Supplementary Figure legends

Supplemental Figure 1. Cytokine production in response to *S. aureus* skin infection. Multiplex cytokine analysis was performed on clarified material from homogenized skin biopsies. Mice, control and hyperglycemic (STZ-treated) were infected with 2 x 10^6 cfu of *S. aureus* for 1 or 5 days. N=3 for PBS uninfected mice, 8 for 1 day infected mice and 12 per group in the 5 day infected. *P<0.05 relative to WT infected.

Supplemental Figure 2. Additional cytokine production in response to *S. aureus* skin infection. Multiplex cytokine analysis was performed on clarified material from homogenized skin biopsies. Mice, control and hyperglycemic (STZ-treated) were infected with 4 x 10^6 cfu of *S. aureus* for 1 or 5 days. N=3 for PBS uninfected mice, 8 for 1 day infected mice and 12 per group in the 6 day infected. *P<0.05 relative to WT infected.

Supplemental Figure 3. Influence of glucose on macrophage function. Macrophages were grown in the presence of varying concentrations of glucose for 2 days. A) Intracellular killing over increasing concentrations of glucose. N=9. B) Viability of cells from A). N=6. C) Influence of galactose on intracellular bacteria numbers. N=6. D) Intracellular killing in high glucose with increasing concentrations of 2DG. N=5. E) Cell viability from D) N=10. F) Ability of macrophages grown in varying glucose levels to phagocytose *S. aureus*. N=15. G) Phagocytosis of *S. aureus* under different concentrations of glucose and 2DG. N=9. ****P<0.0001, ***P<0.001, **P<0.01 and *P<0.05.

Supplemental Figure 4. Effect of glucose exposure on macrophage reactive oxygen species production. Macrophages were grown in normal and high glucose for 2 days before exposure to *S. aureus* and levels of A) cellular ROS and B) mitochondrial ROS were measured. Each dot represents a biological replicate. Influence of hydrogen peroxide on C) cellular ROS production (N=2) and D) intracellular bacterial killing. N=4. E) Intracellular bacterial killing with superoxide dismutase (*sodA*) and catalase (*katE*) mutants of *S. aureus*. N=3. ****P<0.0001, ***P<0.001 and *P<0.05.

