1], Yves Le Loir[1], Fréderic Laurent[3,4], Hélène Bierne[10] and Nadia Berkova[1*]*

frontiers in Cellular and Infection Microbiology

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OPEN

# *Staphylococcus aureus* induces DNA damage in host cell

Martine Deplanche[1], Nassim Mouhali[1], Minh-Thu Nguyen[2], Chantal Cauty[1], Frédéric Ezan[3], Alan Diot[4,5], Lesly Raulin[6], Stephanie Dutertre[6], Sophie Langouet[3], Patrick Legembre[7], Frederic Taieb[8], Michael Otto[9], Frédéric Laurent[4,5], Friedrich Götz[2], Yves Le Loir[1] & Nadia Berkova[1]

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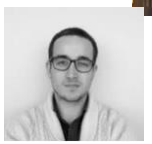


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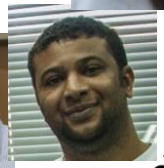
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спасибо
谢谢
GRACIAS
THANK YOU
ありがとうございました
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OBRIGADO


Merci !