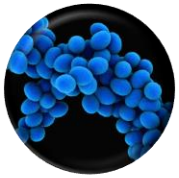
Persistence aspects of Staphylococcus aureus-host interaction

Nadia Berkova

PERSISTENCE ASPECTS OF *Staphylococcus aureus*-HOST INTERACTION

Nadia Nadejda Berkova

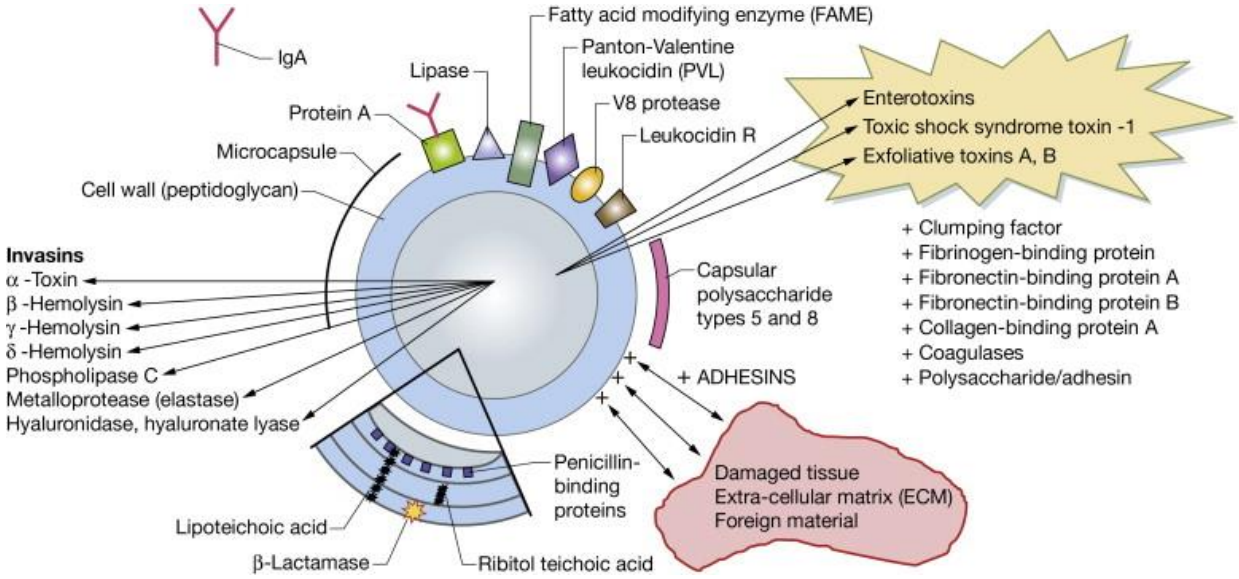
UMR1253 STLO, INRA Agrocampus Ouest, Rennes)



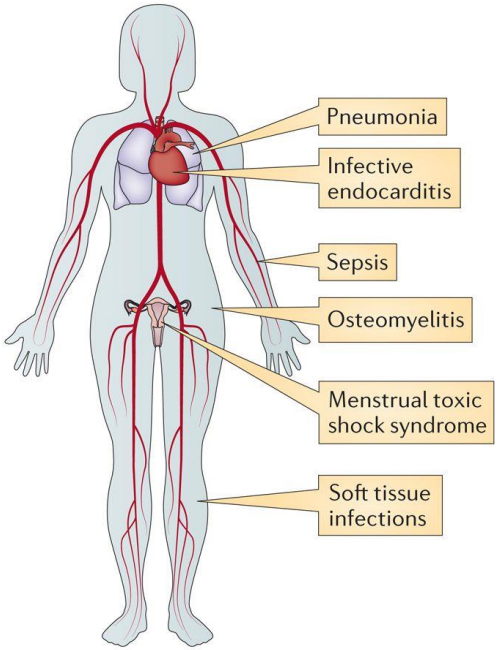
Staphylococcus aureus

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

***S. aureus* can cause infections, ranging from minor skin infections to severe systemic infections**



Life-threatening infections

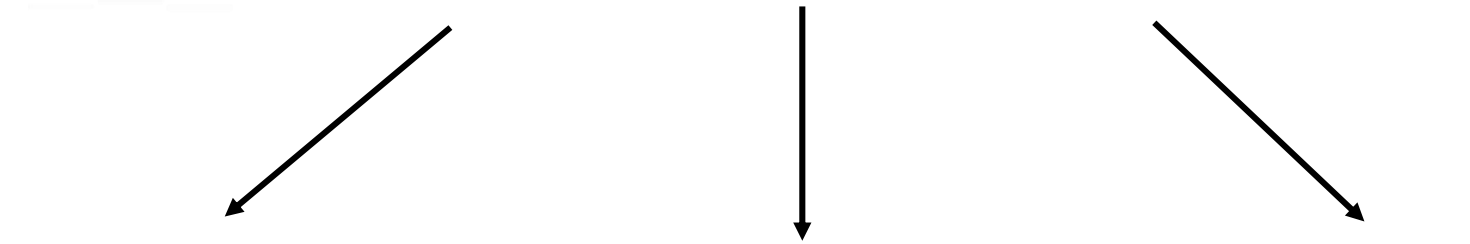


Nature Reviews | Microbiology

***S. aureus* infections present clinical challenges, especially in chronic cases with persistent inflammation**

PERSISTENT INFECTIONS

a prolonged presence of Infectious agent in the host

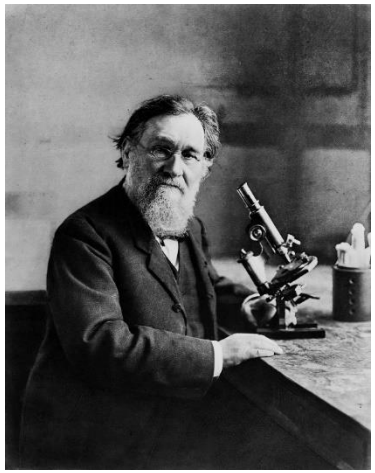


PERSISTENCE

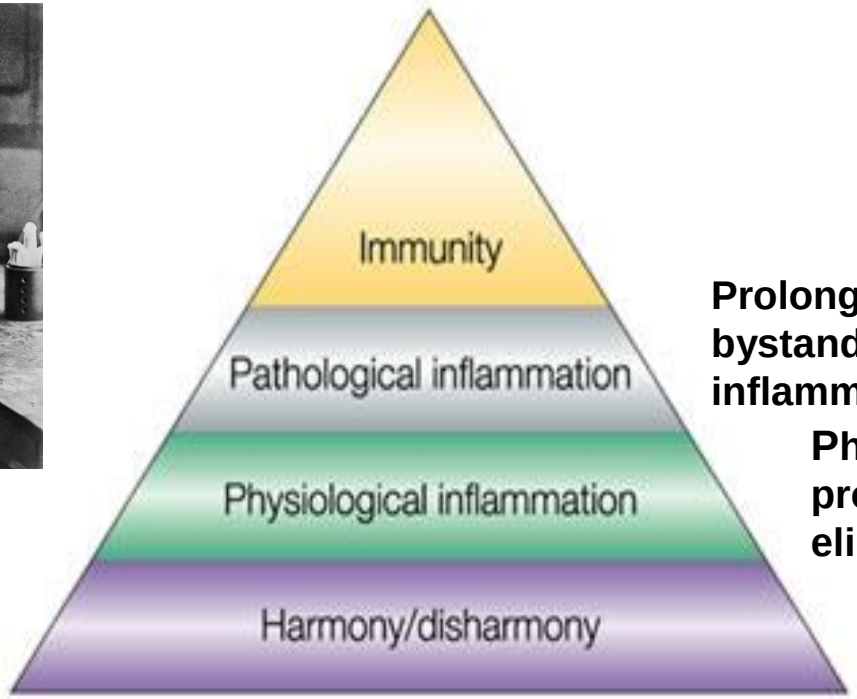
REPROGRAMMING OF THE TRANSCRIPTIONAL PROFILES OF PATHOGEN AND HOST CELLS

PERSISTENT INFECTIONS ARE ASSOCIATED WITH CHRONIC INFLAMMATION

Metchnikoff's theory of inflammation



1845-1916



Nature Reviews | Molecular Cell Biology

Prolonged inflammation causes harm in bystander normal tissues and promotes inflammatory diseases

