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Staphylococcus aureus induces DNA damage in host cell

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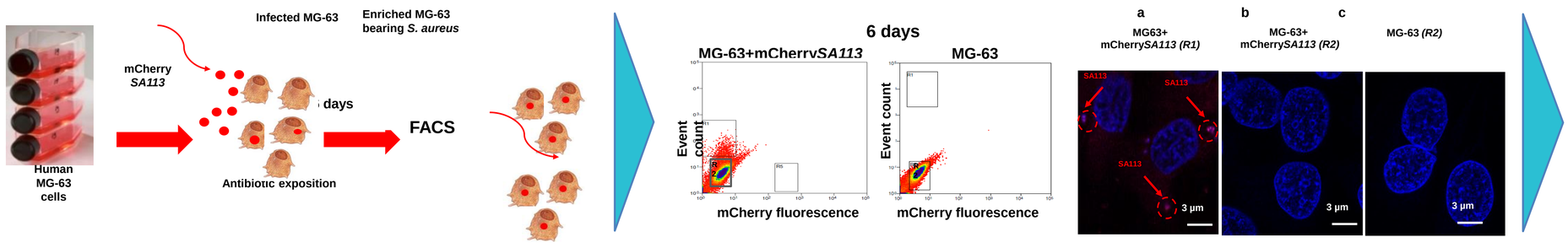


CONTEXT

Eukaryotic cells are permanently exposed to environmental and endogenous factors that induce DNA damage, thus affecting genomic integrity. The host cells counteract the consequences of lesions by DNA damage response and checkpoint systems that repair DNA structure or trigger cell death when DNA is irredeemably damaged. *S. aureus*, a highly versatile gram-positive bacterium, can cause a multitude of human diseases ranging from mild superficial skin to life-threatening disseminated infections. *S. aureus* is one of the most prevalent pathogen that cause chronic ruminant mastitis. Chronic *S. aureus* infection is likely to be associated with the internalization of the pathogen by host cells, where bacteria are protected from host defenses.
We aimed to investigate whether *S. aureus* can compromise host genomic integrity.

EXPERIMENT DESIGN

DEVELOPMENT OF AN INFECTION MODEL TO ISOLATE SOLELY CELLS CONTAINING INTERNALIZED *S. aureus*

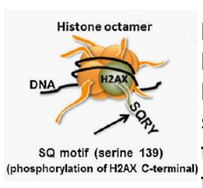


RNA sequencing of hosting intracellular *S. aureus* cells or non-infected cells.

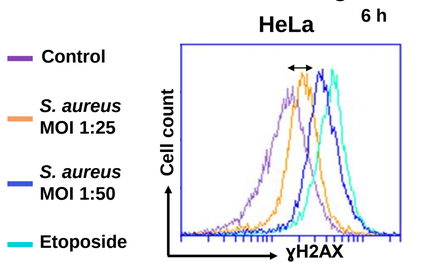
RESULTS

1 *S. aureus* INDUCES DNA DAMAGE IN HOST CELLS

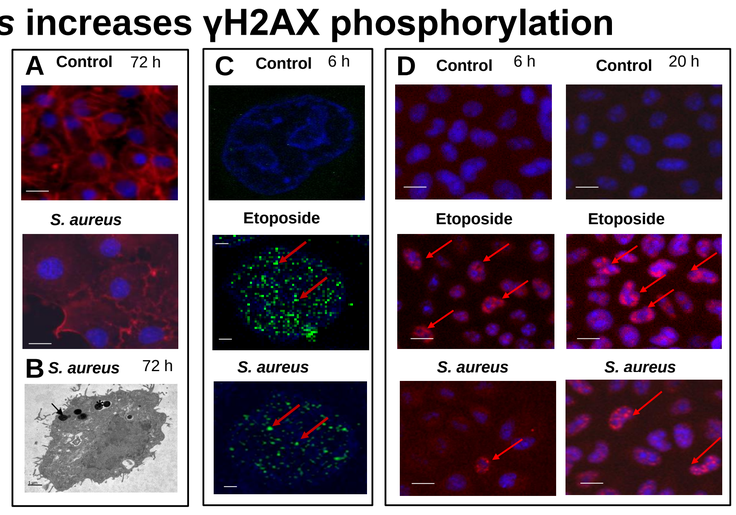
S. aureus increases γH2AX phosphorylation



Phosphorylation of H2AX at Ser 139 (γ-H2AX) is the most sensitive marker for the examination of the DNA damage



