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Colloque annuel de l'ITMO I3M

Institut Pasteur de Lille,
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Metabolic and innate immune cues merge into a specific inflammatory response via UPR

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CEA CHRU CNRS INRA INRIA Inserm Institut Pasteur IRD

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Association between psoriasis and metabolic disorders

Epidemiological evidences

In psoriasis patients, risk factor significantly increases for :

- myocardial infarction (Gelfand et al., 2006)
- atherosclerosis (Alexandroff et al., 2009; Spah, 2008)
- obesity (Sterry et al., 2007)
- dyslipidaemia (Rocha-Pereira et al., 2001)
- non-alcoholic fatty liver disease (Gisondi et al., 2009)
- insulin-resistance and diabetes (Boehncke et al., 2007; Brauchli et al., 2008b)
- metabolic syndrome (Gisondi et al., 2007).

Clinical evidences

Psoriasis improved by interventions on metabolism :

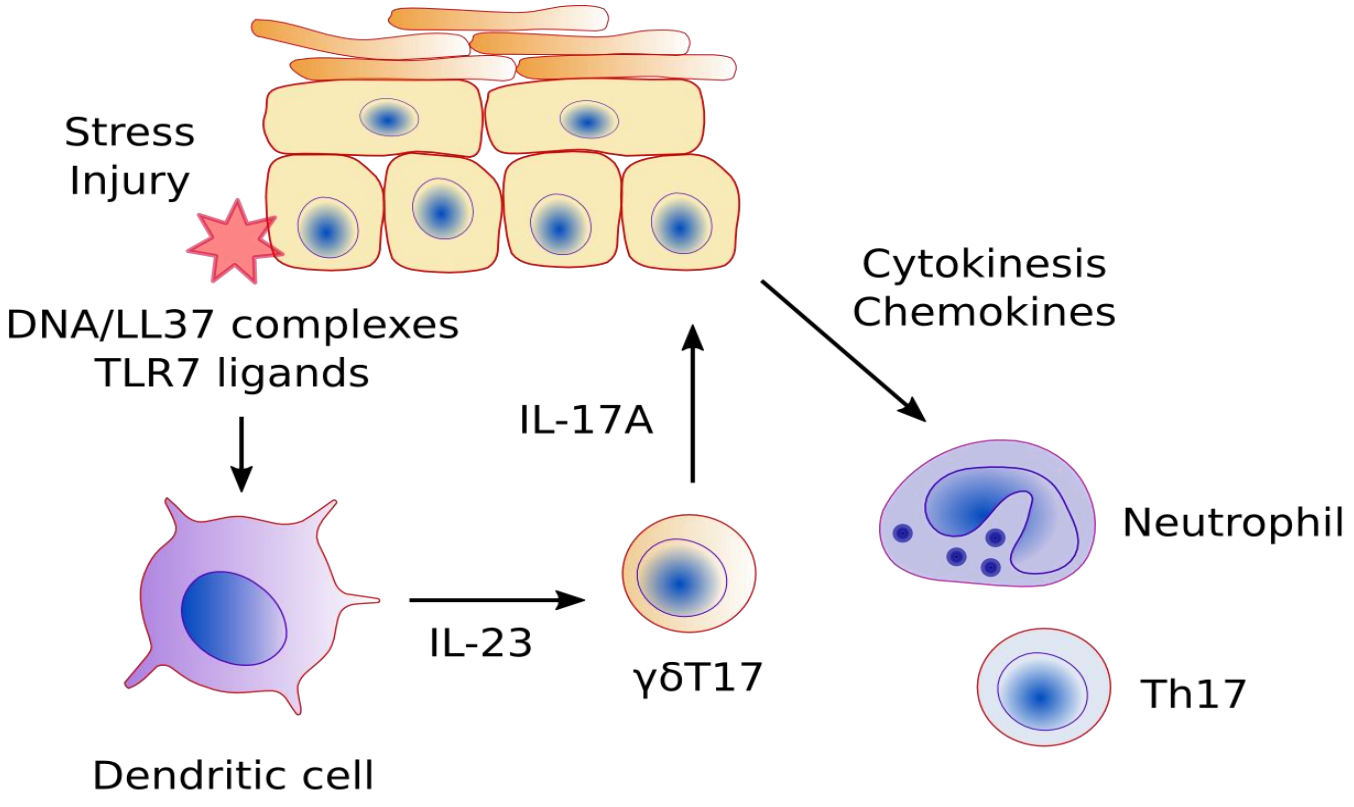
- PPARγ agonist (antidiabetic thiazolidinedione)

(Brauchli et al., 2008a; Robertshaw and Friedmann, 2005; Shafiq et al., 2005)

- Simvastatin (hypolipidemic) (Shirinsky and Shirinsky, 2007).
- Weight loss (diet) (Gisondi et al., 2008)
- Gastric bypass (Hossler et al., 2010)

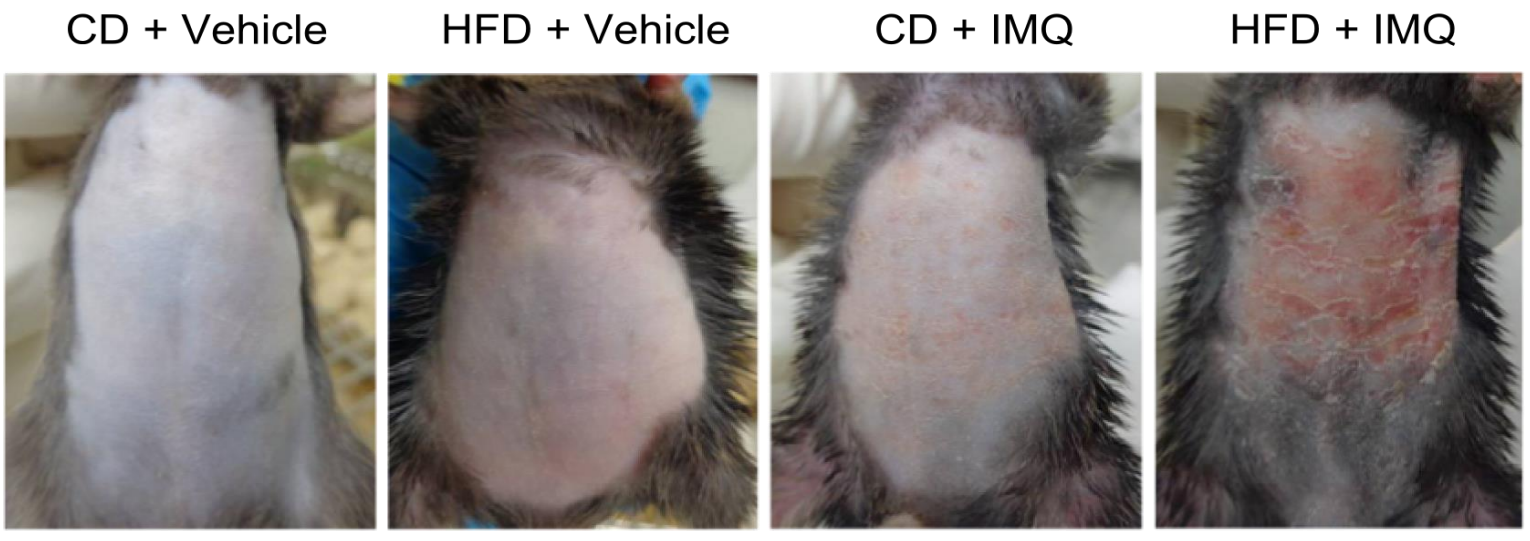
$\Rightarrow$ No mechanism demonstrated

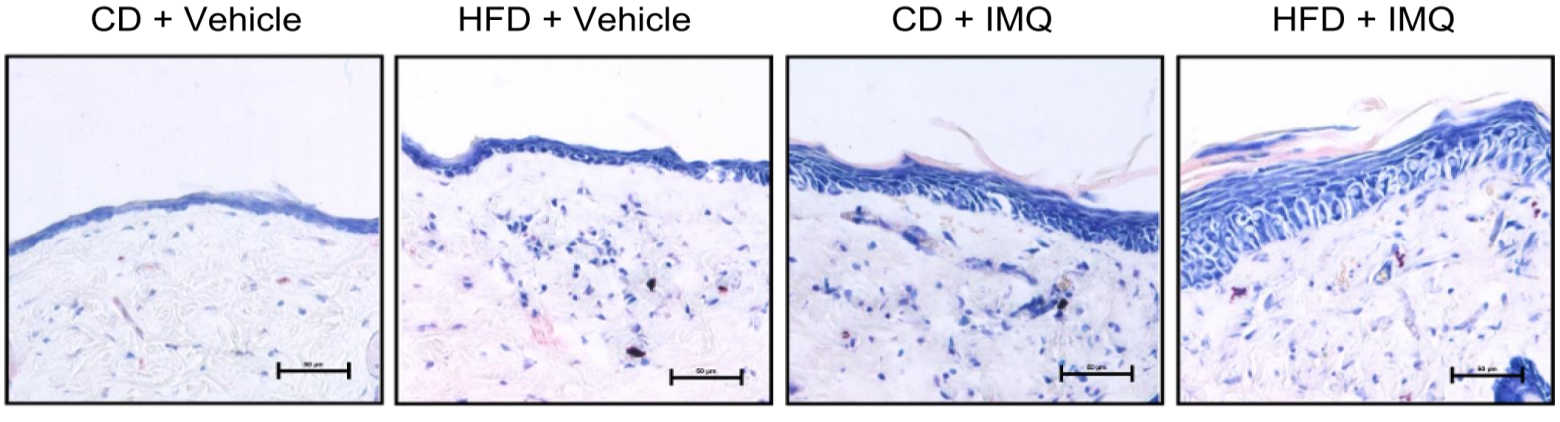
IL-23-producing dendritic cells play a critical role in the pathogenesis of psoriasis



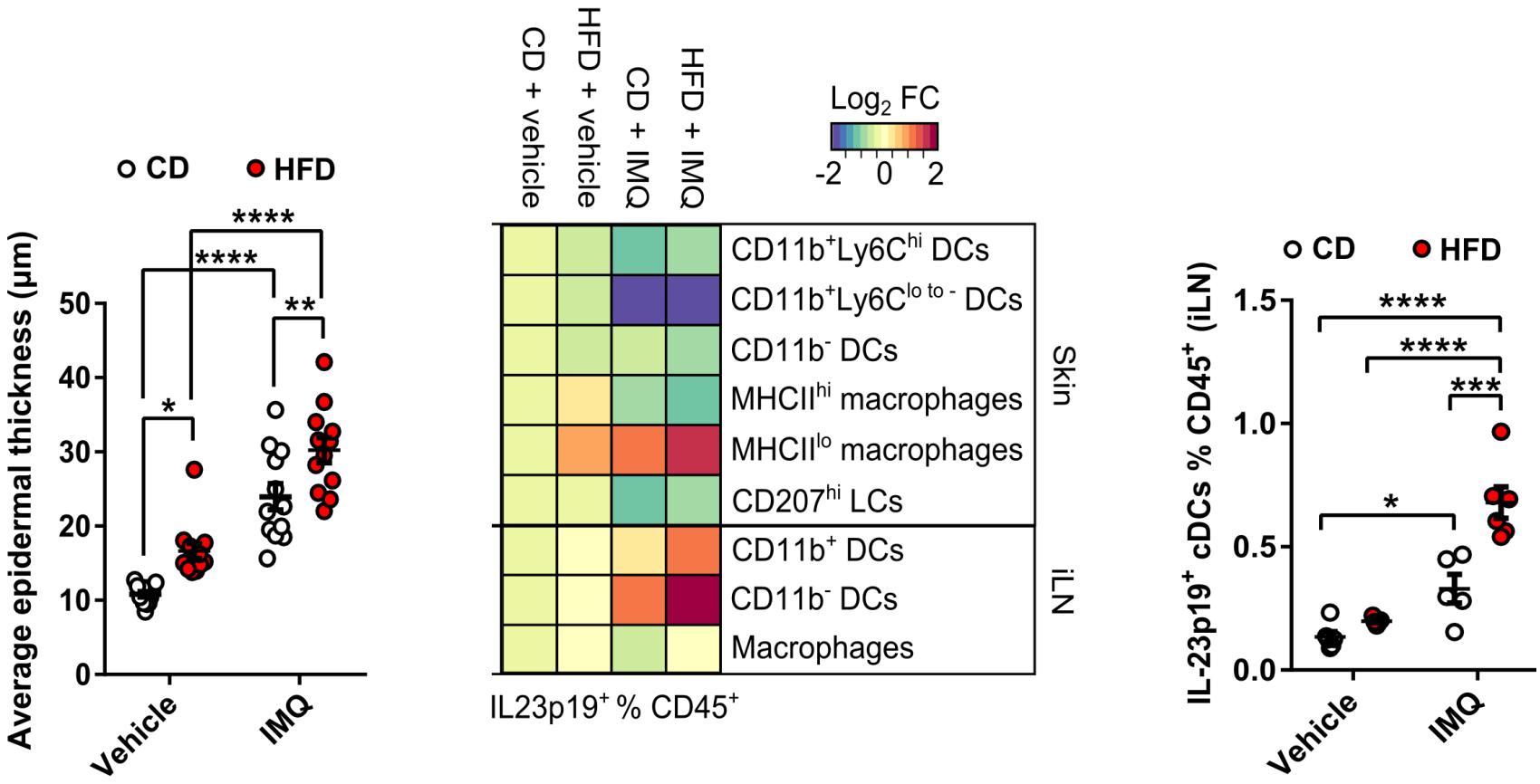
Based on: Boehncke & Schön. Lancet. 2015