Physiological inflammation is a protective response mediating the elimination of injurious agents

Homeostasis

Alfred Tauber

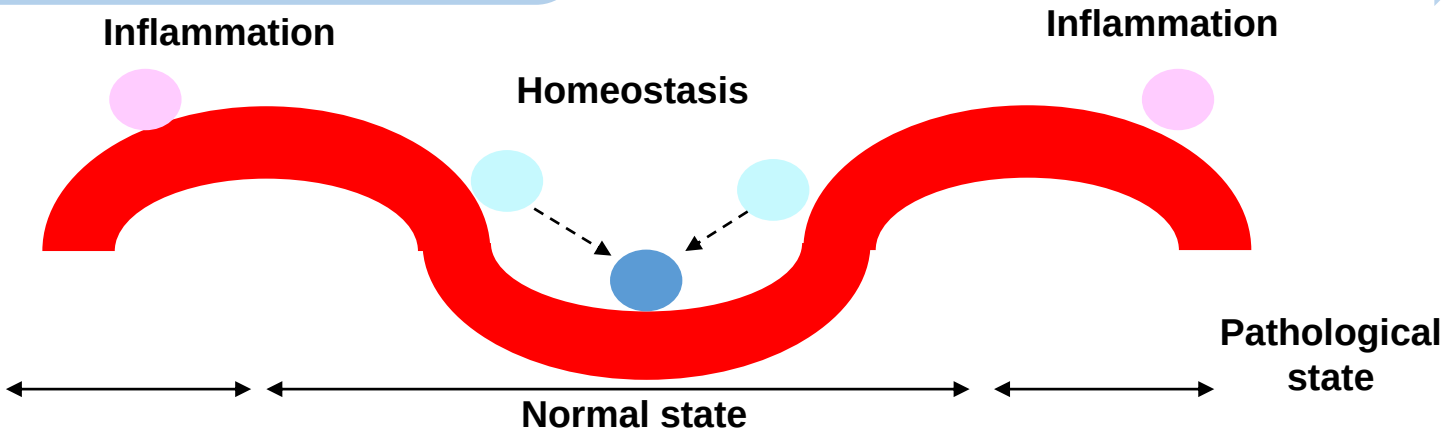
HOMEOSTATIS AND INFLAMMATION

Homeostasis

- Maintains the stability of biological system

Inflammation

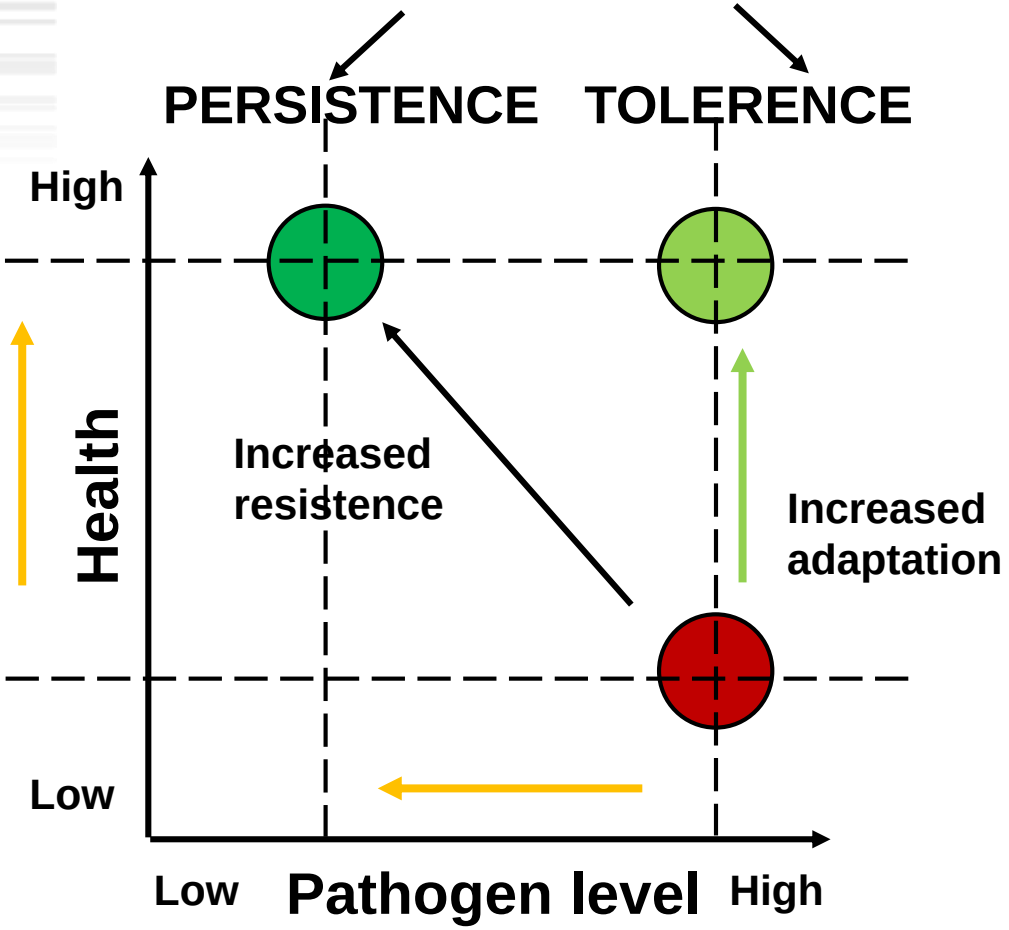
- Result of perturbations that exceed the homeostatic capacity of the system



Medzhitov R. IBiology

INFECTION

TWO DEFENSE STRATEGIES

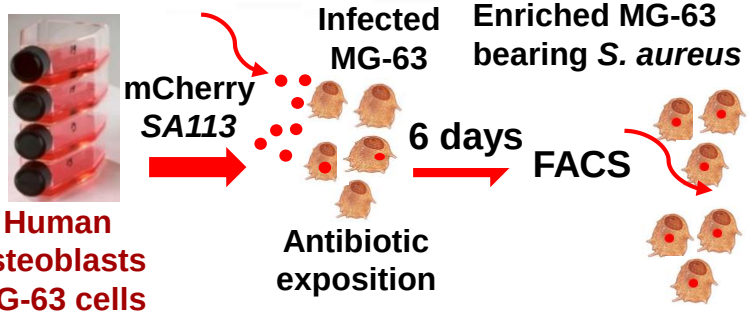


Adapted from J.S.Ayres and D.S.Schneider, 2008

UNRAVELING NON-IMMUNE CELL RESPONSES DURING CHRONIC *S. aureus* INFECTION: PRIMING versus TOLERANCE

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

a



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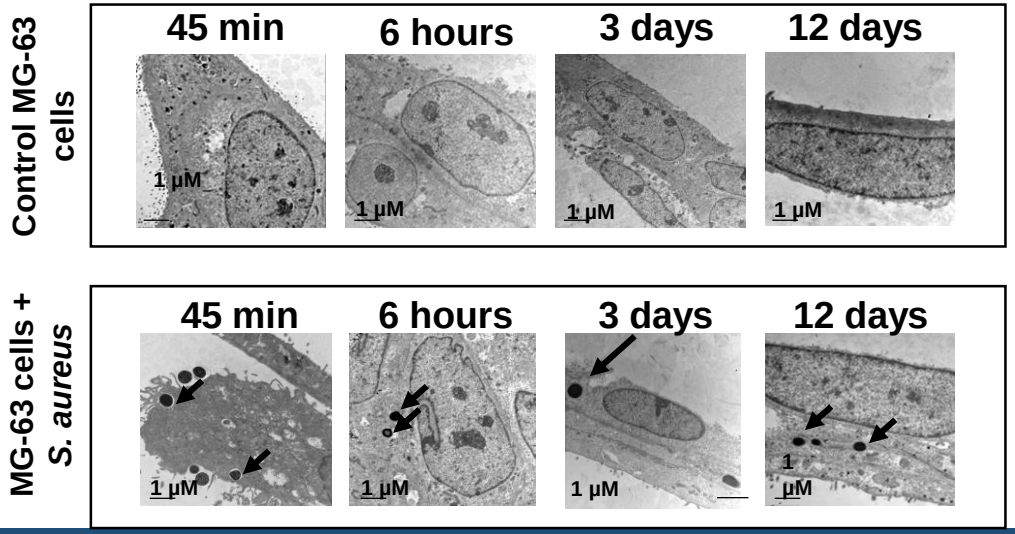