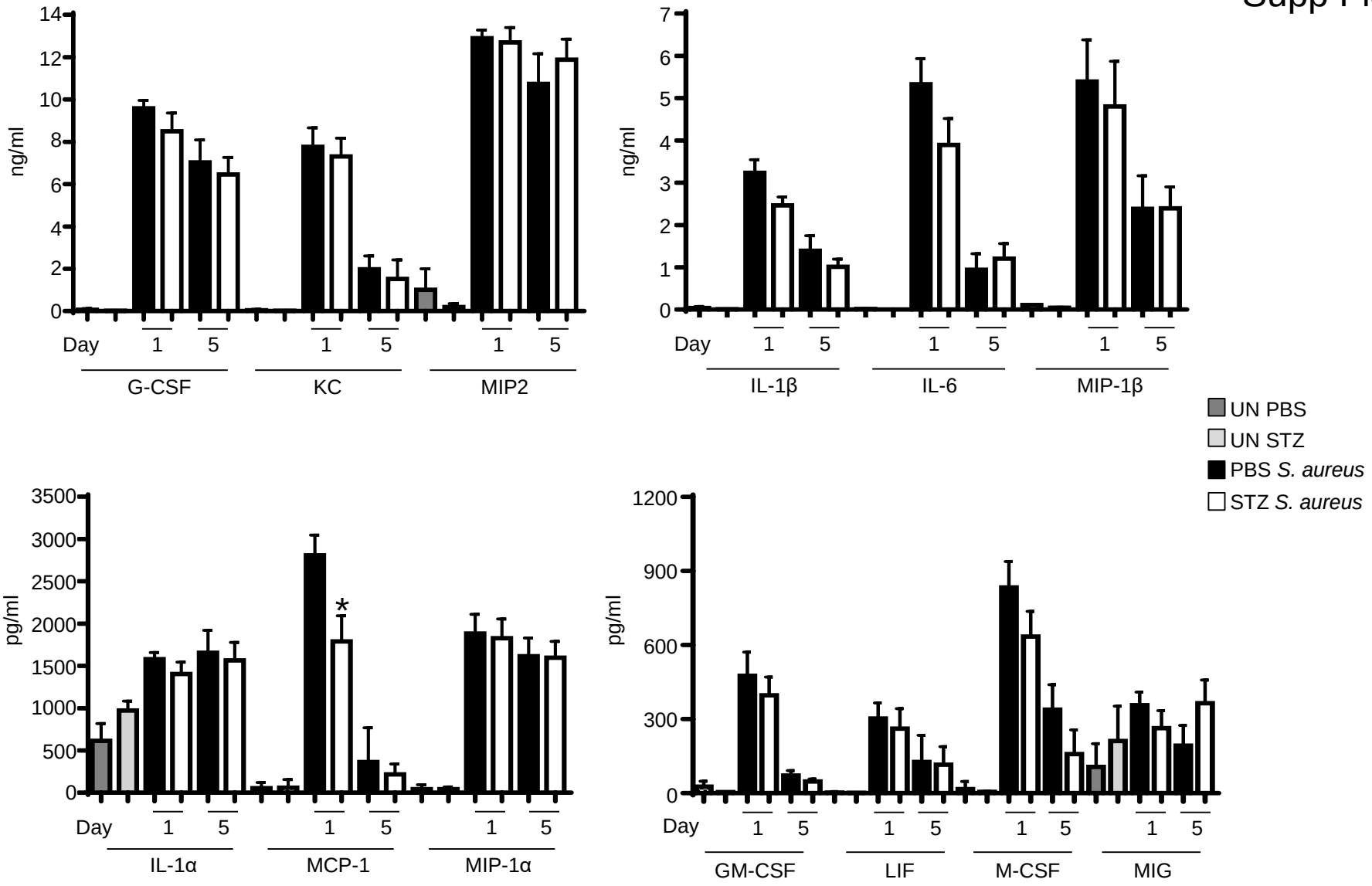
Supplemental Figure 5. Effect of glucose on the glycolytic function of macrophages. A) Glycolytic stress test performed on a Seahorse analyzer with macrophages treated under normal or hyperglycemic conditions. N=18. Macrophages were incubated with WT or a *pyk* deficient strain of *S. aureus* and assessed for B) intracellular survival (N=15) and C) ability to be taken up by the cells (N=3).

Supplemental Figure 6. Influence of glucose on human keratinocyte cell function. The human keratinocyte cells, HaCaTs or primary keratinocytes were grown under normal (6 mM) or high (50 mM) glucose conditions for 2 days. A) Intracellular survival of *S. aureus* in a gentamicin protection assay. N=10. B) Survival of *S. aureus* in extracellular milieu. N=14. C). Gentamicin protection again with primary keratinocytes. N=15. D) Uptake of AF647 labelled *S. aureus*. N=2 for PBS and 7 for *S. aureus*. E) Viability of keratinocytes after gentamicin protection assays. N=7.