High Fat Diet exacerbates TLR7-induced psoriasis



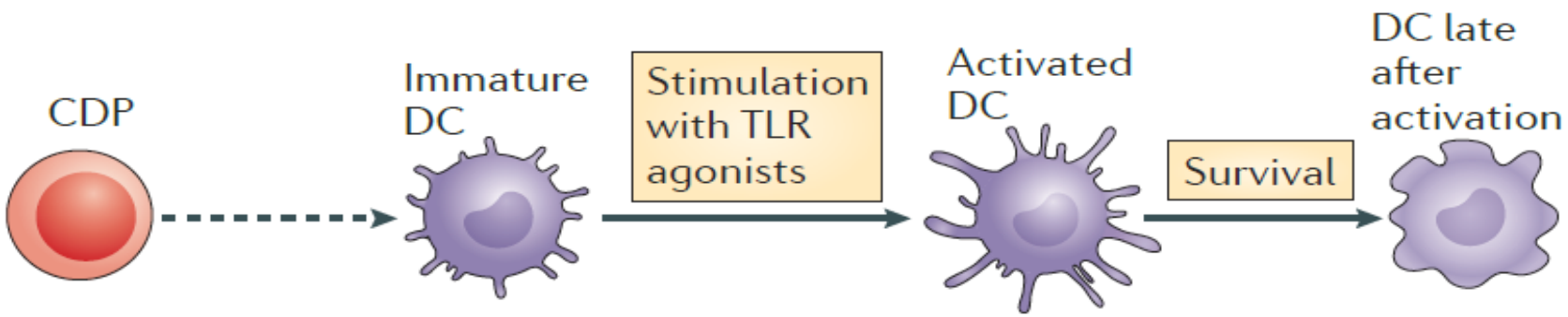


HFD increases IL-23^{+} cDC in TLR7-induced psoriasis



How does metabolic stress affect TLR-induced inflammation?

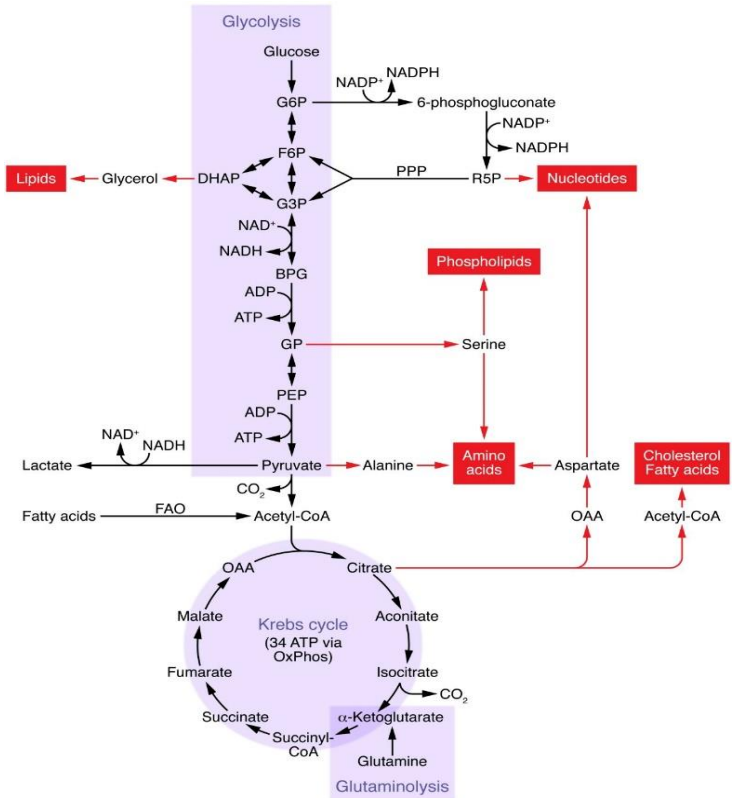
DC metabolism

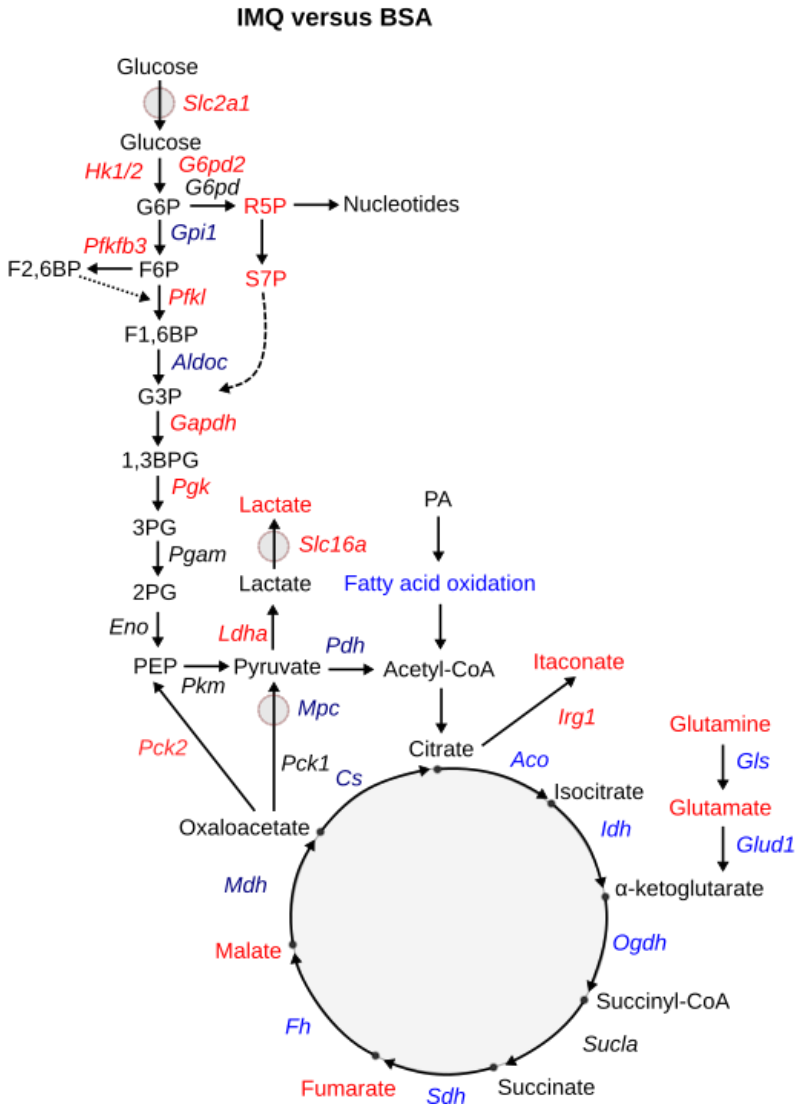


Metabolic profile	↑ Mitochondrial biogenesis	↑ Glycolysis ↑ Fatty acid synthesis	↑ Glycolysis ↓ OXPHOS
Signalling pathways involved	• PPARγ • mTOR, • PGC1α	• AKT • TBK1–IKKε	• HIF1α • mTOR

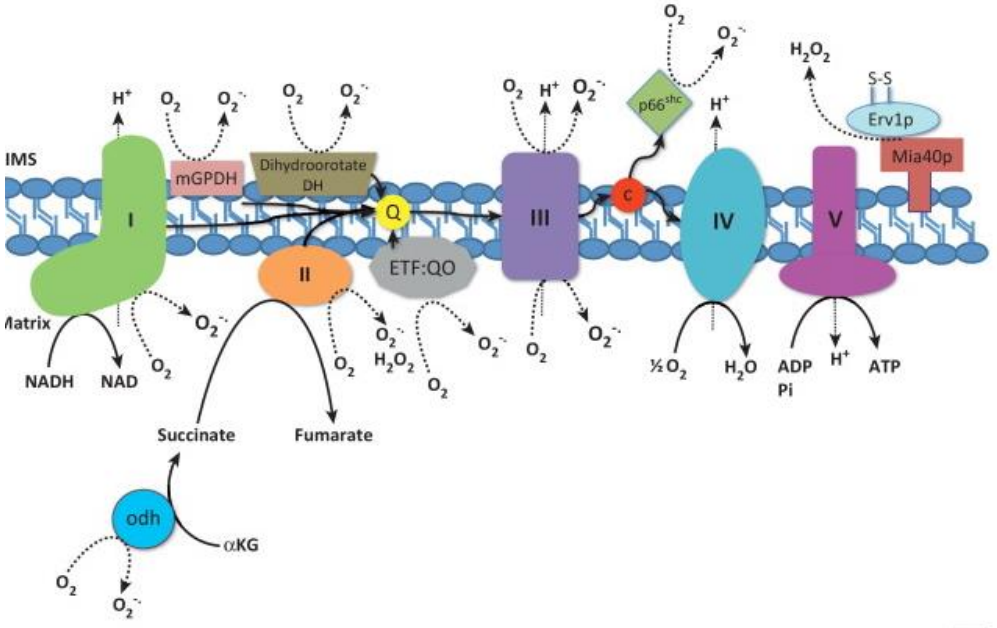
Pearce & Everts. *Nat Rev Immunol.* (2015)

Glucose metabolism





Mitochondrial Electron Transport Chain, mtROS and inhibitors

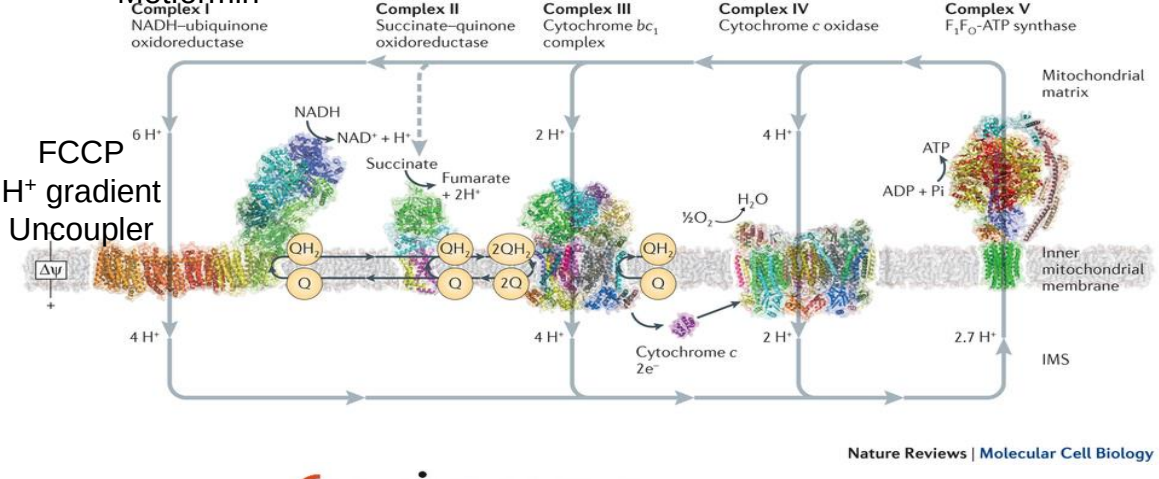


Rotenone
Metformin

Antimycin A

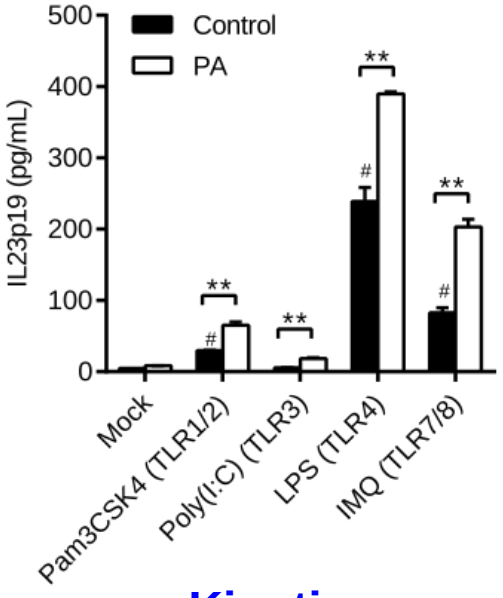
Oligomycin

FCCP
H^+ gradient
Uncoupler

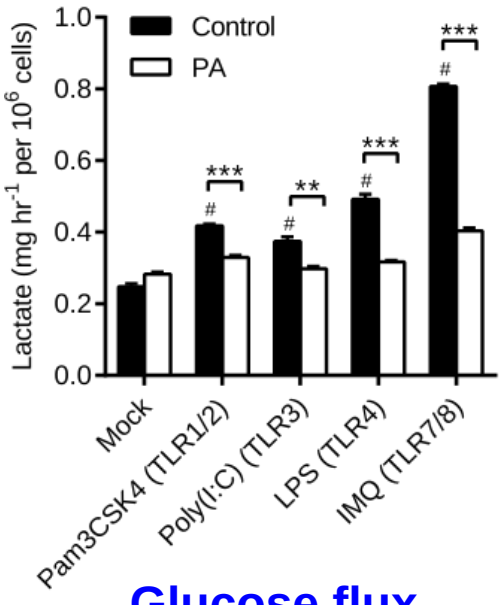


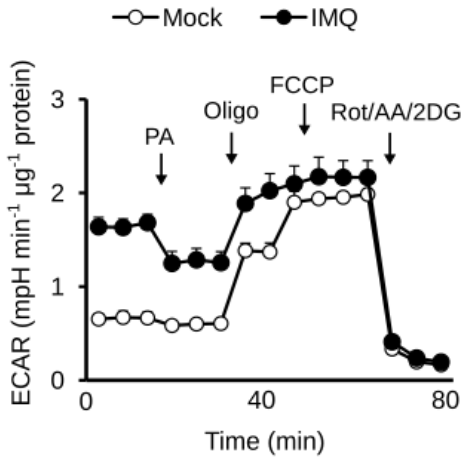
Palmitic acid rewires inflammatory response and metabolism in TLR-activated DC