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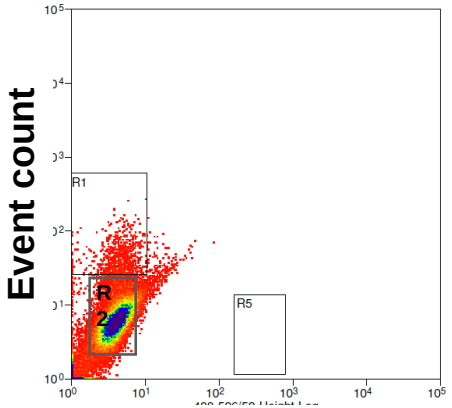

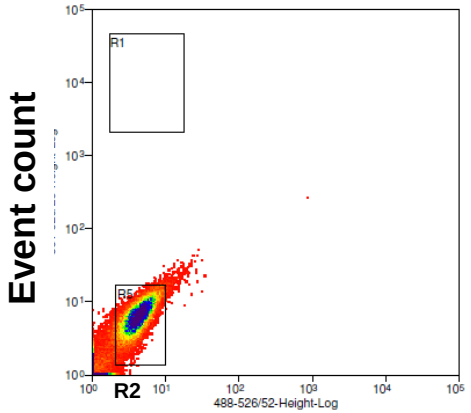

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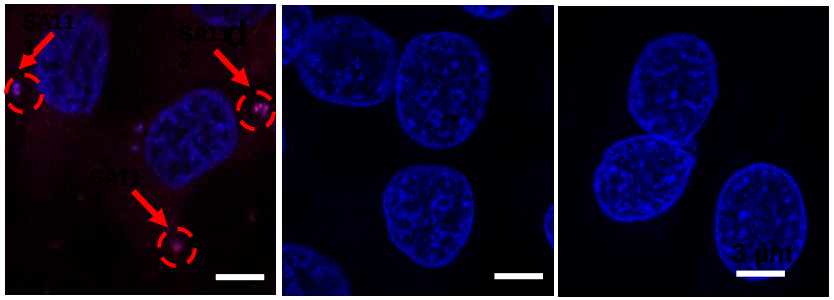
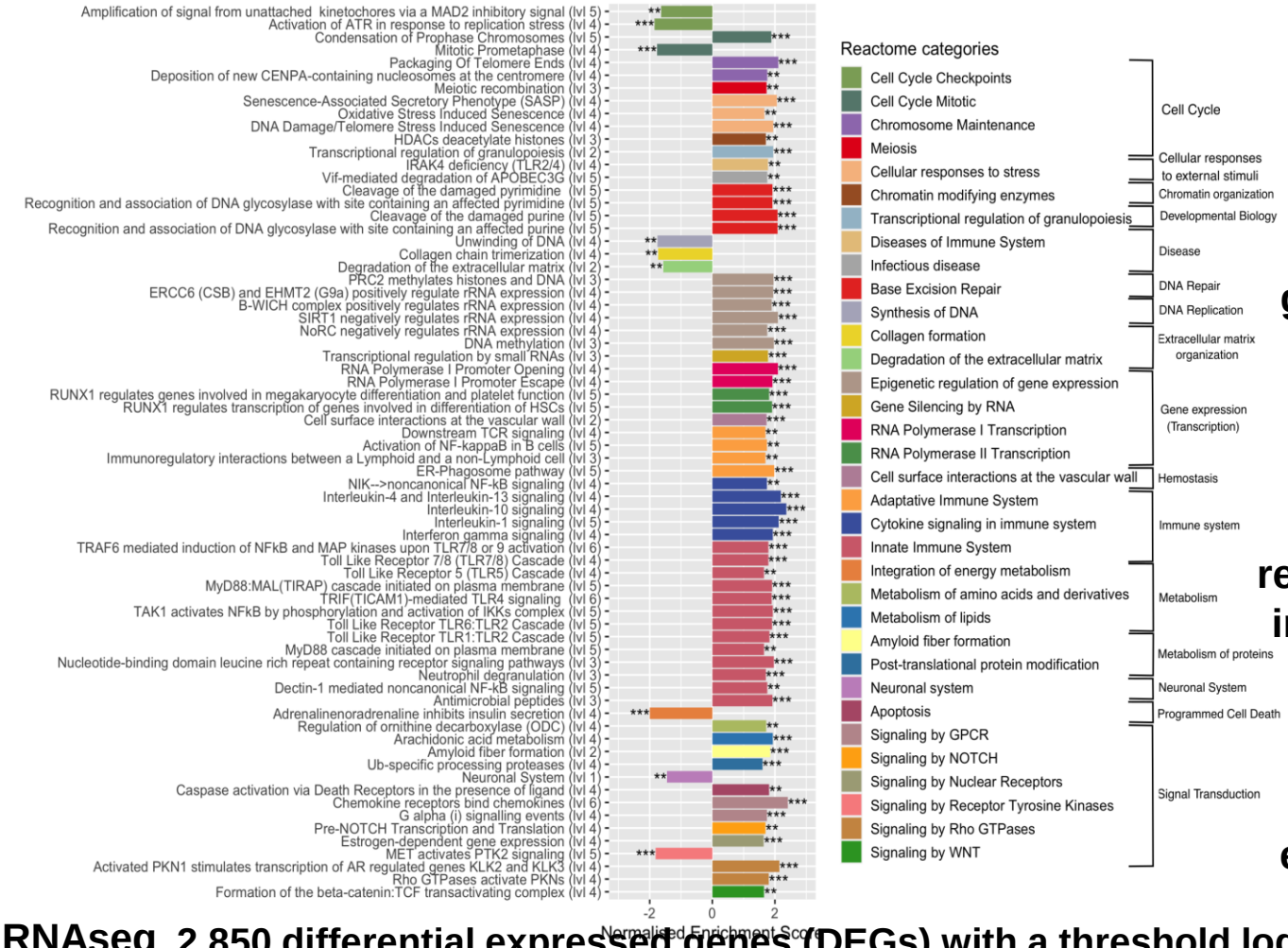


Nicolas et *al.*, Front. Cell. Infect. Microbiol, 2022

ENRICHED REACTOME PATHWAYS



Immune system 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

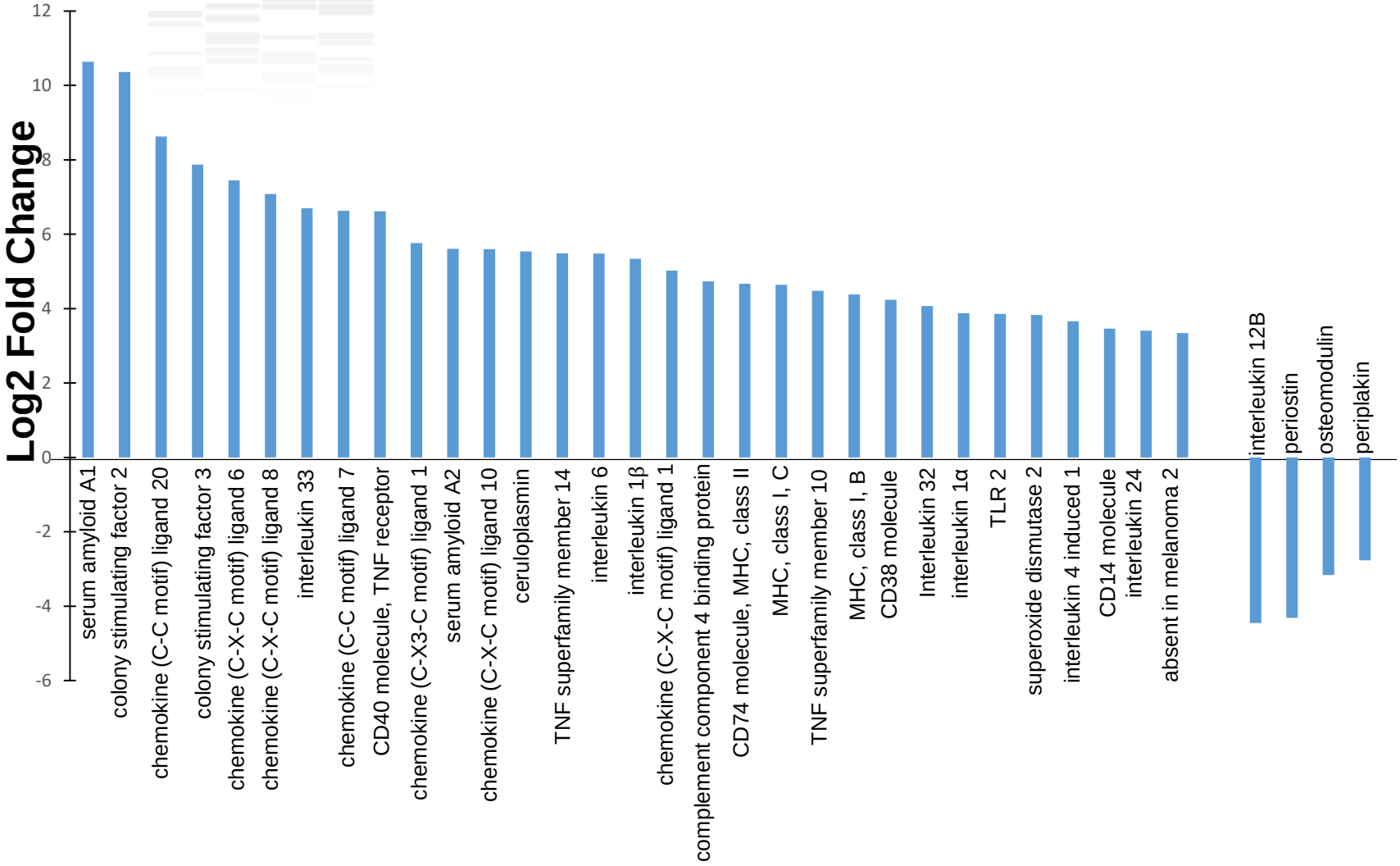
Transcriptional reprogramming of genes involved in epigenetic regulation