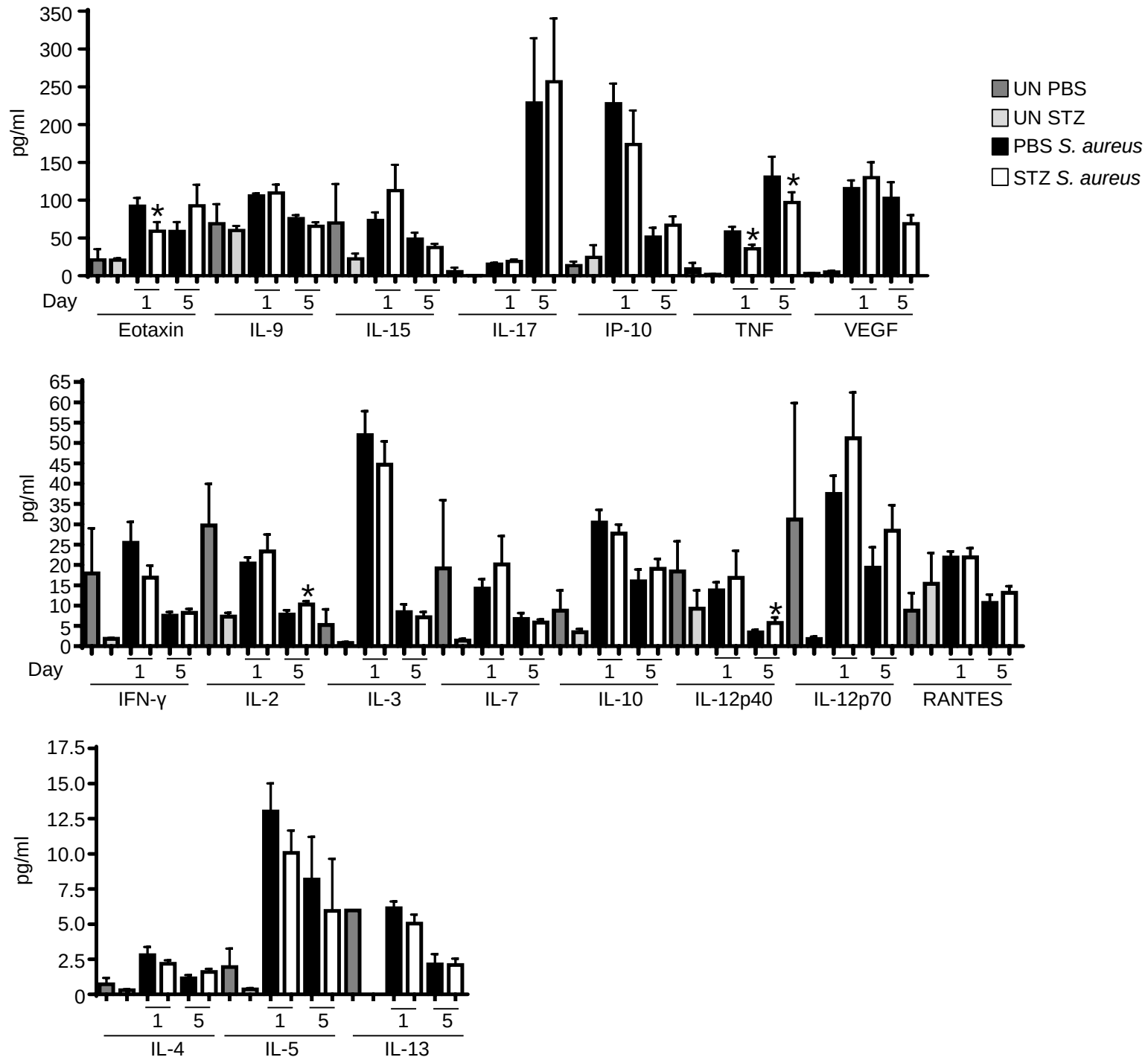
Supplemental Figure 7. *S. aureus* gene expression after isolation from 1 day skin biopsies in normal or diabetic (STZ treated) mice. Control and STZ mice were subcutaneously infected with 2 x 10^6 cfu of *S. aureus* USA300 for 1 day before RNA isolation from punch biopsies. N=4. *P<0.05.

Supplemental Figure 8. Functional complementation of *clp* mutants. A) Restoration of protease activity in *clpP* and *clpX* mutants. B) Restoration of growth defect at 43.5°C of *clpC* mutant upon complementation.