IL-23

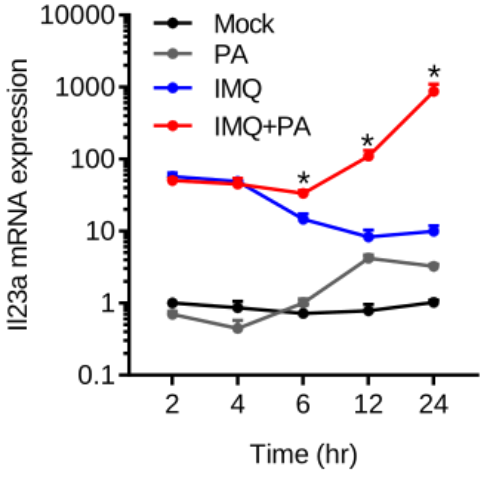


Glycolysis

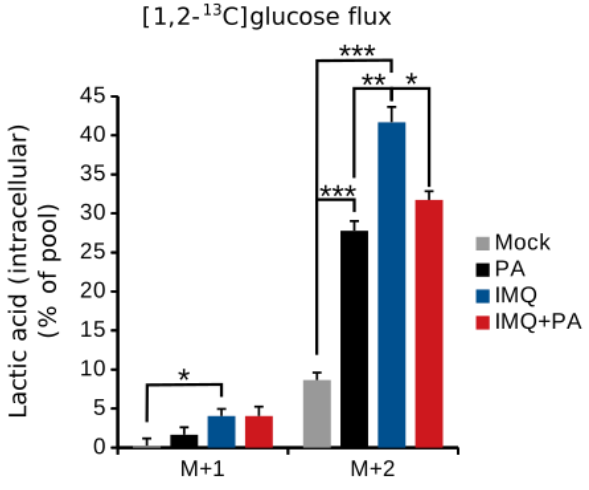




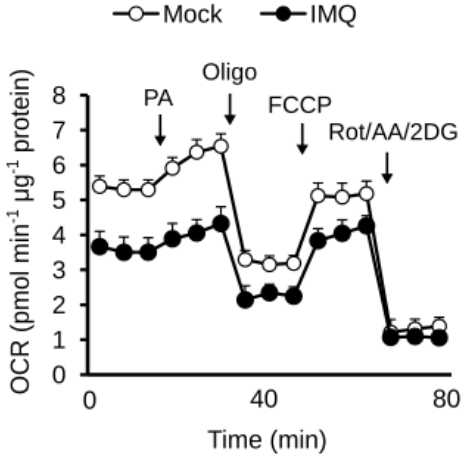
Kinetics



Glucose flux



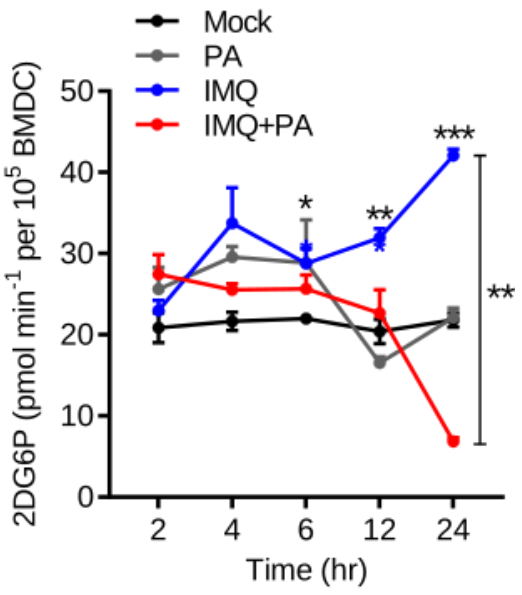
Respiration



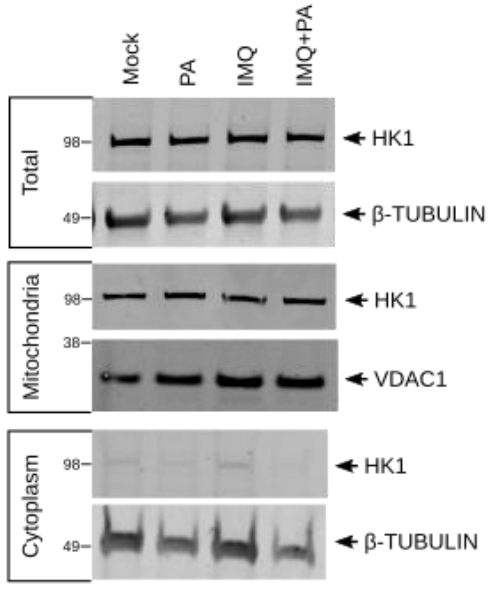
Mogilenko *et al*. *Cell* 2019

PA inhibits hexokinase (I) activity and affect its cytoplasmic content in TLR-activated DC

Activity



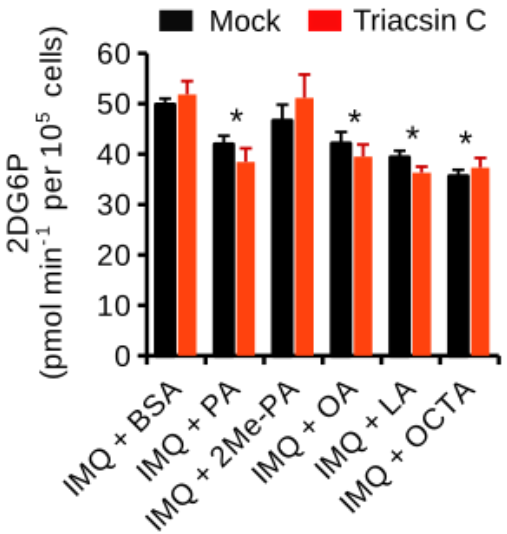
Localization

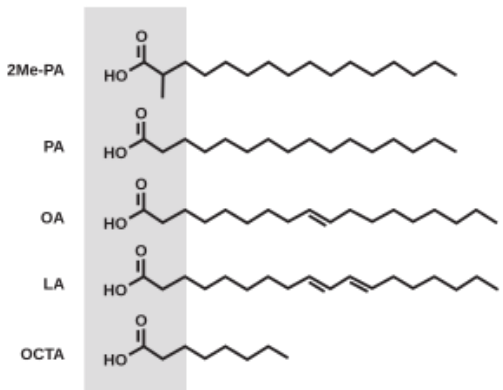


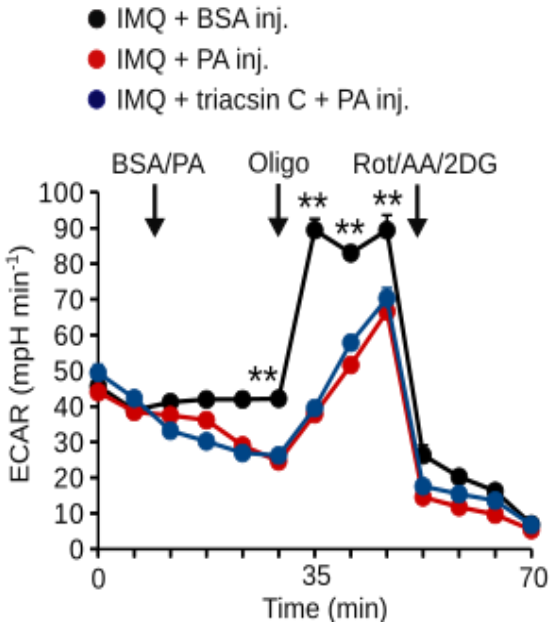
Mogilenko *et al*. *Cell* 2019

Non metabolized PA inhibits glycolysis and hexokinase in TLR-activated DC

FA metabolization



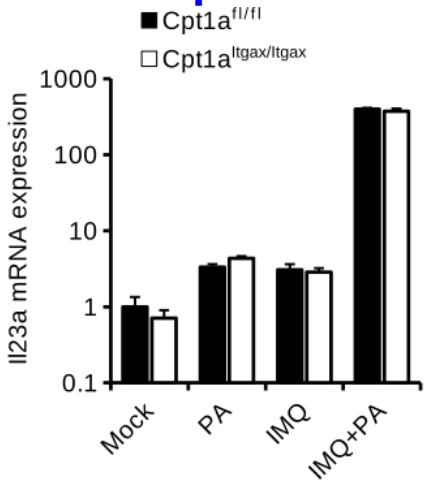




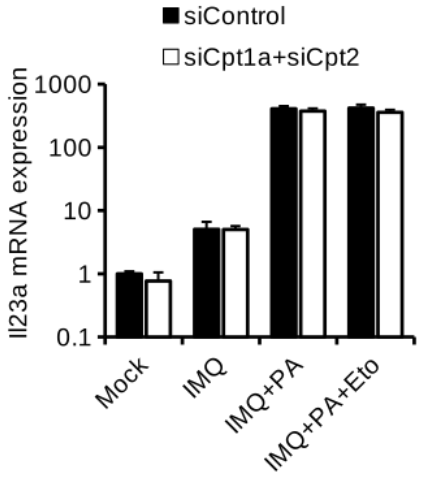
Mogilenko *et al*. *Cell* 2019

PA and HFD effects on TLR-induced IL-23 production are independent of Fatty Acid Oxidation in DC