RNAseq **2,850 differential expressed genes (DEGs) with a threshold log2 FC -0.3 > log2FC > 0.3**
1,514 of DEGs were upregulated, 1,336 were downregulate

Gene-Set Enrichment Analysis using Reactome Database
70 Reactome enriched pathways: 61 upregulated and 9 downregulated pathways

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

IMMUNE SYSTEM AND SIGNAL TRANSDUCTION GENES ARE AMONG THE TOP HIGHLY INDUCED DEGs



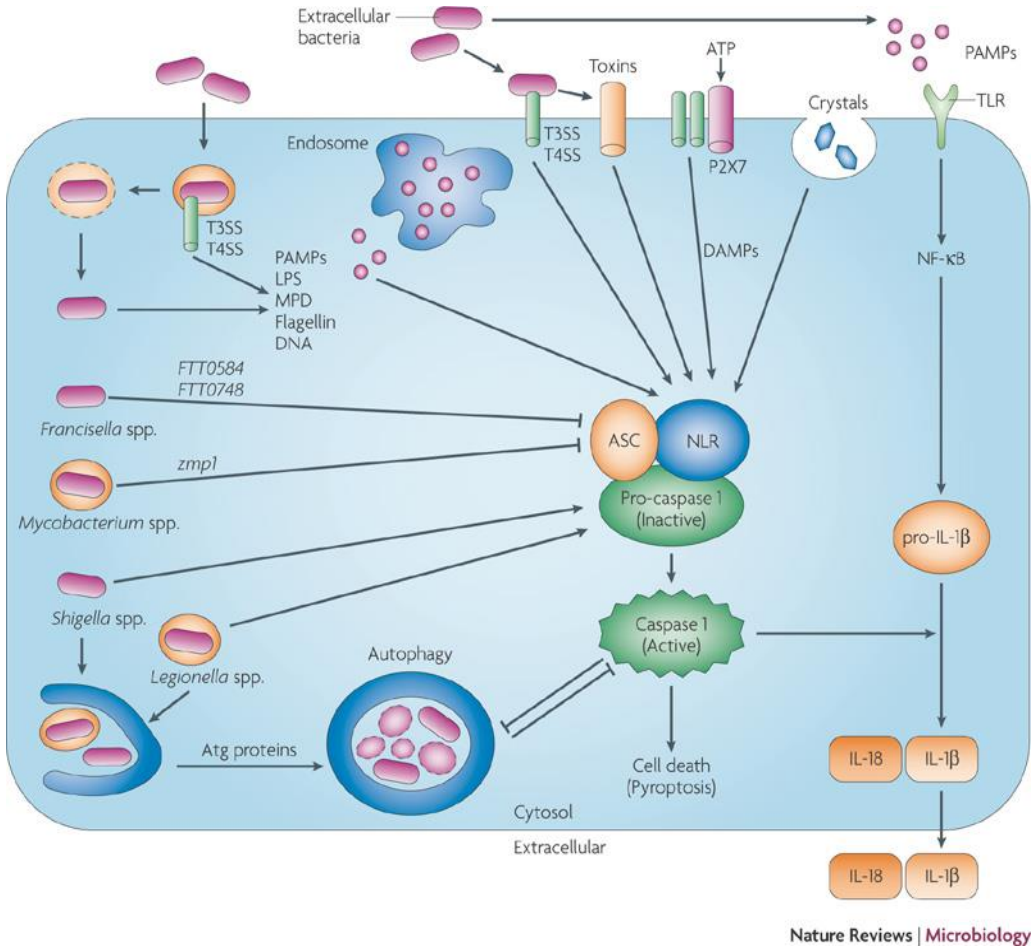
22 upregulated pathways were associated with the immune system

INFLAMMATION
as a defense mechanism against infection and injury

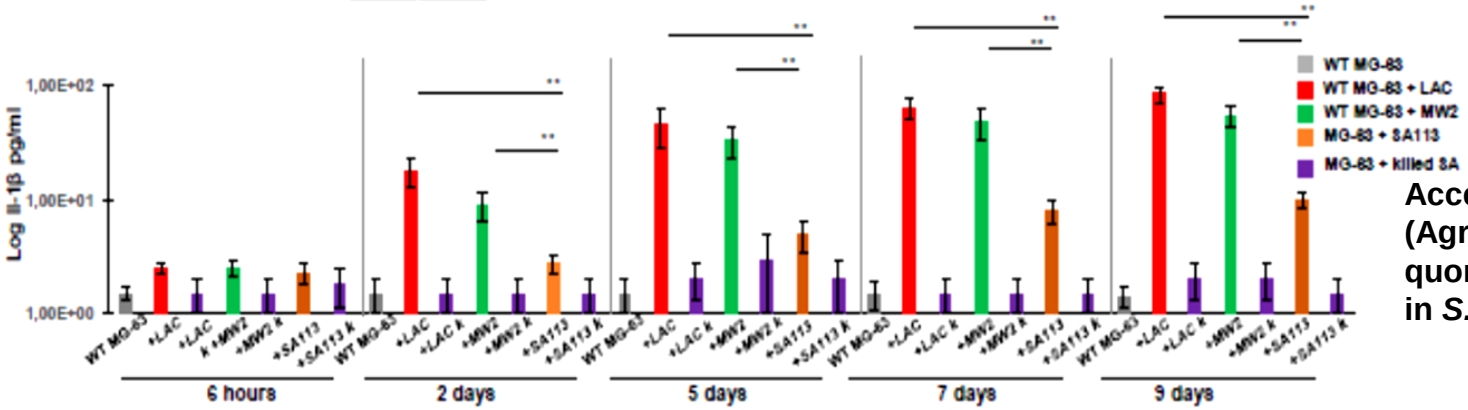
Persistent inflammation activates inflammasomes that are central players of immunity

Inflammasomes are composed of a sensor (NLR), an adaptor (ASC), and a zymogen procaspase-1

Inflammasomes acivate downstream proteases, most notably Caspase-1, which then proteolytically mature pro-IL-1β and pro-IL-18