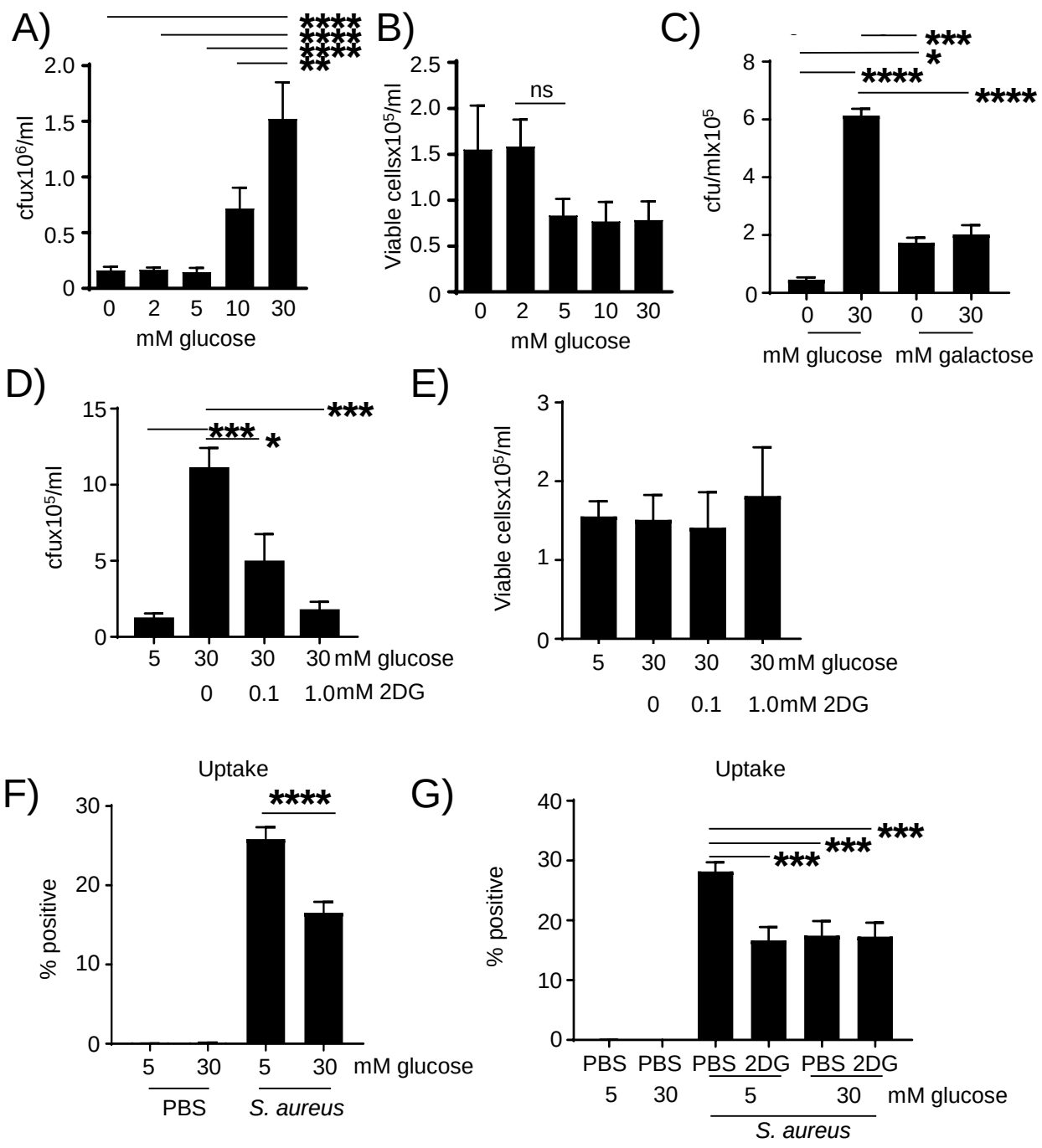
Supp Fig 1

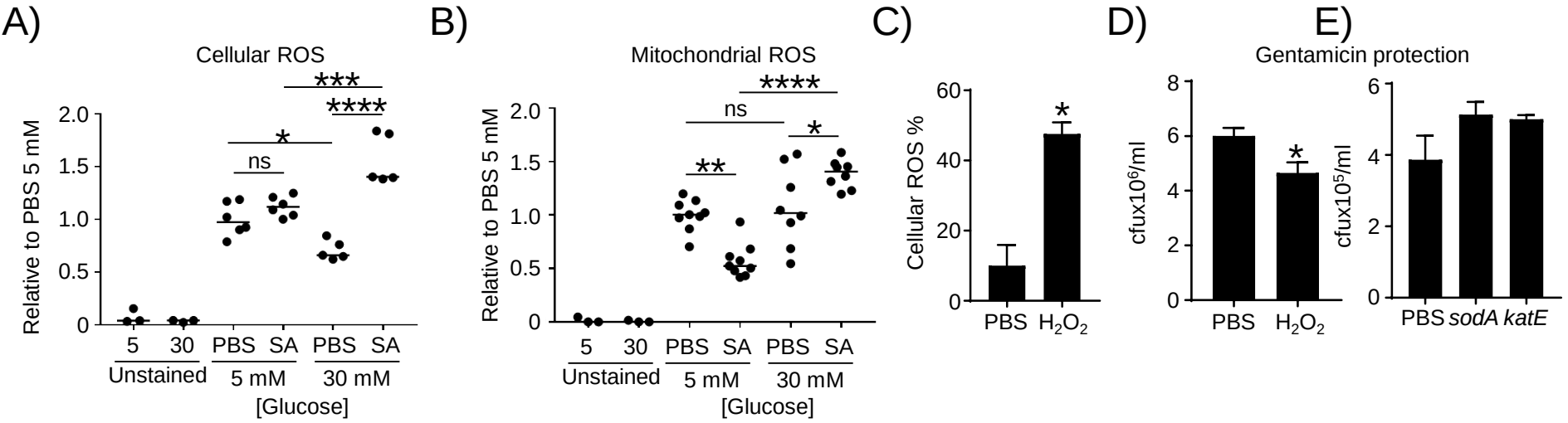

ng/ml
Day
G-CSF
KC
MIP2
IL-1β
IL-6
MIP-1β
UN PBS
UN STZ
PBS S. aureus
STZ S. aureus
pg/ml
*
IL-1α
MCP-1
MIP-1α
GM-CSF
LIF
M-CSF
MIG

Supp Fig 2


pg/ml
350
300
250
200
150
100
50
0
Day
1
5
Eotaxin
IL-9
IL-15
IL-17
IP-10