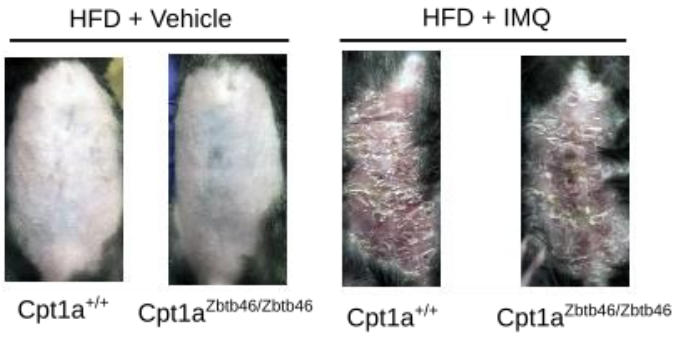
Cpt1a

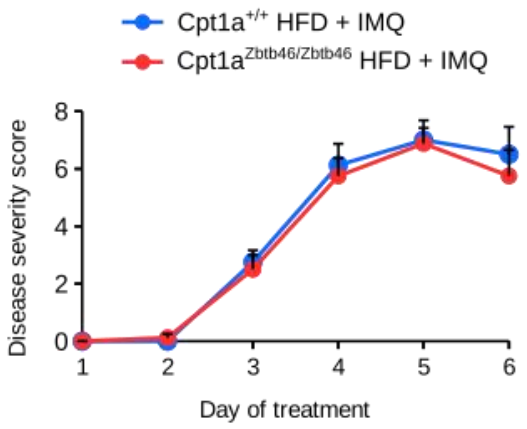


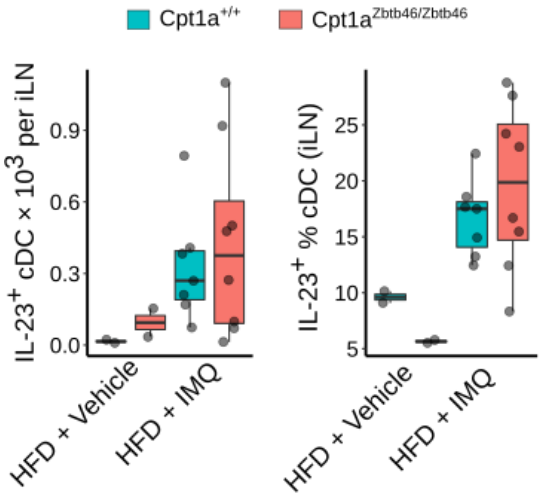
Cpt1a & Cpt2



Cpt1a



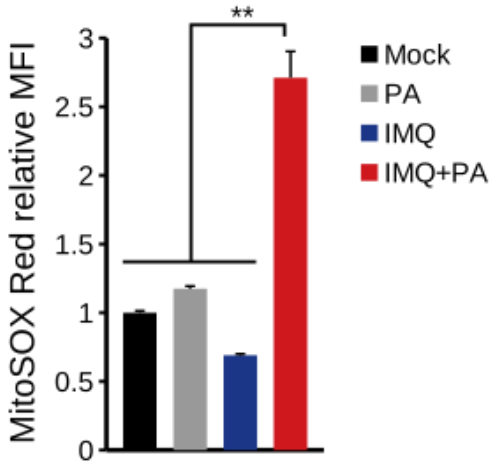




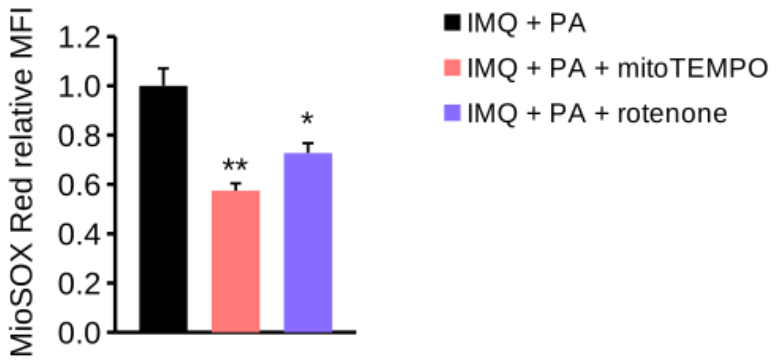
Mogilenko *et al*. *Cell* 2019

PA increases TLR-induced IL-23 production through mtROS generation

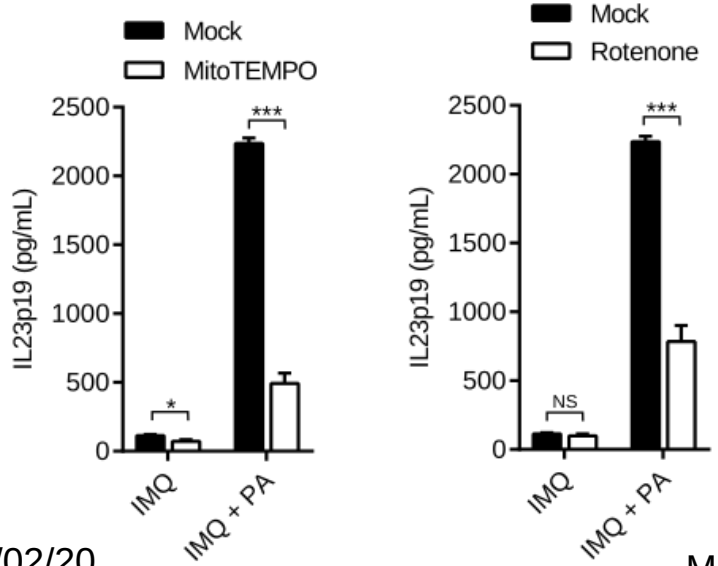
mtROS



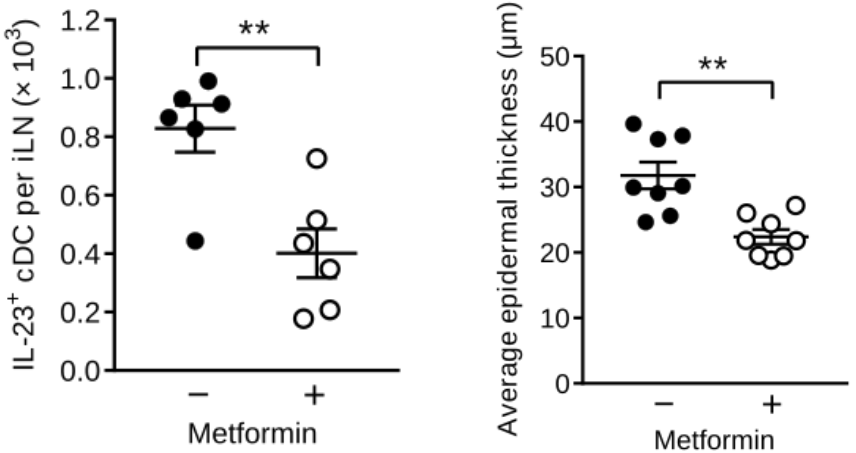
mtROS/Complex 1 Inhibition



IL-23: *in vitro*



IL-23: *in vivo*



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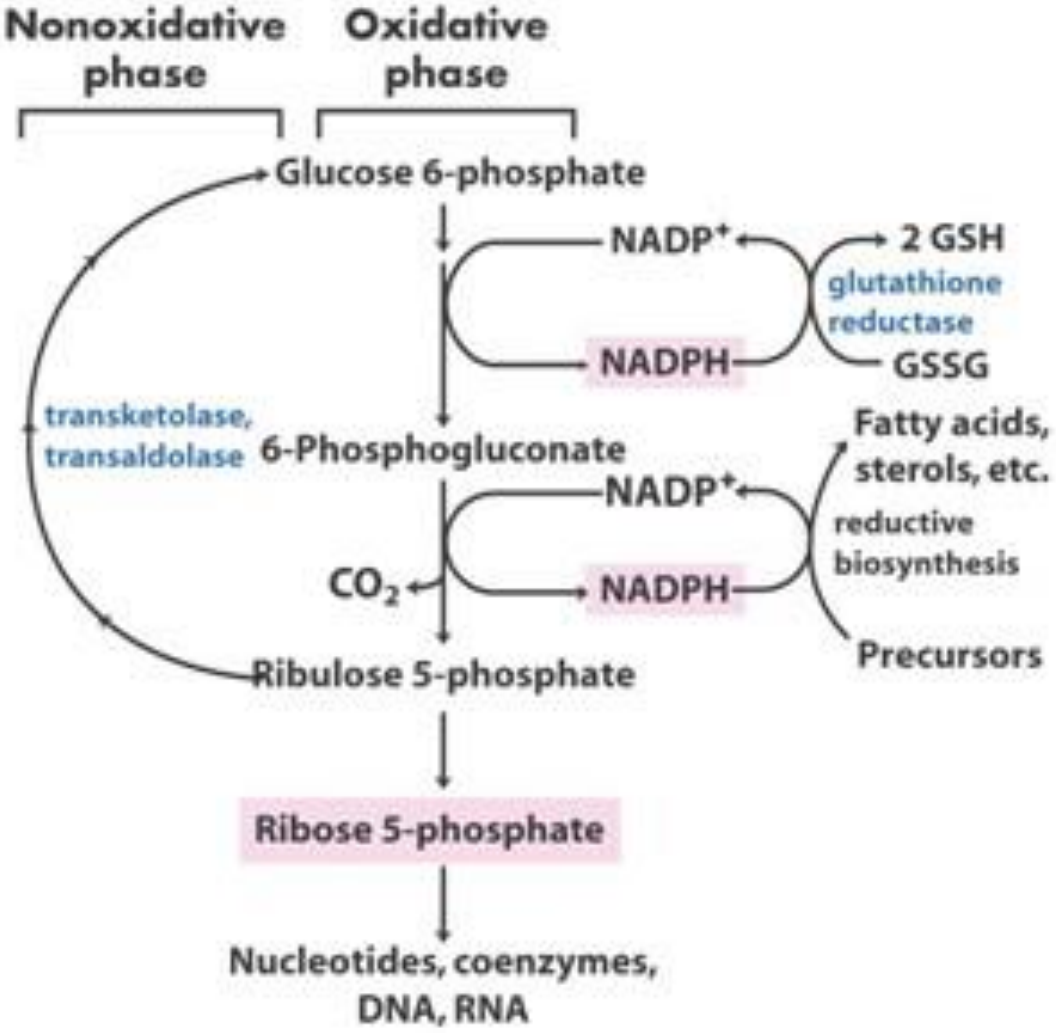
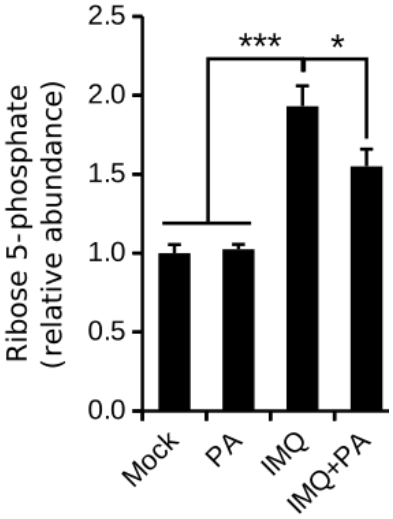
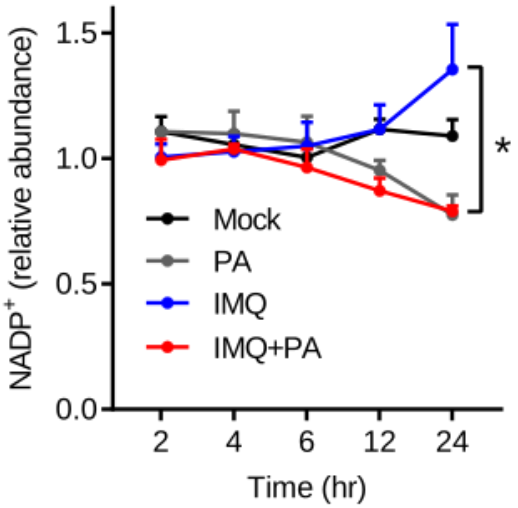

Nonoxidative phase
Oxidative phase
Glucose 6-phosphate
NADP+
2 GSH
glutathione reductase
NADPH
GSSG
transketolase, transaldolase
6-Phosphogluconate
Fatty acids, sterols, etc.
NADP+
reductive biosynthesis
CO2
NADPH
Precursors
Ribulose 5-phosphate
Ribose 5-phosphate
Nucleotides, coenzymes, DNA, RNA

