OPEN ACCESS
CellPress

Impact factor: 9.995

Cell Reports
Article

Mitochondrial Dysfunction Prevents Repolarization of Inflammatory Macrophages

Jan Van den Bossche,[1,5,*] Jeroen Baardman,[1] Natasja A. Otto,[1,2,3] Saskia van der Velden,[1] Annette E. Neele,[1] Susan M. van den Berg,[1] Rosario Luque-Martin,[1] Hung-Jen Chen,[1] Marieke C.S. Boshuizen,[1] Mohamed Ahmed,[1] Marten A. Hoeksema,[1] Alex F. de Vos,[2,3] and Menno P.J. de Winther[1,4]

[1]Department of Medical Biochemistry, Experimental Vascular Biology, Academic Medical Center, University of Amsterdam, Meibergdreef 9, Amsterdam 1105, the Netherlands

[2]Center for Experimental and Molecular Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, Amsterdam 1105, the Netherlands

[3]Center for Infection and Immunity, Academic Medical Center, University of Amsterdam, Meibergdreef 9, Amsterdam 1105, the Netherlands

[4]Institute for Cardiovascular Prevention (IPEK), Ludwig Maximillian's University, Pettenkoferstrasse 9, Munich 80336, Germany

[5]Lead Contact

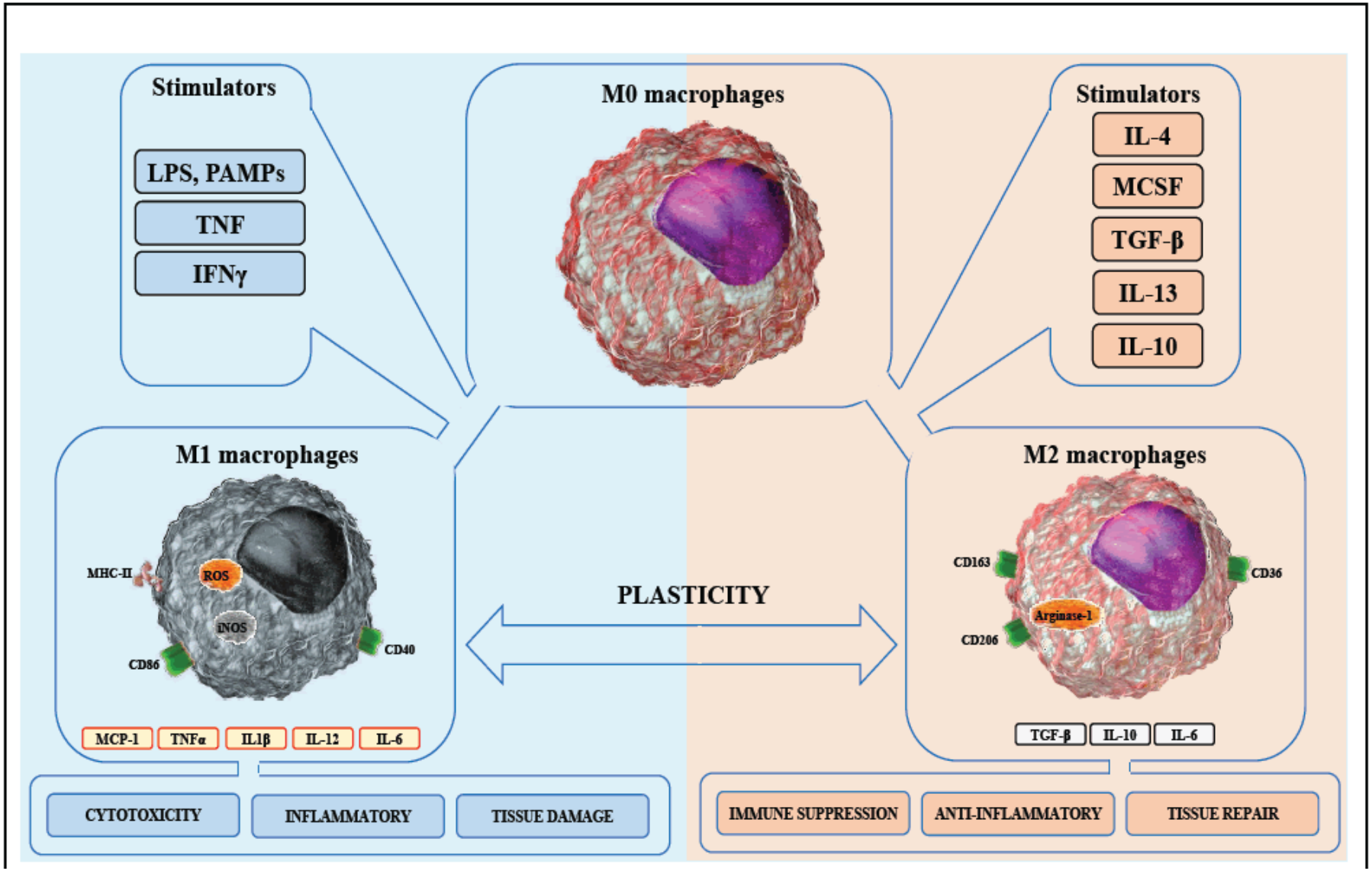
*Correspondence: j.vandenbossche@amc.uva.nl