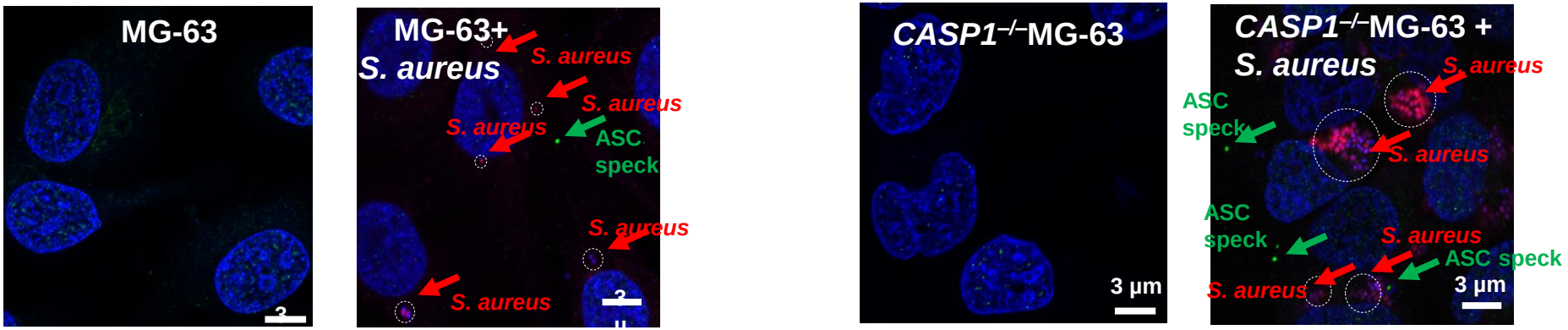
IMMUNE RESPONSE AGAINST *S. aureus* THROUGH INFLAMMASOMES ACTIVATION



Accessory gene regulator (Agr) encodes the peptide quorum-sensing system in *S. aureus*

Agr-defective SA113 strain induce a low levels of IL-1β
MW2 strain, which harbor a functional Agr induce a high level of IL-1β

Caspase-1 is required for the killing of internalized *S. aureus*



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

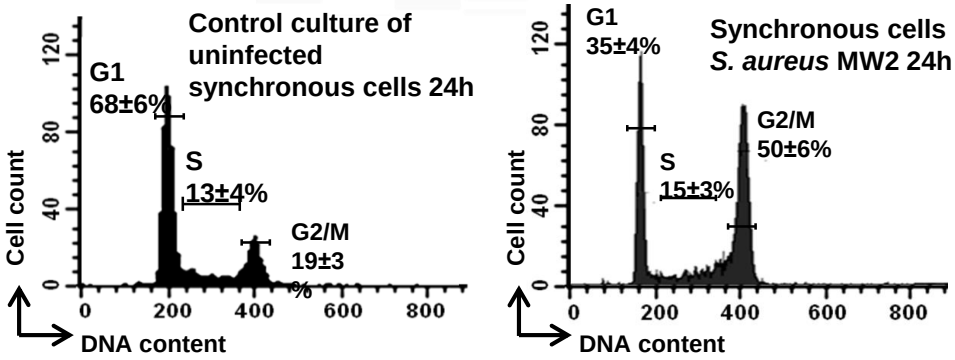
S. aureus INFECTION TRIGGERS TRANSCRIPTIONAL REPROGRAMMING OF GENES INVOLVED IN METABOLISM

UniProt ID	Gene name	Gene description	FC	Log2FC	Adj.p-value	
		Upregulated genes				
P14555	pla2g2a	phospholipase A2 group IIA	75.85	6.25	3.52E-03	Lipid metabolism
P28845	hsd11b1	hydroxysteroid (11-beta) dehydrogenase 1	53.22	5.73	3.69E-04	Hormone metabolism
134339	saa2	serum amyloid A 2	48.93	5.61	1.58E-04	
P00167	cyb5a	cytochrome b5 type A	24.61	4.62	7.45E-05	
P04179	sod2	superoxide dismutase 2. mitochondrial	14.24	3.83	3.17E-23	Metabolic reprogramming
Q8TDS4	hcar2	hydroxycarboxylic acid receptor 2	13.22	3.72	5.34E-07	Regulates lipolysis
C9JRZ8	akr1b15	aldo-keto reductase family 1	10.51	3.39	1.21E-02	
A1L3X0	elovl7	ELOVL fatty acid elongase 7	7.70	2.94	1.68E-06	Synthesis of fatty acids
O95992	ch25h	cholesterol 25-hydroxylase	6.26	2.65	3.36E-03	Converts cholesterol to oxysterol
P43490	nampt	nicotinamide phosphoribosyltransferase	5.51	2.46	6.99E-56	
Q9H2J7	slc6a15	solute carrier family 6 member 15	4.56	2.19	3.76E-09	
Q99541	plin2	Perilipin2	4.46	2.16	2.42E-23	Lipid droplet binding protein
Q9NXB9	elovl2	ELOVL fatty acid elongase 2	3.56	1.83	2.06E-19	Synthesis of fatty acids
Q9Y5L2	hilpda	hypoxia inducible lipid droplet-associated	3.16	1.66	5.29E-13	
		glycolysis genes				
		Upregulated genes				
Q9BYZ2	ldhal6b	lactate dehydrogenase A-like 6B	6.52	2.71	2.74E-02	Conversion of pyruvate into lactic acid
Q6PCE3	pgm2l1	phosphoglucomutase 2-like 1	4.37	2.13	9.55E-19	Interconversion of glucose
P06733	eno1	Enolase. phosphopyruvate hydratase	1.79	0.84	1.22E-02	
P00338	ldha	lactate dehydrogenase A	1.67	0.74	5.45E-02	
P04075	aldoa	aldolase. fructose-bisphosphate A	1.66	0.73	8.12E-03	
		Downregulated genes				
P08237	pfkm	Phosphofructokinase	0.69	- 0.54	2.29E-02	
O43175	phgdh	phosphoglycerate dehydrogenase	0.61	- 0.72	4.48E-02	

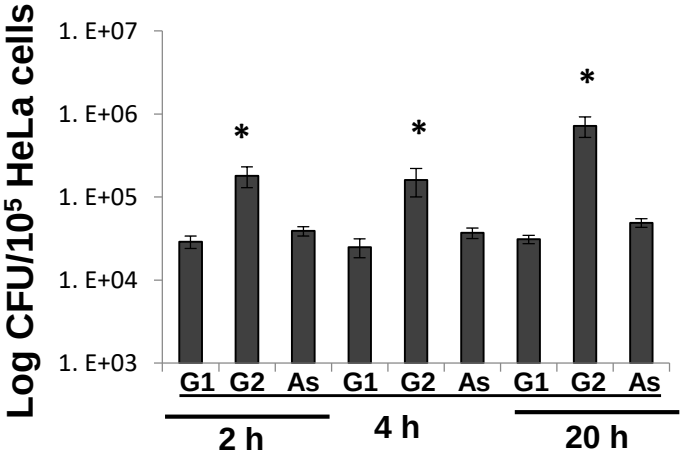
The second group of the top highly regulated genes and enriched pathways belongs to the metabolism category

TRANSCRIPTIONAL REPROGRAMMING OF GENES ASSOCIATED TO THE CELL CYCLE PROGRESSION, DNA DAMAGE AND REPAIR

S. aureus induces a G2/M phase delay

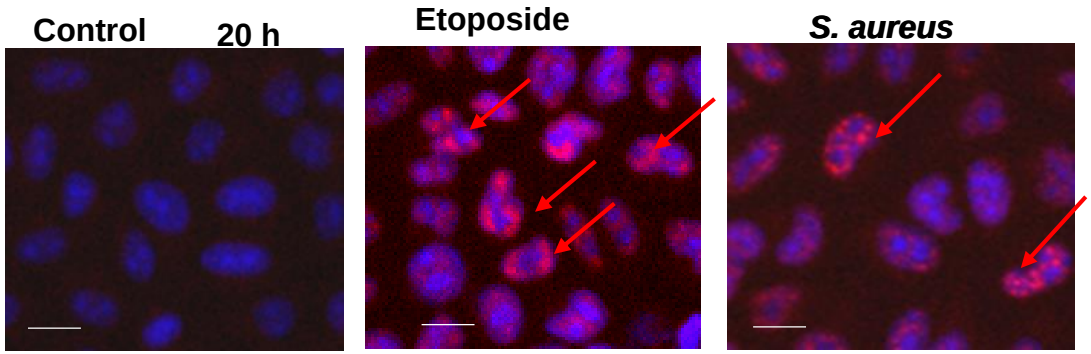


Reactome GSEA highlighted 7 enriched pathways that belong to cell cycle progression