PA inhibits PPP and production of antioxidant GSH in TLR-activated DC

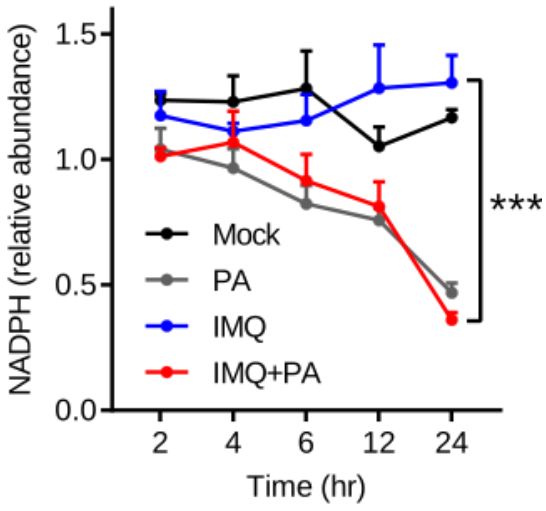
Ribose 5-phosphate



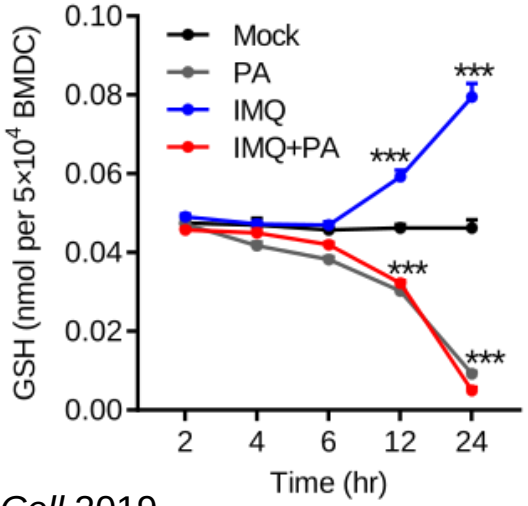
NADP+



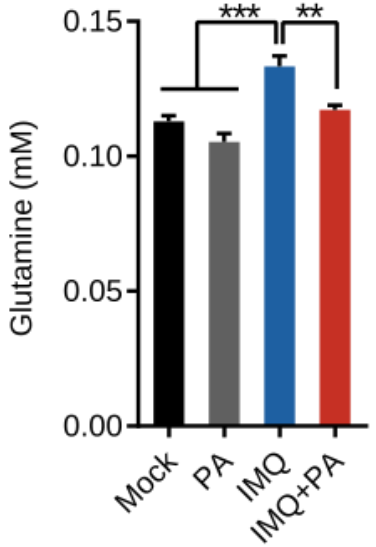
NADPH



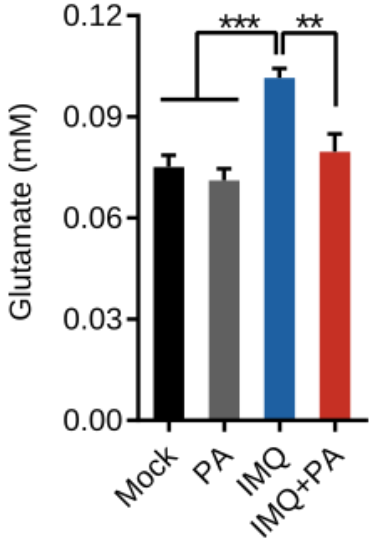
GSH



Glutamine



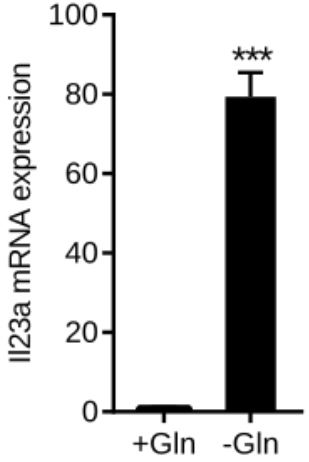
Glutamate



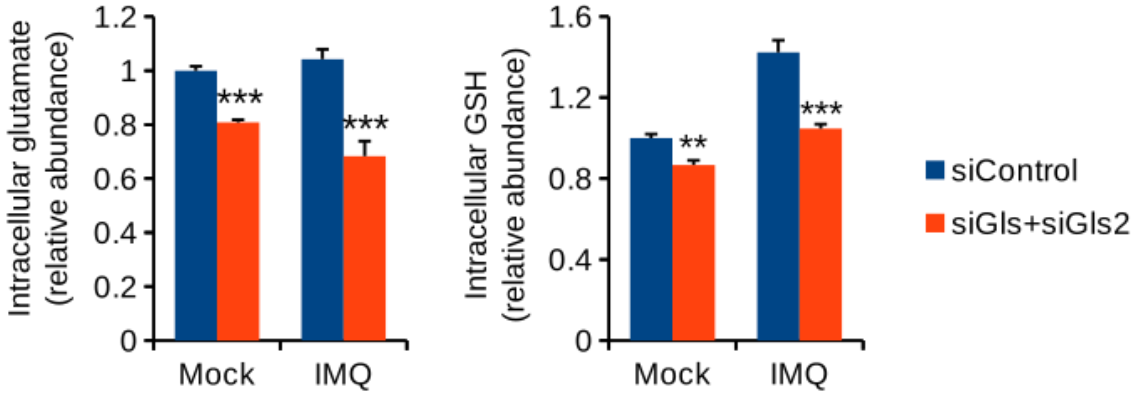
Mogilenko *et al*. *Cell* 2019

Glutamine regulates TLR-induced IL-23 through control of mtROS levels by antioxidant GSH

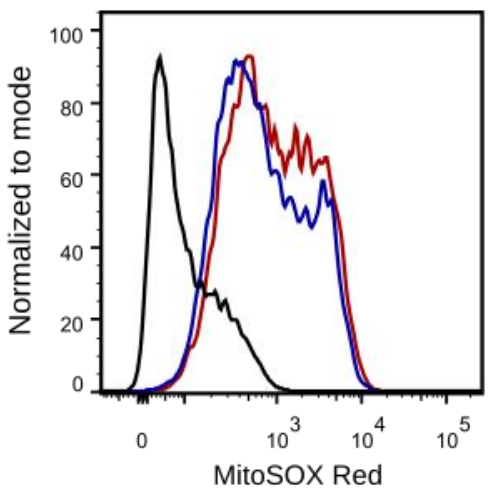
Depletion



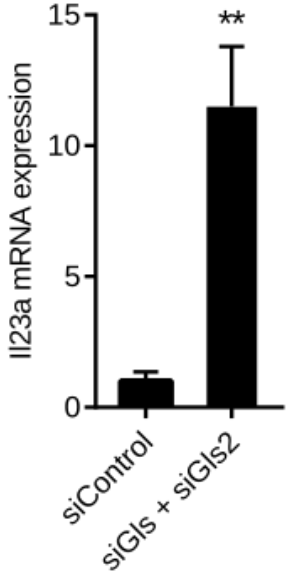
Gls inactivation



mtROS



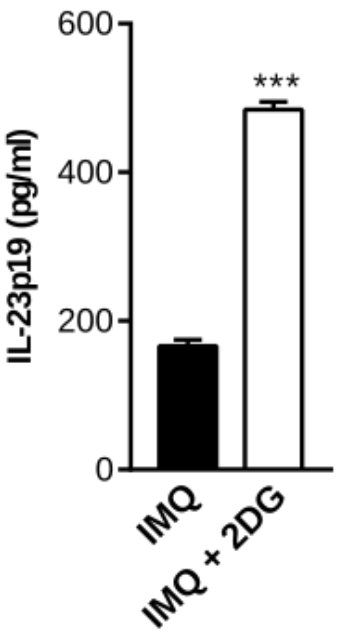
IL-23

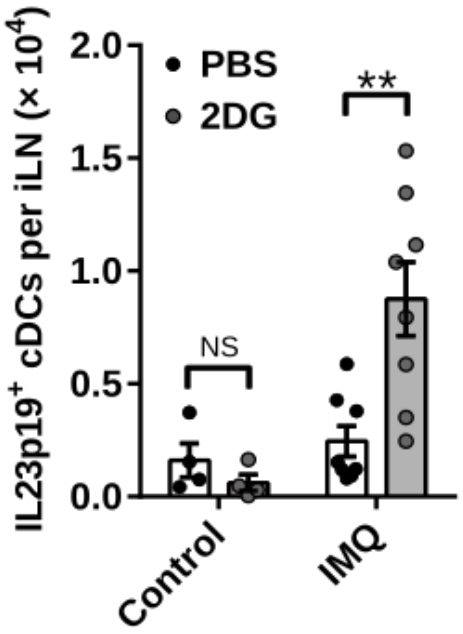


Mogilenko *et al*. *Cell* 2019

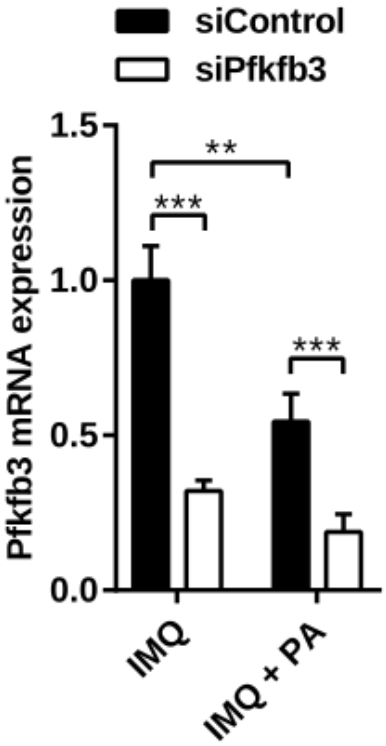
Inhibition of upper glycolysis enhances TLR-induced IL-23 expression

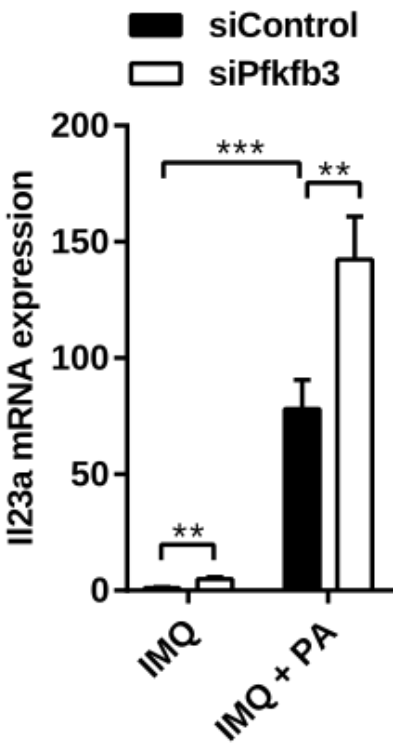
Hexokinase





Pfkfb3





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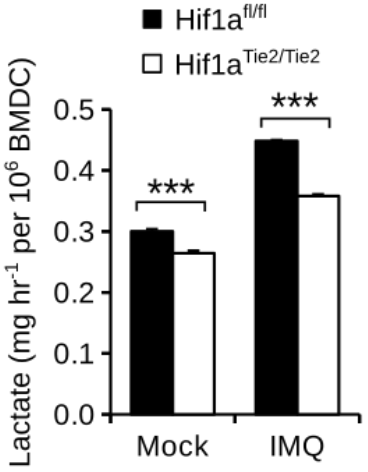
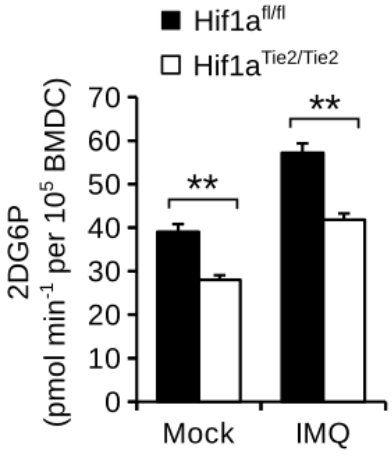
Mogilenko *et al*. *Cell* 2019

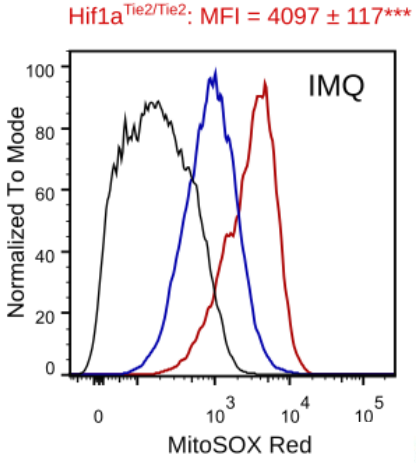
Inhibition of glycolysis by HIF1α inactivation enhances TLR-induced IL-23 expression