Quantification of γH2AX by flow cytometry

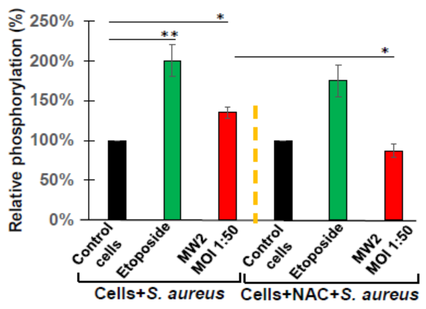


High Content Screening analysis. Cells were stained for γH2AX

2 *S. aureus* INDUCES 8-OXOG DNA LESIONS IN THE HOST CELLS

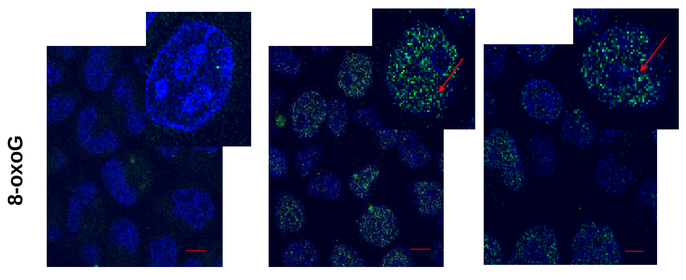
S. aureus infection induces reactive oxygen species (ROS)

ROS inhibitor reduces a *S. aureus*-induced H2AX phosphorylation



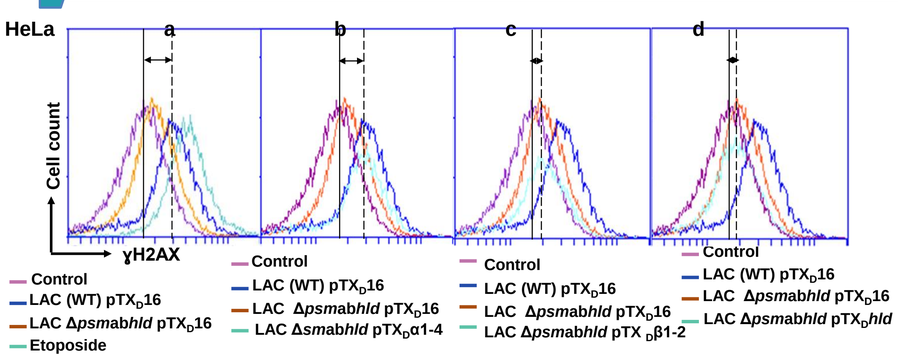


ROS primarily damage guanine among the DNA bases. Guanine's oxidized product 7,8-dihydro-8-oxoguanine (8-oxoG) is the most predominant DNA oxidative lesion in the genome



Cells were stained with anti 8-oxoG DNA lesion antibody

3 *S. aureus* PHENOL-SOLUBLES MODULINES PSMα1–4 INDUCE, WHILE LPLs DAMPEN HOST DNA DAMAGE

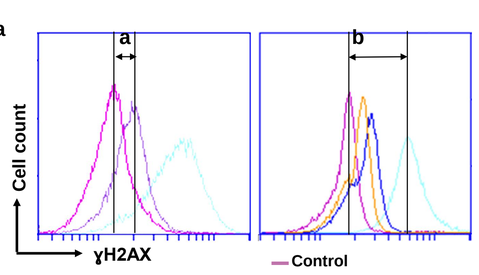


LAC (WT) pTXΔ16 contains plasmid pTXΔ16 (blue line)
LAC Δ*psmαβhld* pTXΔ16- PSM deletion mutant (yellow line)
Complemented mutants: LACΔ*psmαβhld* pTXΔα1-4 (blue-green line, b)
LACΔ*psmαβhld* pTXΔβ (blue-green line, c)
LACΔ*psmαβhld* pTXΔhld (blue-green line d)

Constructed in the Michael Otto laboratory, NIH, USA

Lipoproteins

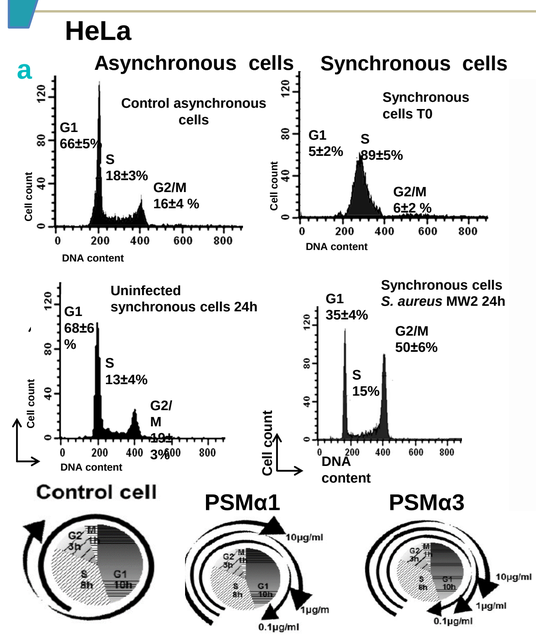
A pathogenicity island that contains a cluster of lipoprotein-encoding genes, lpl