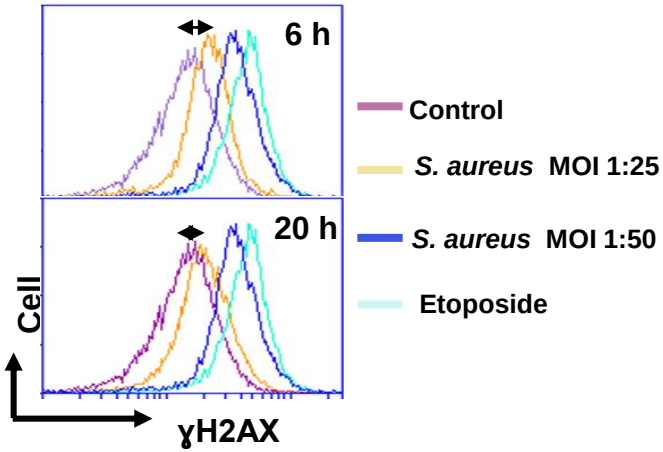


The G2 phase delay is associated with an increased internalization and intracellular replication of *S. aureus*

S. aureus induces DNA damage



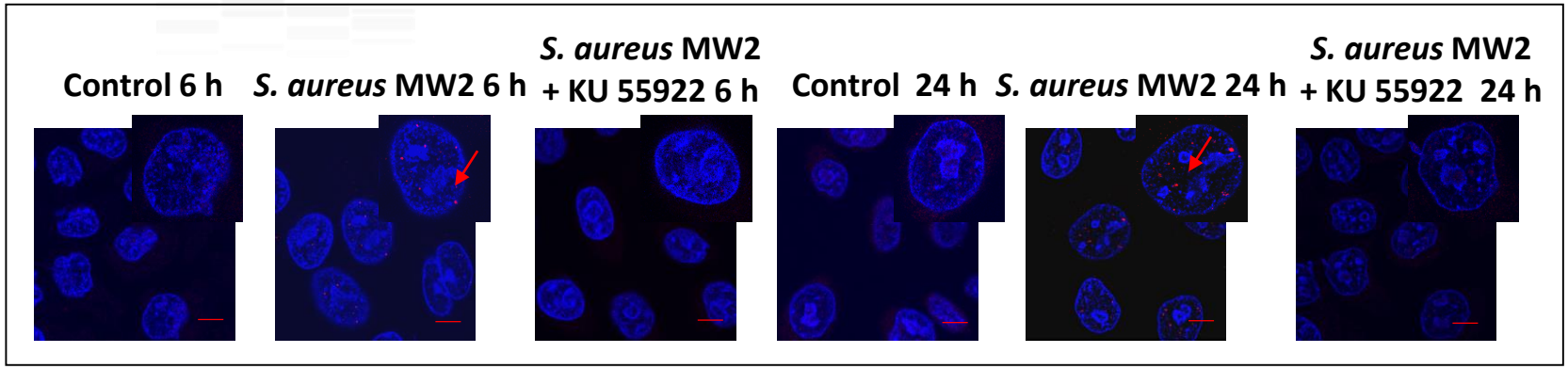
γH2AX is a marker for DNA damage in the absence of apoptosis



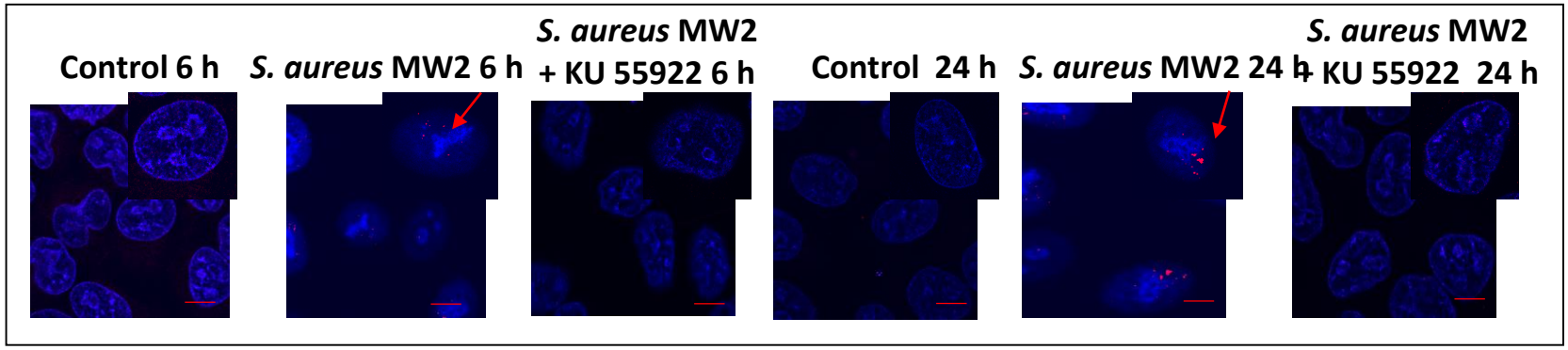
Alekseeva et *al., Plos. One* 2013 Deplanche et *al.,* FASEB J., 2015 Deplanche et *al., Scient., Reports* 2019