Glycolysis

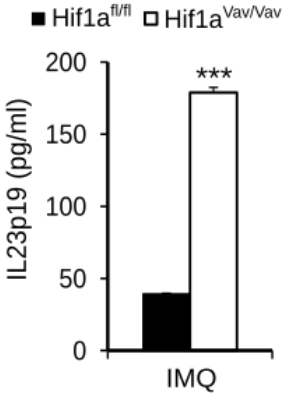




mtROS

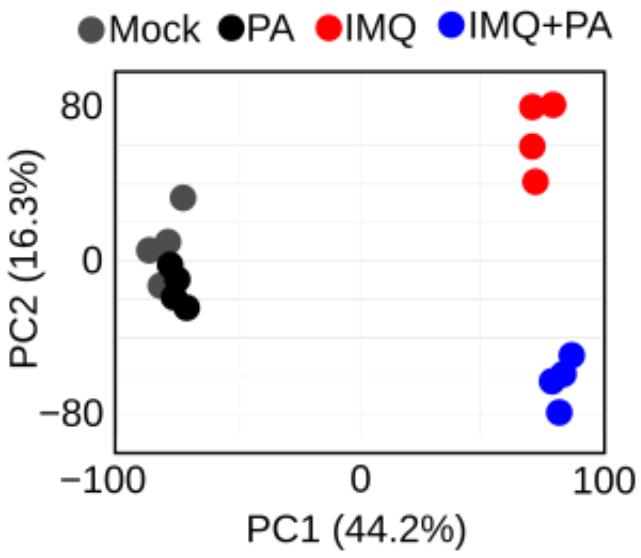


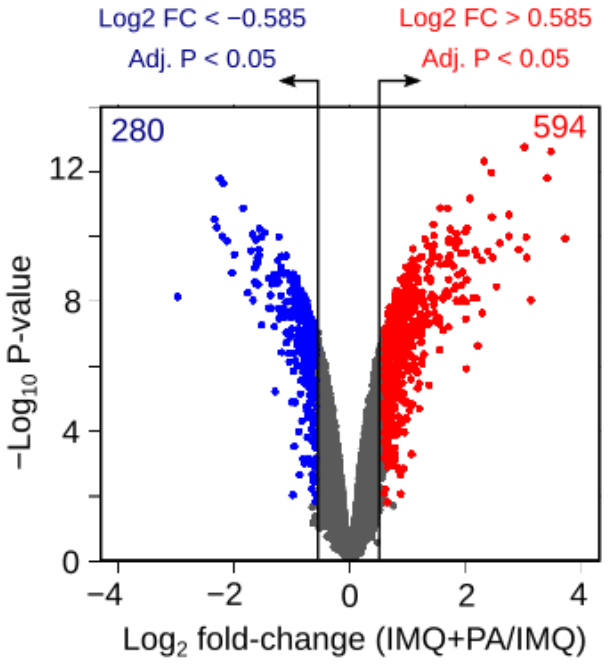
IL-23



Mogilenko *et al*. *Cell* 2019

PA and HFD feeding alter transcription program in IMQ-activated DC

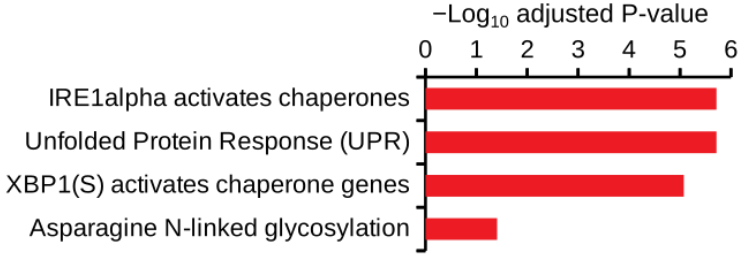




Mogilenko *et al*. *Cell* 2019

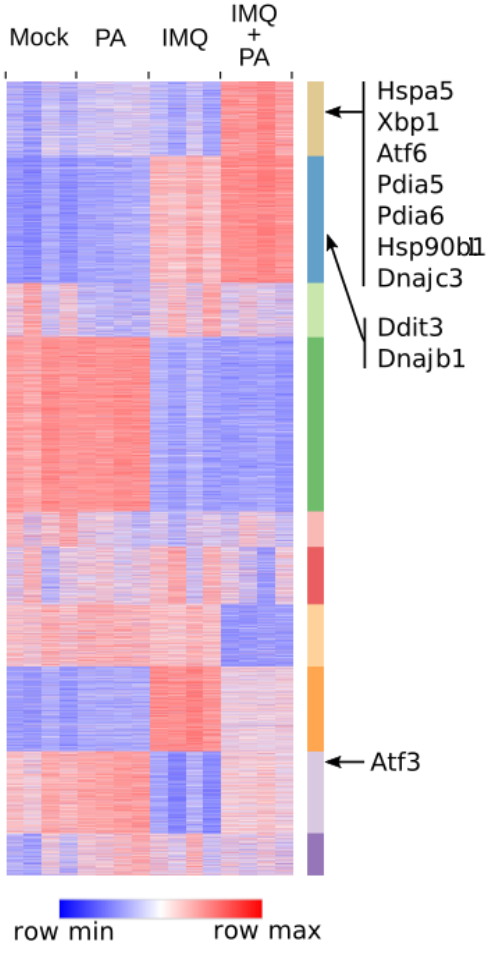
PA and HFD feeding alter transcription program and induce the UPR in IMQ-activated DC