TNF
VEGF
IFN-γ
IL-2
IL-3
IL-7
IL-10
IL-12p40
IL-12p70
RANTES
IL-4
IL-5
IL-13
UN PBS
UN STZ
PBS S. aureus
STZ S. aureus

Supp Fig 3

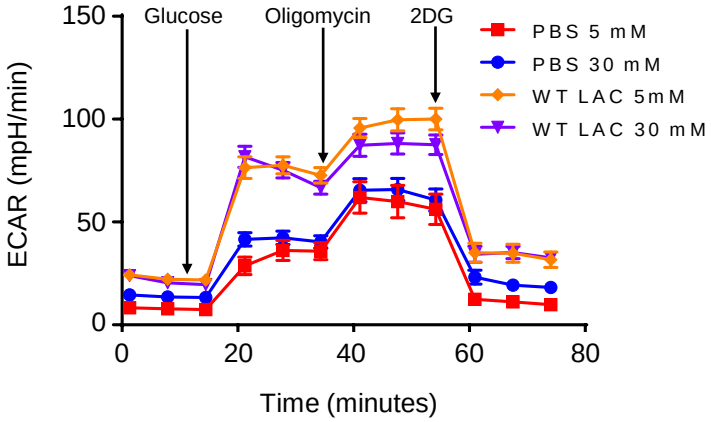

A)
B)
C)
D)
E)
F)
G)
cfux10⁶/ml
Viable cellsx10⁵/ml
cfu/mlx10⁵
cfux10⁵/ml
mM glucose
mM galactose
mM 2DG
ns
Uptake
% positive
PBS
S. aureus