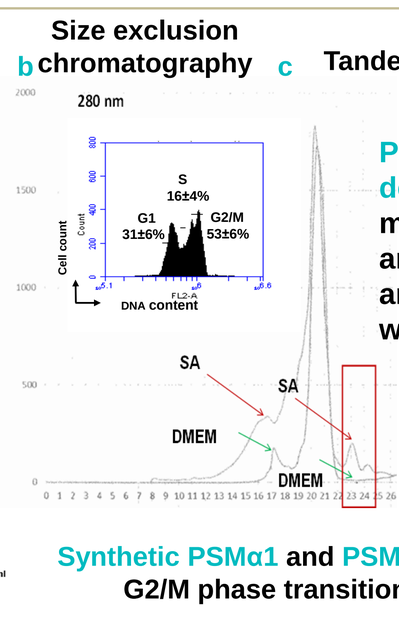


USA300 wt (a, b, blue)
USA300Δlpl, the deletion mutant (b, blue-green)
USA300Δlpl (pTX30-*lpl*) the complemented mutant (b, yellow)

Constructed in the Fritz Götz laboratory, University of Tubingen, Germany

4 *S. aureus* INDUCED A G2/M PHASE TRANSITION DELAY

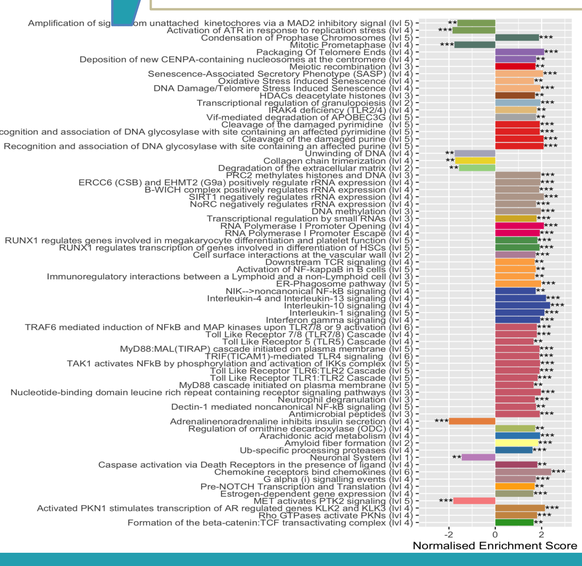




PSM peptide derivatives: the majority were PSMα1 and PSMα3. PSMα2 and PSMa4 derivatives were also identified

Synthetic PSMα1 and PSMα3 induce a G2/M phase transition delay

5 GENE-SET ENRICHMENT ANALYSIS USING REACTOME DATABASE



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

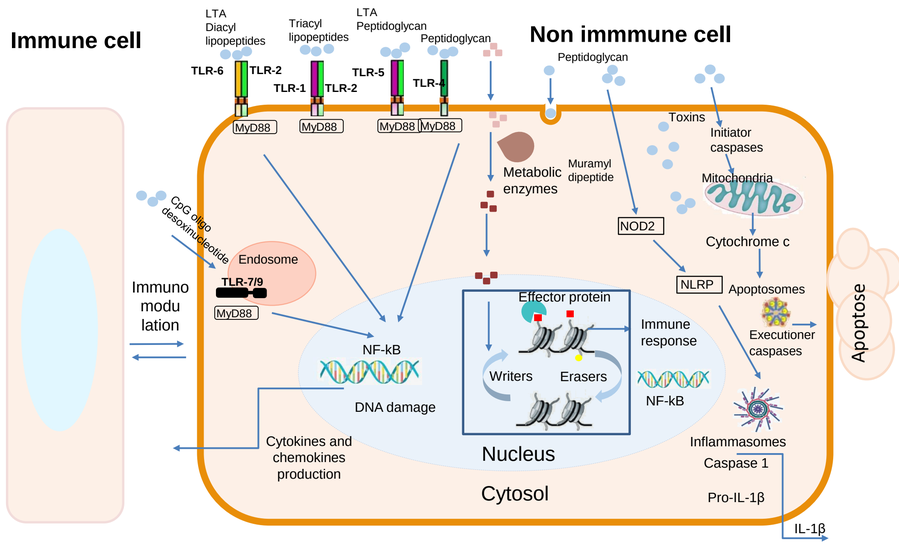
Transcriptional reprogramming of genes associated to the cell cycle progression, DNA damage and repair

Transcriptional reprogramming of genes involved in metabolism

Transcriptional reprogramming of genes involved in epigenetic regulation

CONCLUSION

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



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