Pathway analysis

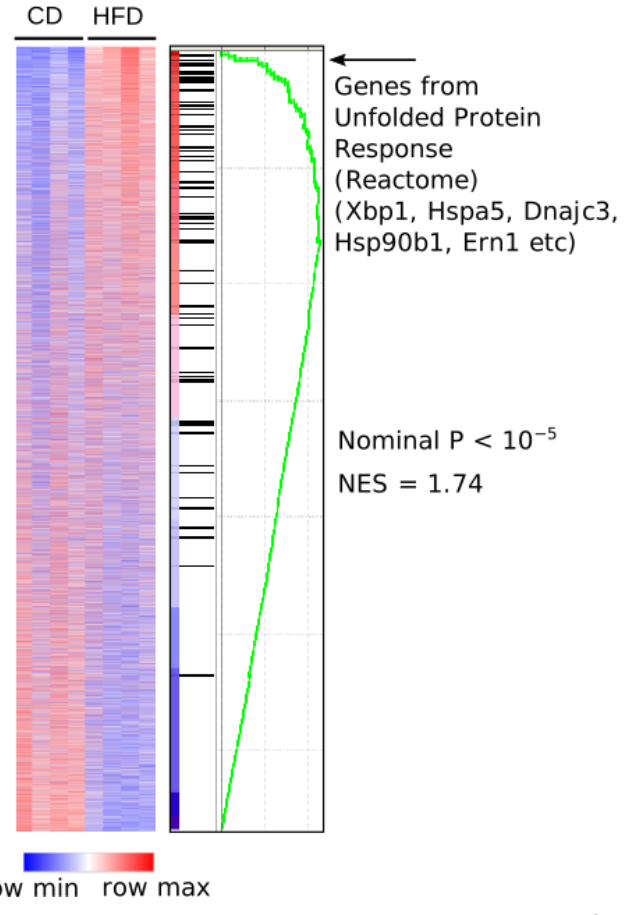


Mogilenko *et al*. *Cell* 2019

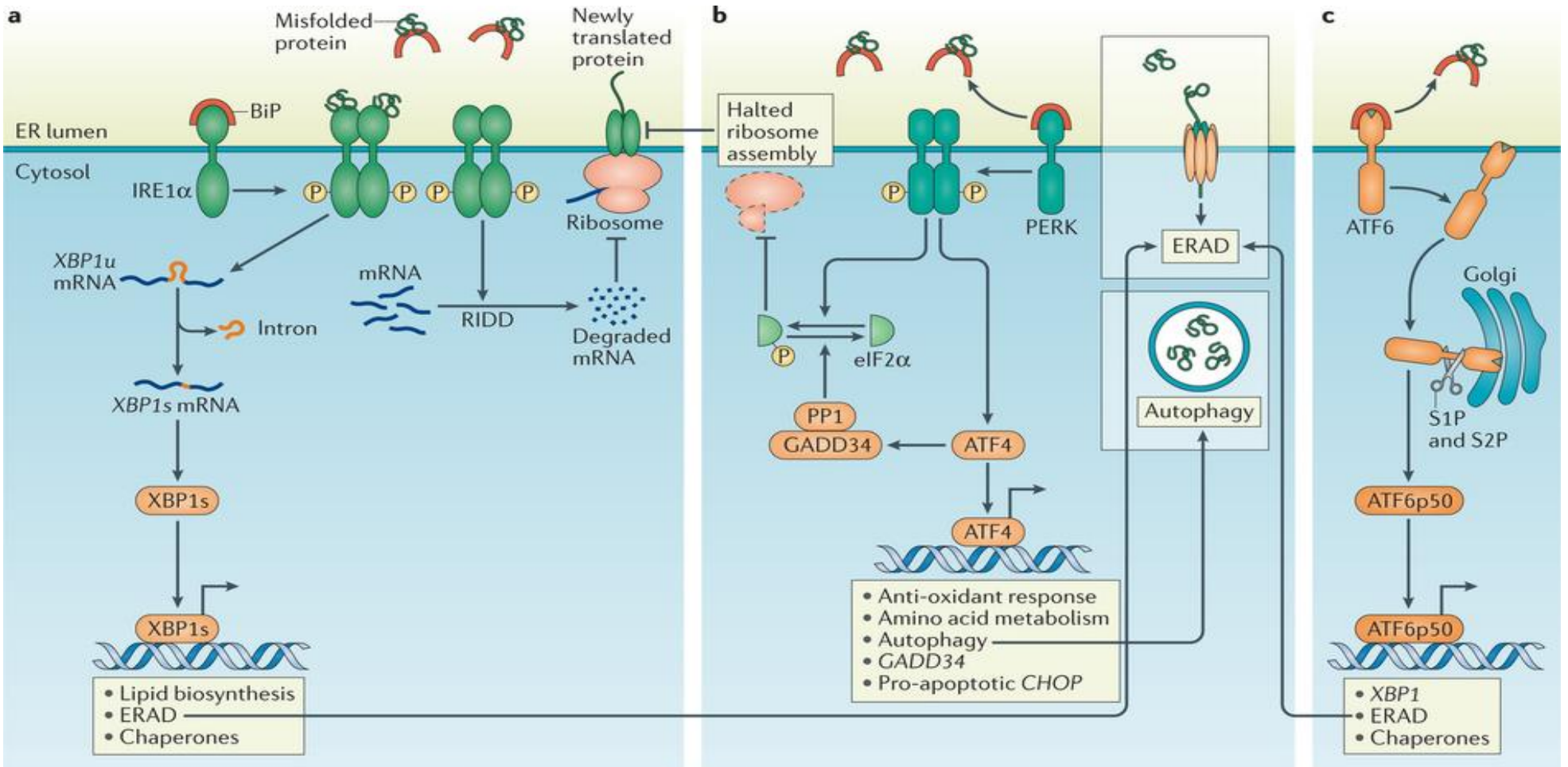
In vitro BMDC



In vivo LN DC

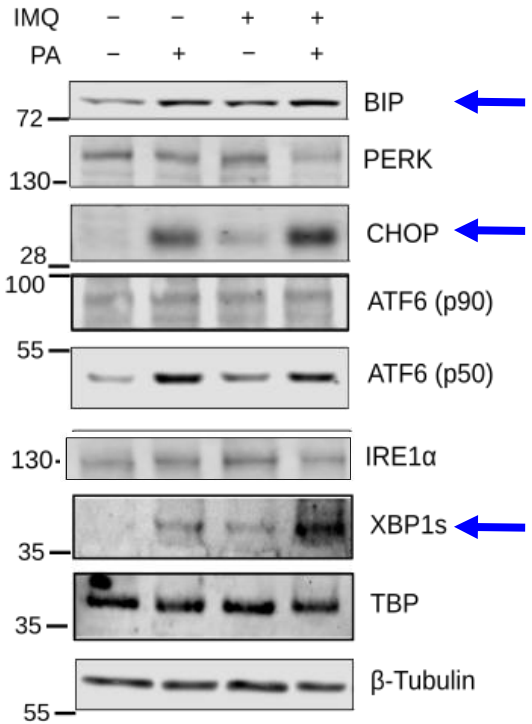


Unfolded Protein Response

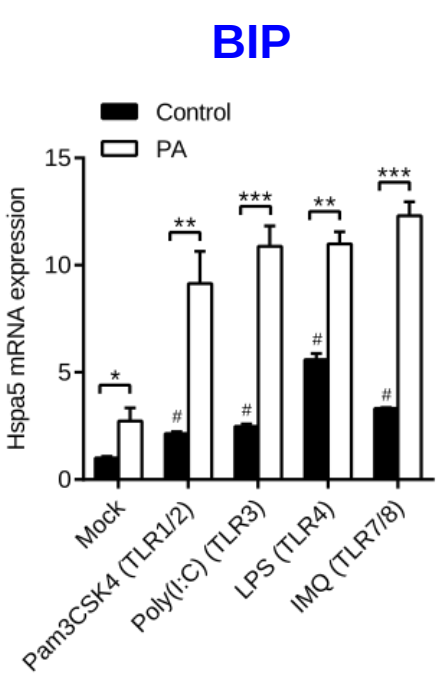


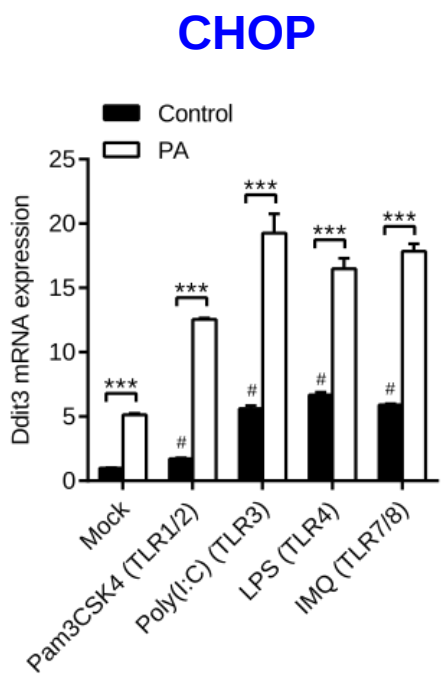
Grotjans *et al.* 2016

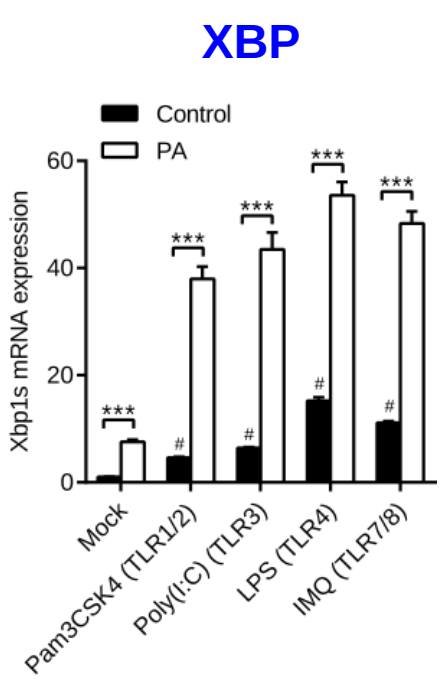
PA enhances TLR-induced UPR activation



ATF6: no change







aviesan

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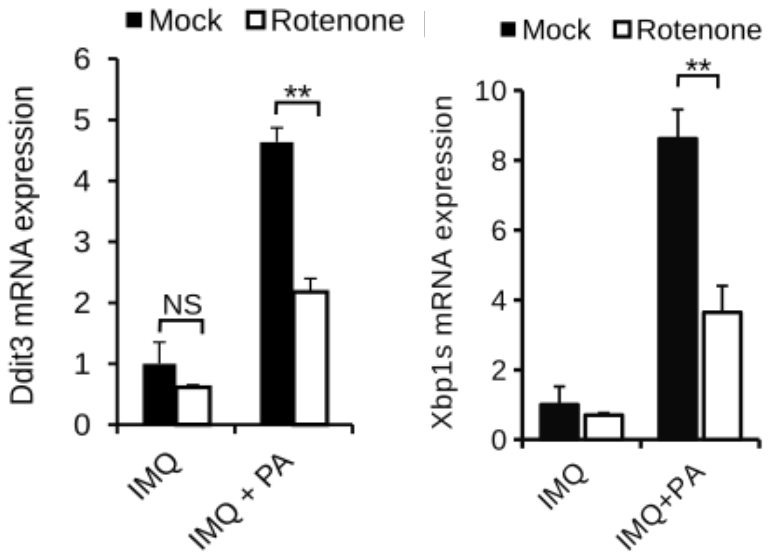
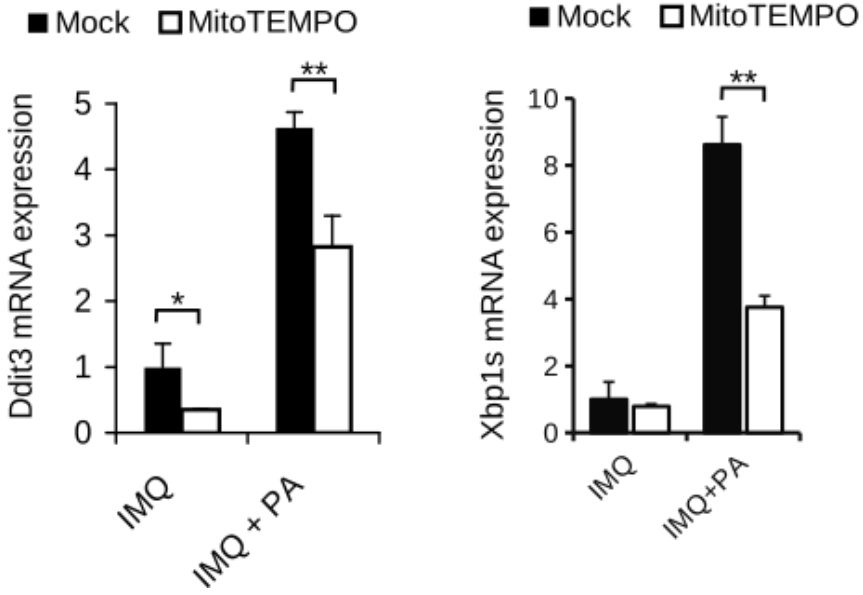
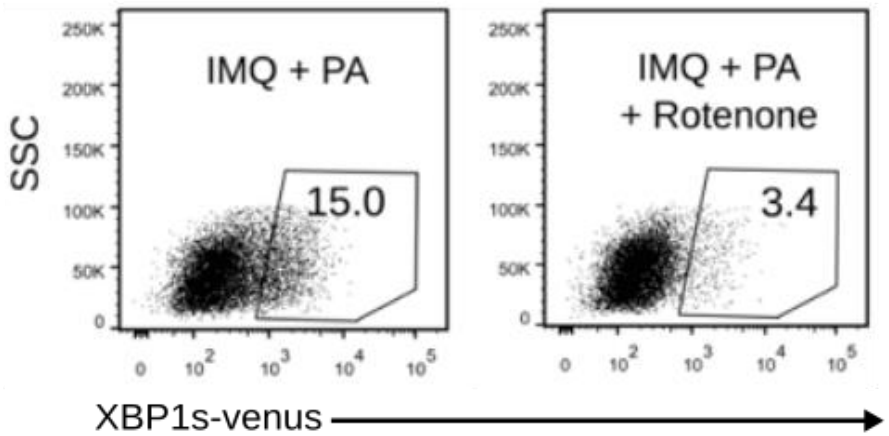
PA enhances UPR through mtROS generation

Complex I inhibition



mtROS inhibition





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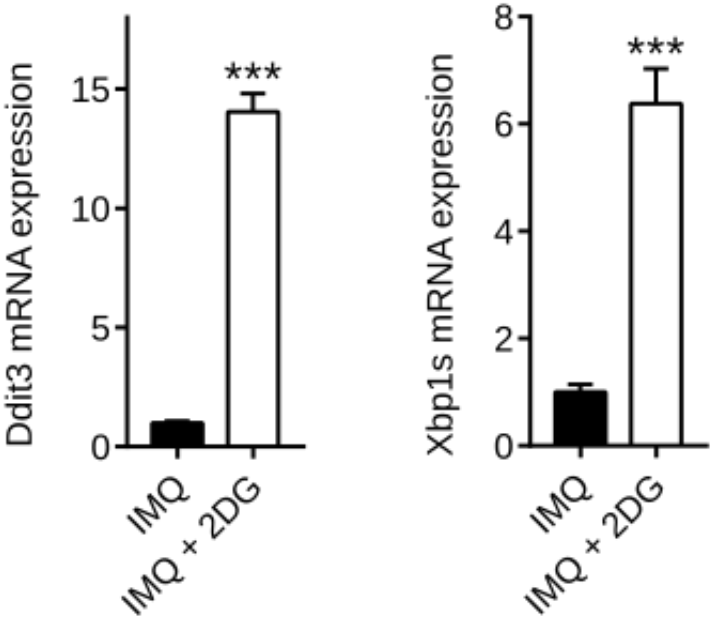
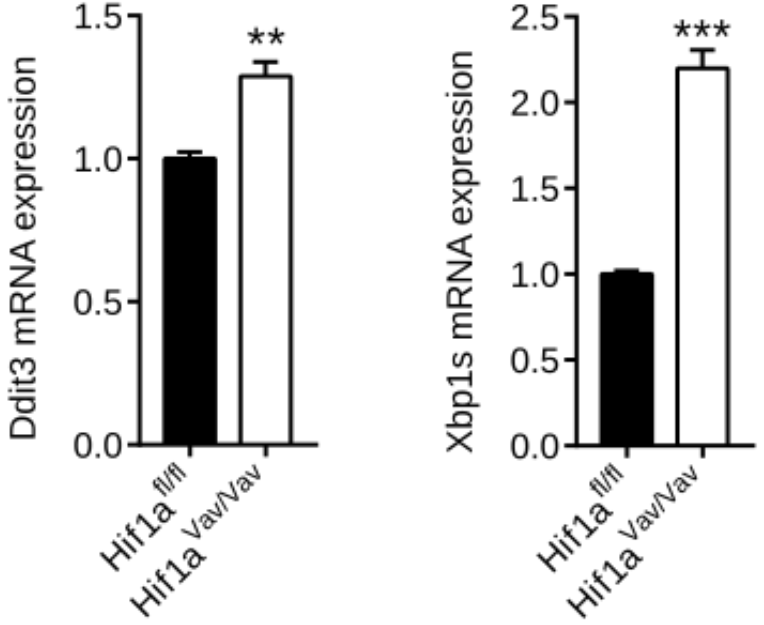
Glycolysis inhibition potentiates TLR-mediated induction of UPR

2DG



HIF1α deficiency



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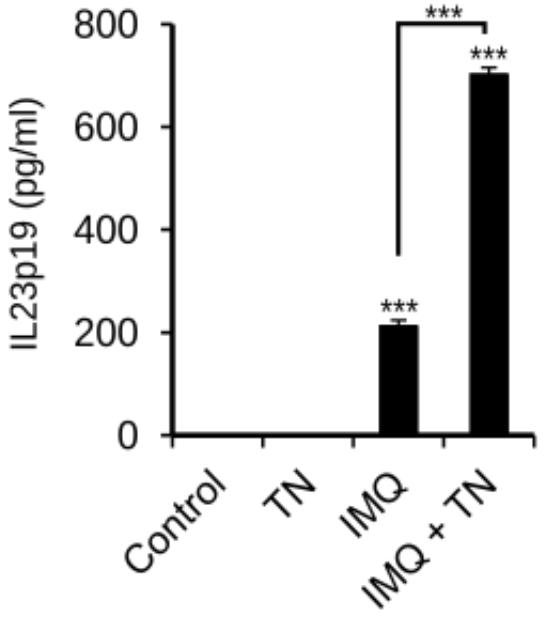
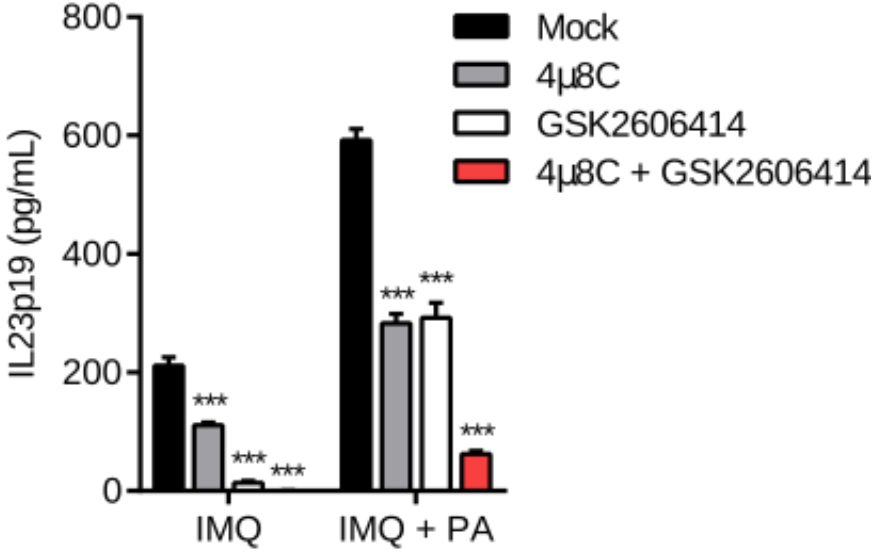
PA increases IL-23 expression through PERK and IRE1α branches of UPR





TN: Tunicamycin

4μ8C: IRE1α inhibitor
GSK2606414: Perk inhibitor

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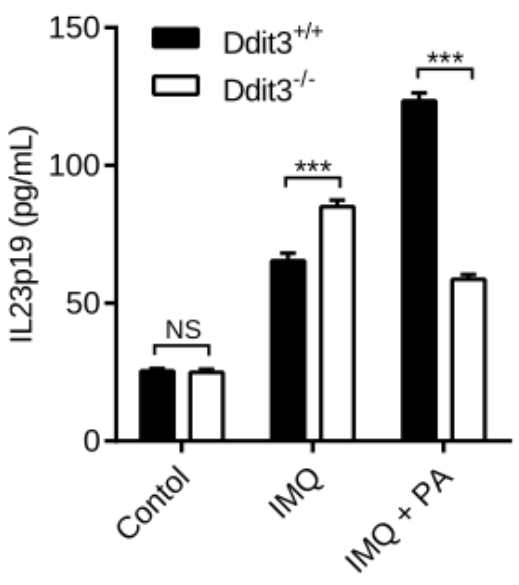
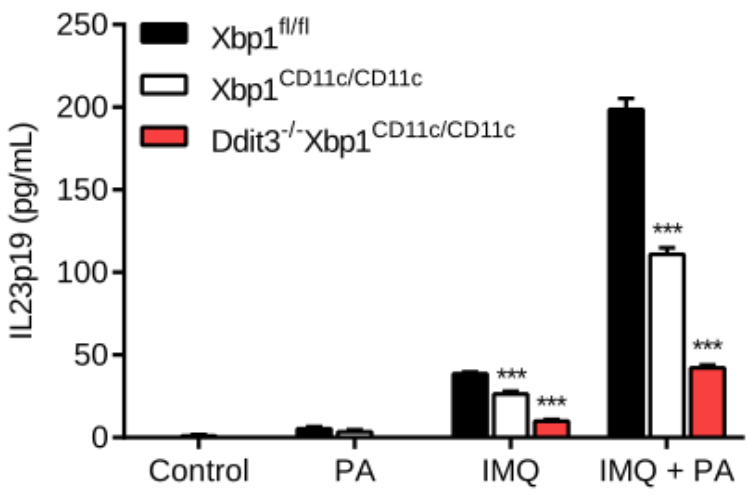
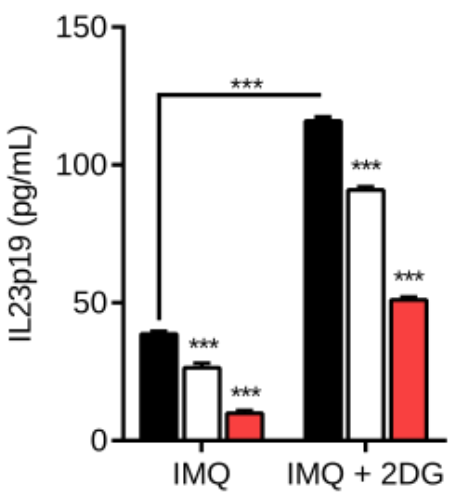
Glycolysis inhibition by PA and 2DG increases IL-23 expression through CHOP and XBP1