A)
Cellular ROS
Relative to PBS 5 mM
2.0
1.5
1.0
0.5
0
***
****
*
ns
5
30
PBS
SA
PBS
SA
Unstained
5 mM
30 mM
[Glucose]
B)
Mitochondrial ROS
Relative to PBS 5 mM
2.0
1.5
1.0
0.5
0
****
ns
*
**
5
30
PBS
SA
PBS
SA
Unstained
5 mM
30 mM
[Glucose]
C)
Cellular ROS %
60
40
20
0
*
PBS
H2O2
D)
Gentamicin protection
cfux10⁶/ml
8
6
4
2
0
*
PBS
H2O2
E)
cfux10⁵/ml
6
4
2
0
PBS
sodA
katE

Supp Fig 4

Supp Fig 5

A)



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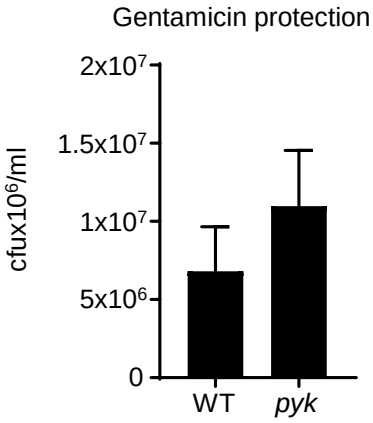