S. aureus triggers DNA repair

HeLA



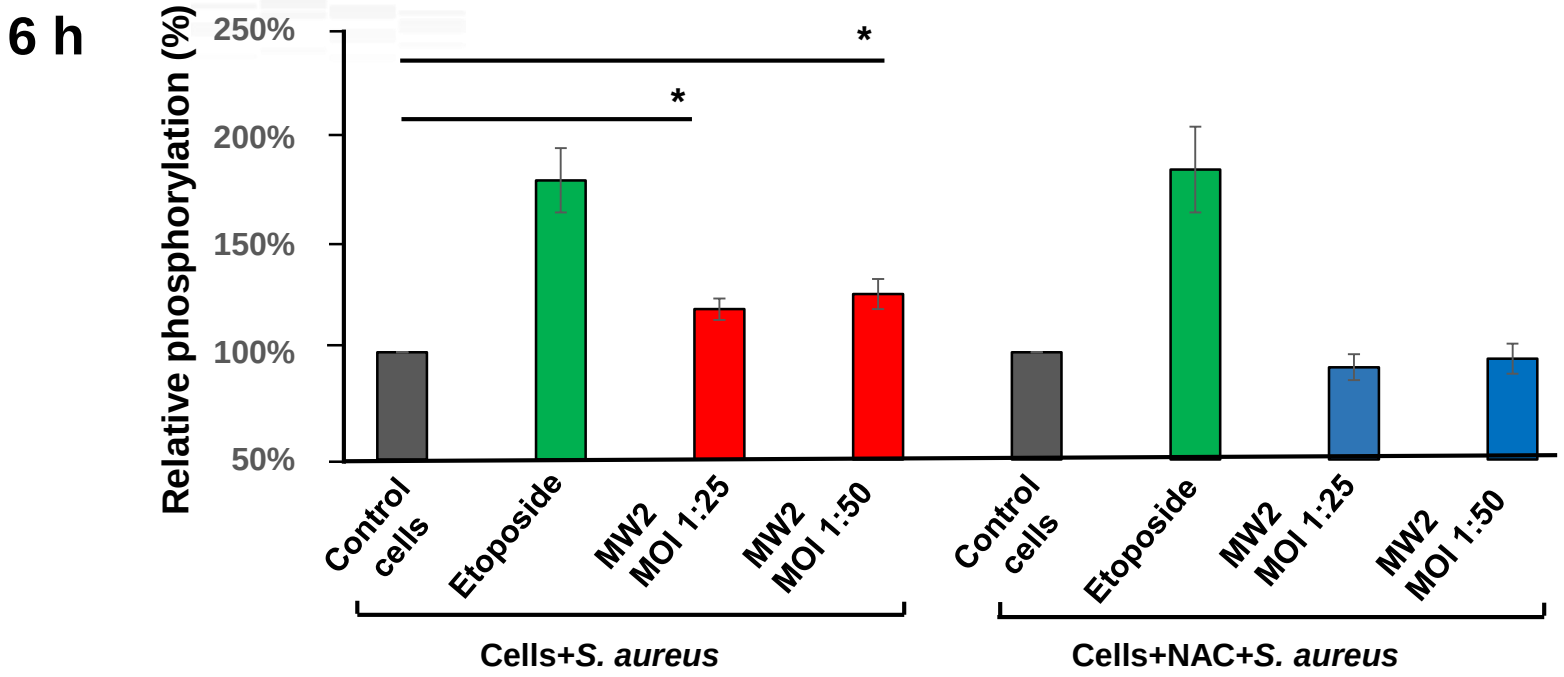
MG-63



53BP1 is the early repair protein

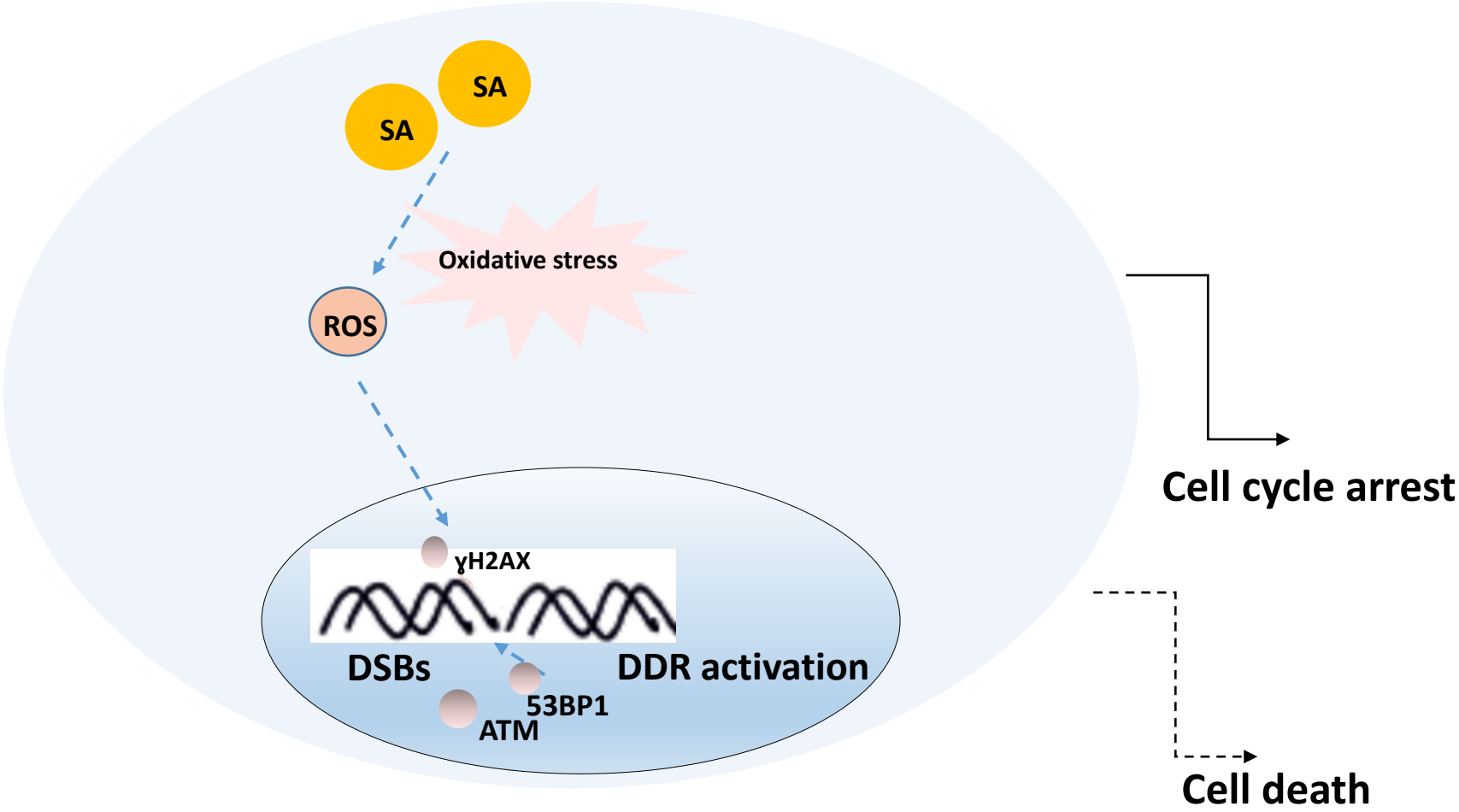
To define whether the formation of 53BP1 foci was associated with a canonical DDR comprising the triggering of the ATM kinase-signaling pathway, HeLa and MG-63 cells were treated with the ATM inhibitor KU-55933.

ROS inhibitor, N-acetyl-L-cysteine (NAC), reduces a *S. aureus*-induced H2AX phosphorylation



HeLa cells were exposed to *S. aureus* MW2 strain. Some cells were treated with NAC before the infection. Etoposide was used as the positive control. Phosphorylated H2AX was quantified by flow cytometry. The relative phosphorylation of the control cells was considered as 100%. Percent of the relative phosphorylation of samples was calculated as fold changes over the control and multiplied by 100. Similar results were observed with MG-63 cells either 6 h or 20 h post-infection.

S. aureus-induced DNA damage



TRANSCRIPTIONAL REPROGRAMMING OF GENES INVOLVED IN EPIGENETIC REGULATION

Gene expression relies on the interaction between transcription factors and 'epifactors' that control DNA accessibility

Epifactor database
720 epifactors:
writers, erasers, readers, chromatin-remodeling enzymes, scaffold proteins, cofactors

117 DEGs encoding epifactors
92 downregulated
25 upregulated

An important number of epifactor genes were downregulated by infection: 7%of all of the downregulated DEGs

GO-BP (Gene Ontology of Biological Processes) enrichment analysis of the DAVID software

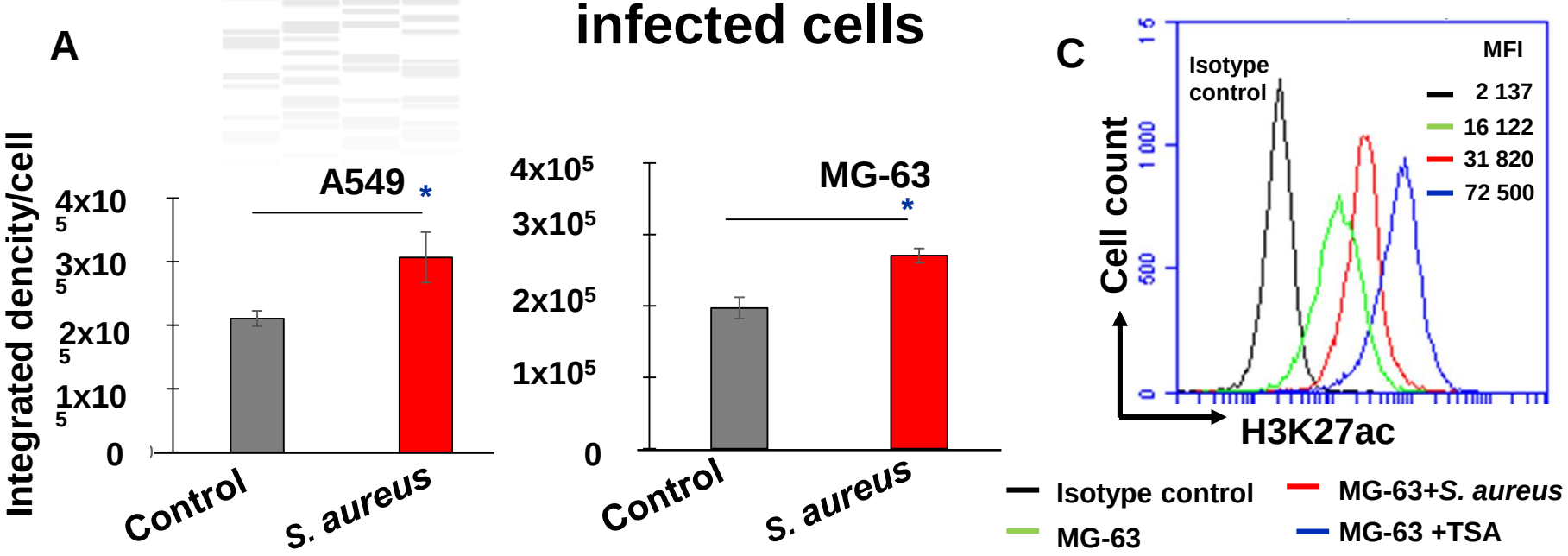
30 genes encoded epifactors with a negative effect on transcription