PA





2DG



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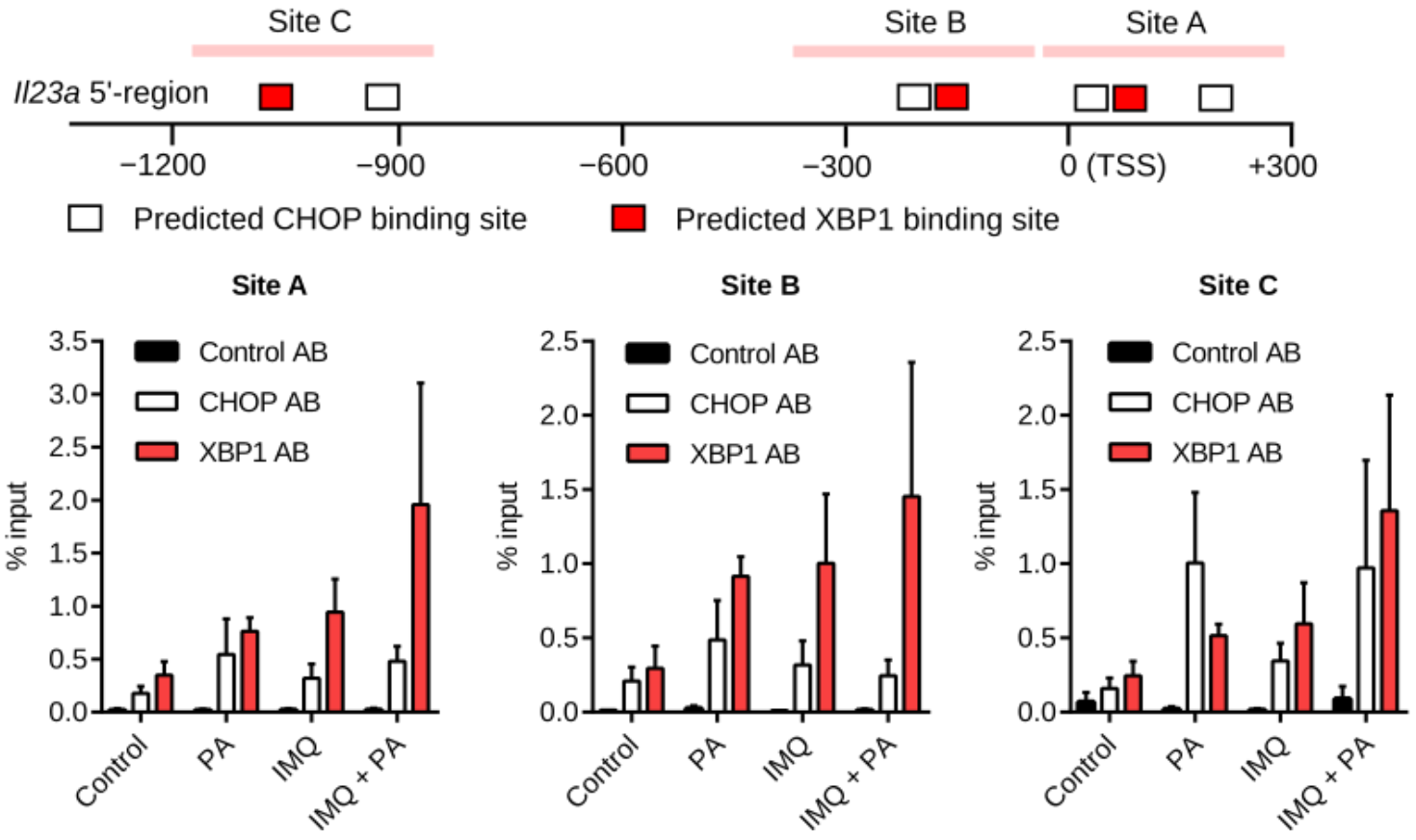
Glycolysis inhibition by PA increases IL-23 expression through CHOP and XBP1 binding to IL-23 promoter

CHIP-PCR



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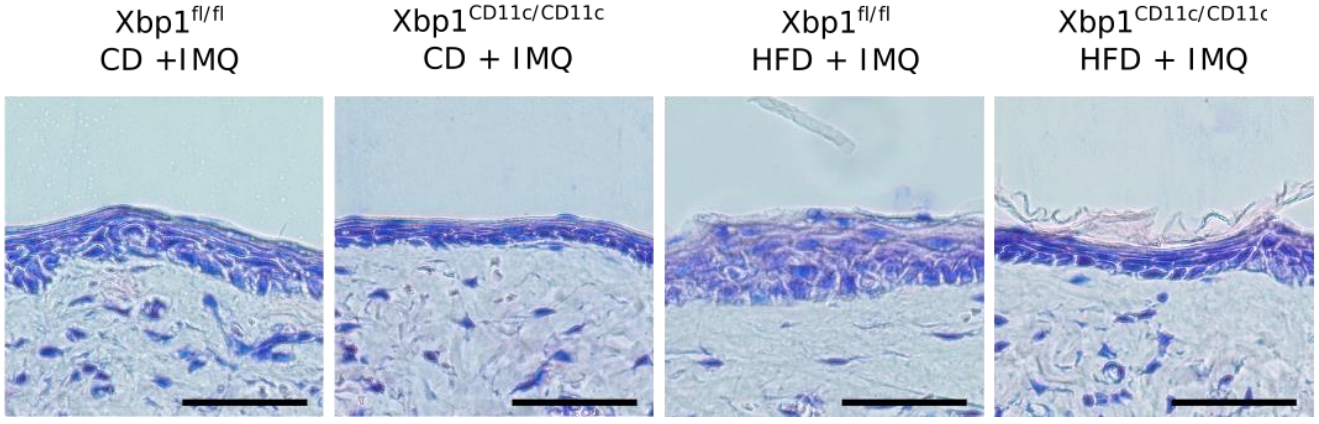
HFD feeding exacerbates psoriasis-like inflammation through the Xbp1-dependent increase of IL-23 expression in cDC

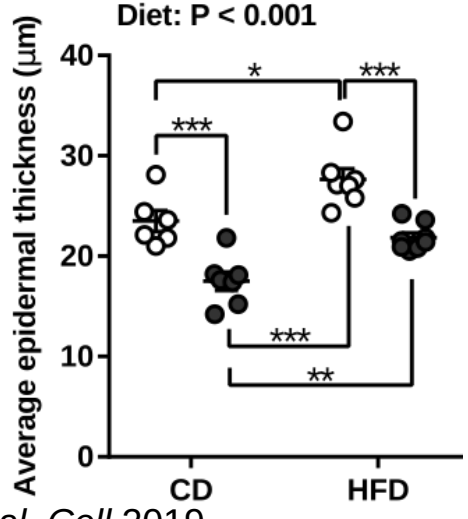


○ Xbp1$^{fl/fl}$

● Xbp1$^{CD11c/CD11c}$

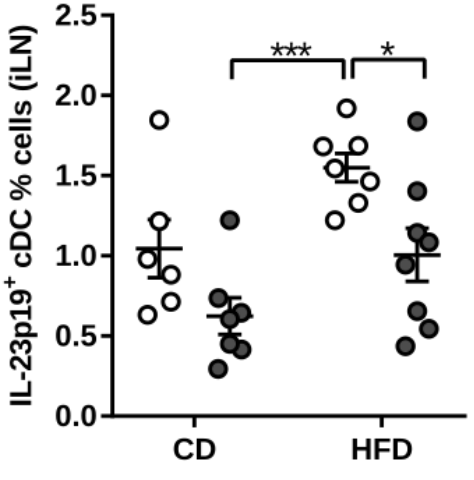
Epidermis

Genotype: P < 0.001
Diet: P < 0.001



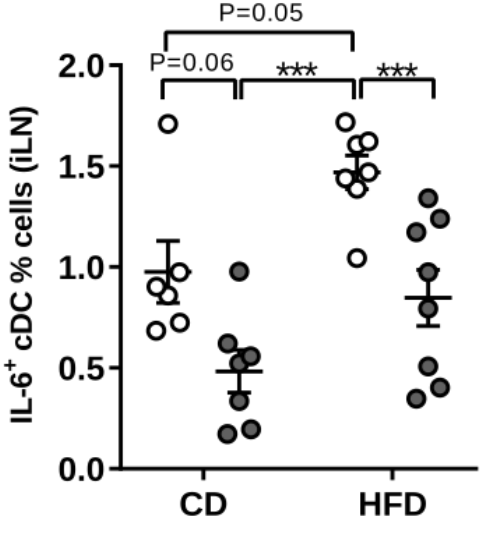
IL-23

Genotype: P < 0.01
Diet: P < 0.01



IL-6

Genotype: P = 0.002
Diet: P = 0.001



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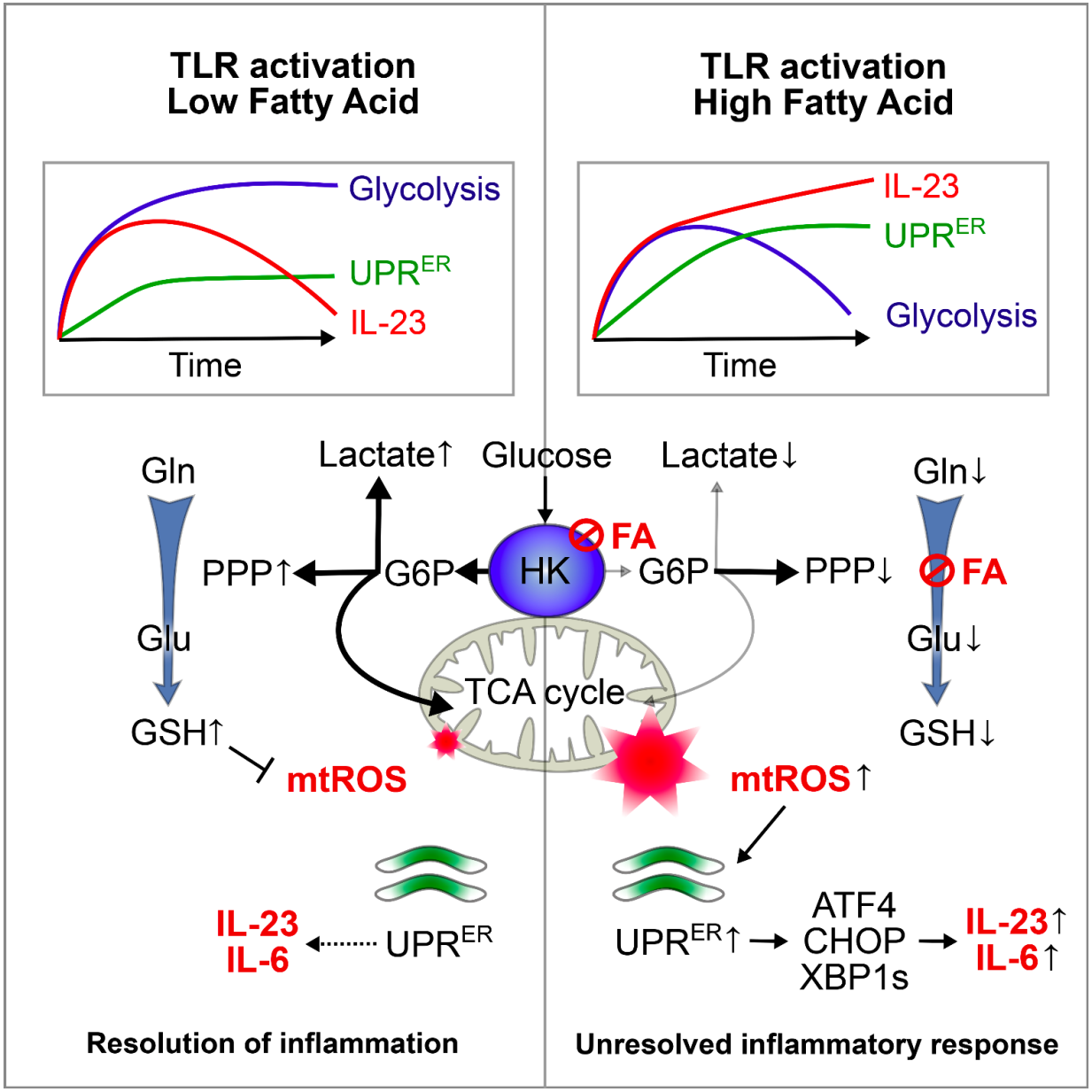

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Post-doc Applications welcome

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