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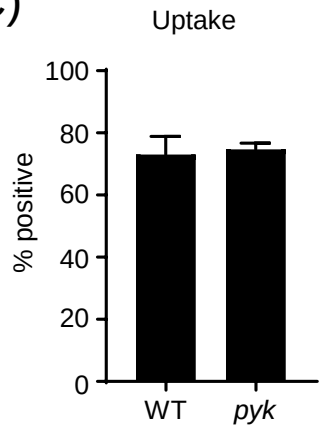
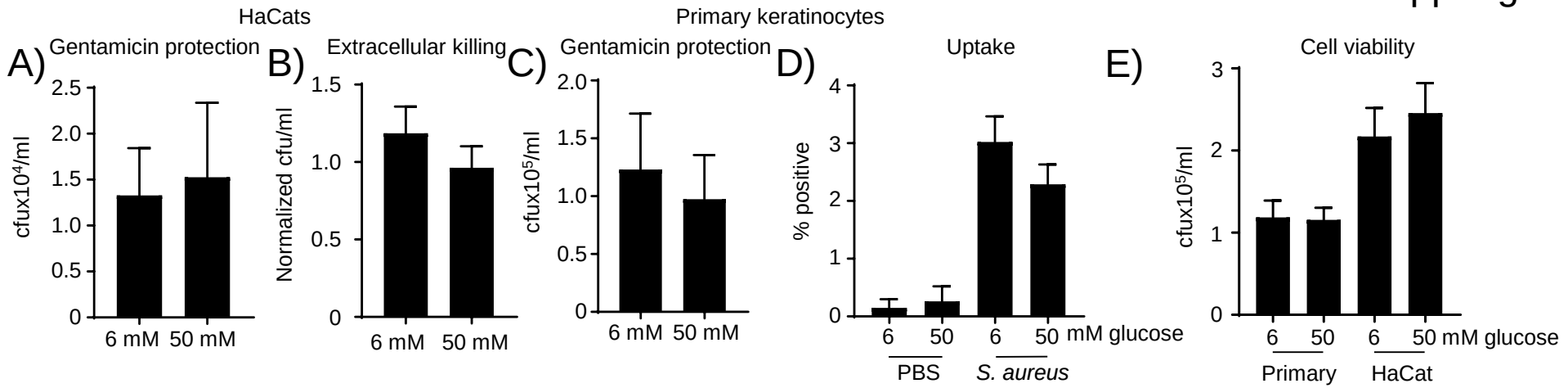
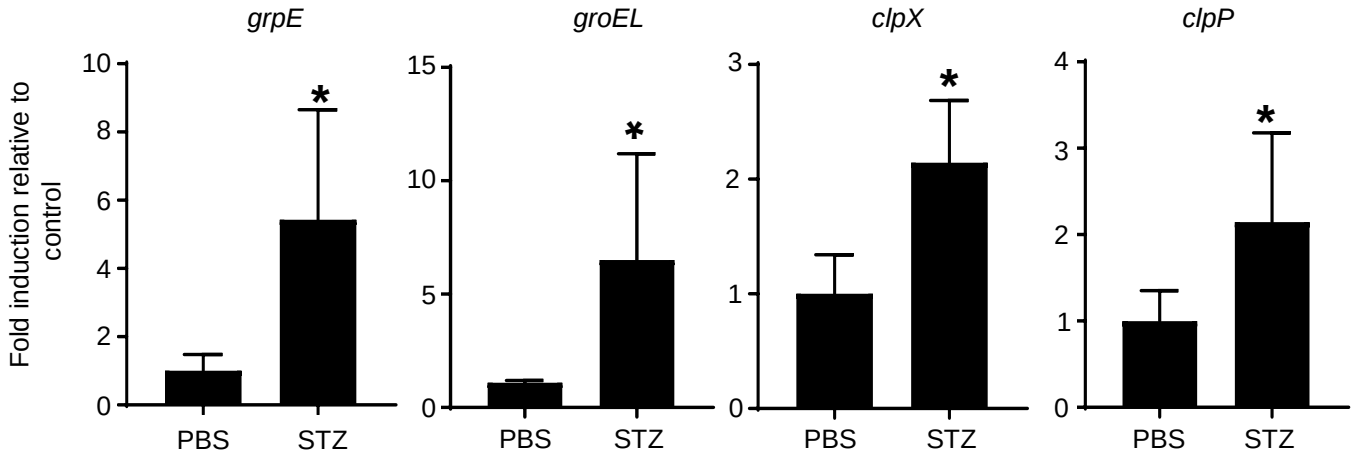


Supp Fig 6

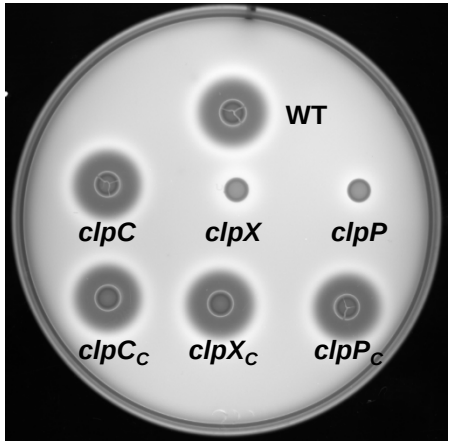

HaCats
Primary keratinocytes
A)
Gentamicin protection
cfux10⁴/ml
2.5
2.0
1.5
1.0
0.5
0
6 mM
50 mM
B)
Extracellular killing
Normalized cfu/ml
1.5
1.0
0.5
0
6 mM
50 mM
C)
Gentamicin protection
cfux10⁵/ml
2.0
1.5
1.0
0.5
0
6 mM
50 mM
D)
Uptake
% positive
4
3
2
1
0
6
50
6
50
mM glucose
PBS
S. aureus
E)
Cell viability
cfux10⁵/ml
3
2
1
0
6
50
6
50 mM glucose
Primary
HaCat

Supp Fig 7


grpE
groEL
clpX
clpP
Fold induction relative to control
PBS
STZ
*

Supp Fig 8

A)



B)