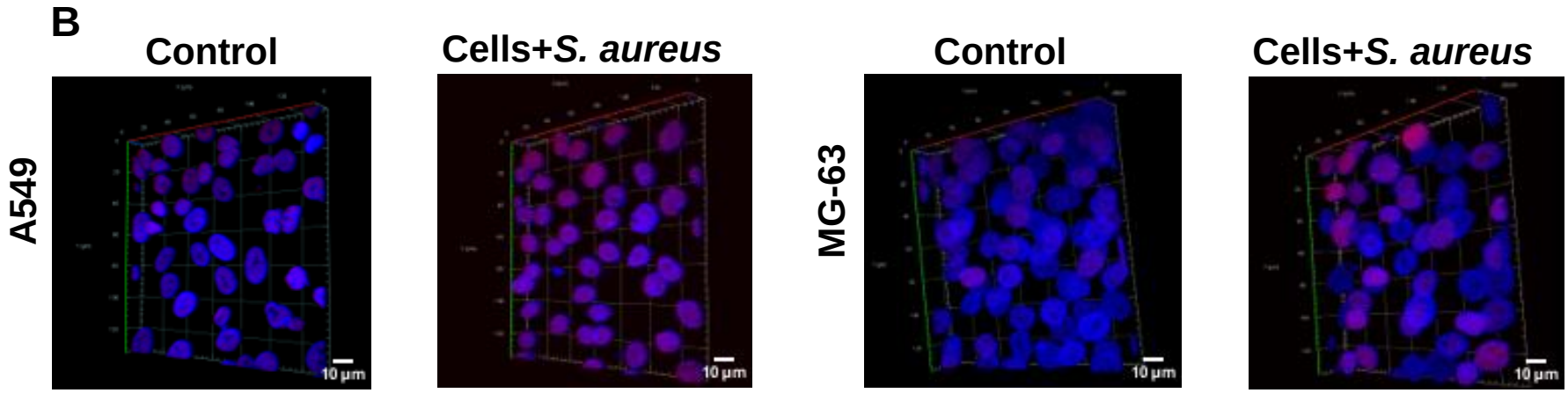
Chromatin-repressive complexes: BAHD1, NurD, Polycomb PRC1, mSin3A and CoRES

Histone deacetylases, components of the DNA methylation and demethylation pathways.

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

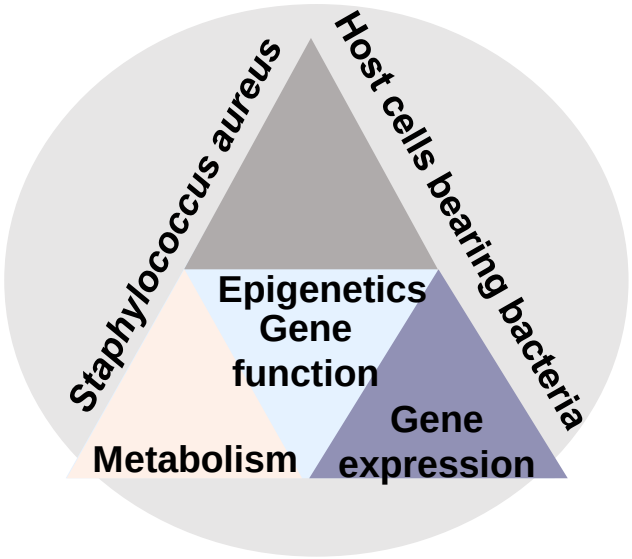
Acetylation of Histone 3 at lysine 27 in *S. aureus*-infected cells





Chaumond et *al.*, *Front Immunol*, 2023

TRANSCRIPTIONAL, EPIGENETIC AND METABOLIC SIGNATURES



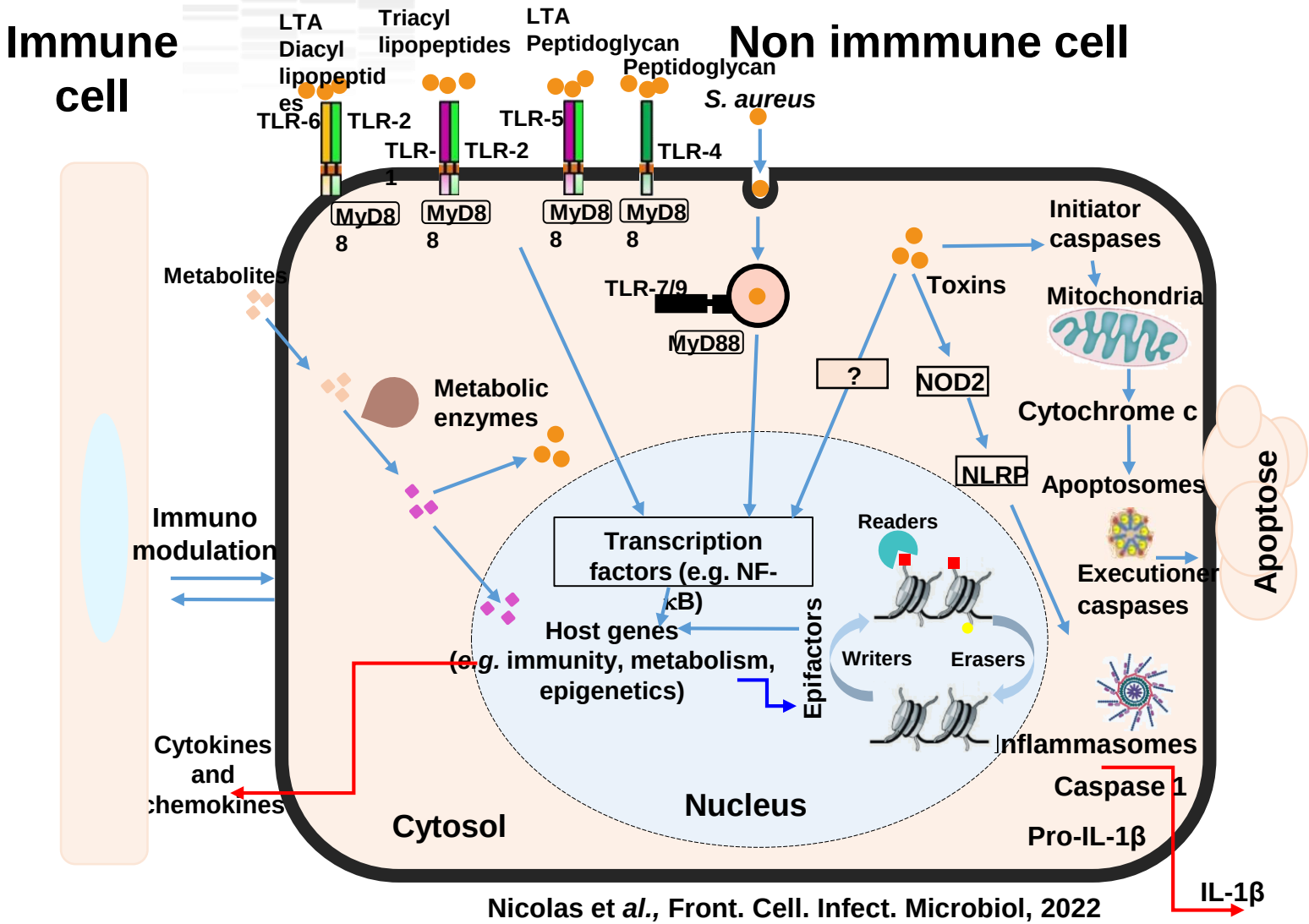
Specific categories and pathways

Epigenetic modifications, Chromatin organization, Senescence pathways, Neuronal system, Integration of energy metabolism, Metabolism of lipids

Cell cycle, DNA repair, DNA damage, DNA replication, Genes expression, Glycolysis, Metabolism of amino acids and derivatives

Innate and adoptative immune systems, Cytokines signaling, Cell death, Cell motility, Signal transduction, Extracellular matrix organization, Post-translational protein modification, Cell surface interactions

MODEL OF THE IMMUNE, METABOLIC AND EPIGENETIC DYSREGULATED SIGNATURES DURING *S. aureus* INFECTION



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

CONCLUSIONS

Transcriptome architecture of non-immune cells bearing internalized *S. aureus* reveals strong inflammatory responses and signatures of metabolic and epigenetic dysregulation

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

Non-professional phagocytes induce an immune response through inflammasomes activation and processing of IL-1β using active Caspase-1, which prevents intracellular replication of *S. aureus*

The deregulation of epigenetic and DNA repair pathways suggests that *S. aureus* infection has a long-term impact on the genome and epigenome of host cells, which may exert patho-physiological dysfunctions

COLLABORATIONS

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Commere PH


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