http://dx.doi.org/10.1016/j.celrep.2016.09.008

23.04.12
유아론

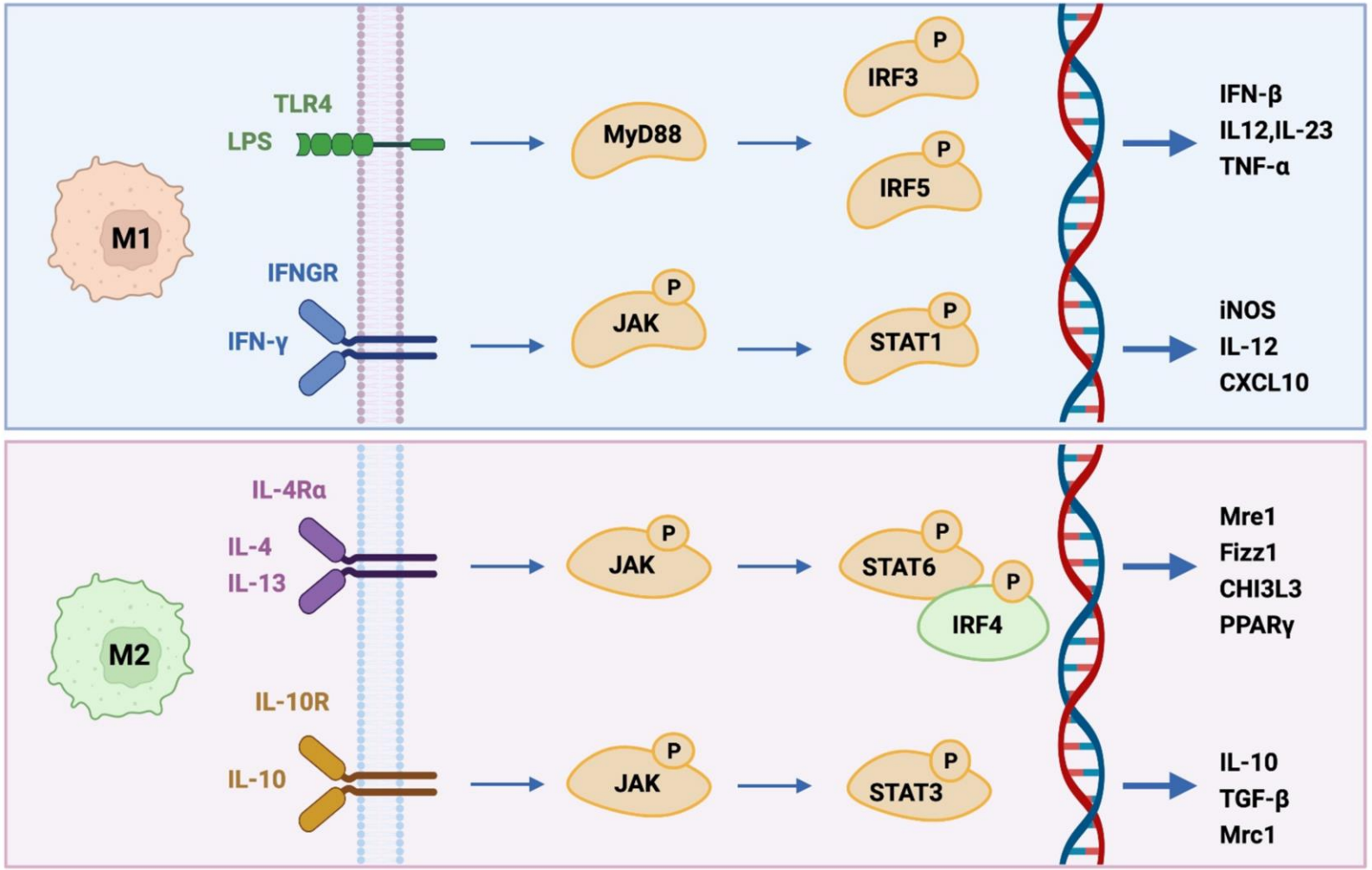
Introduction

Macrophage polarization



Introduction

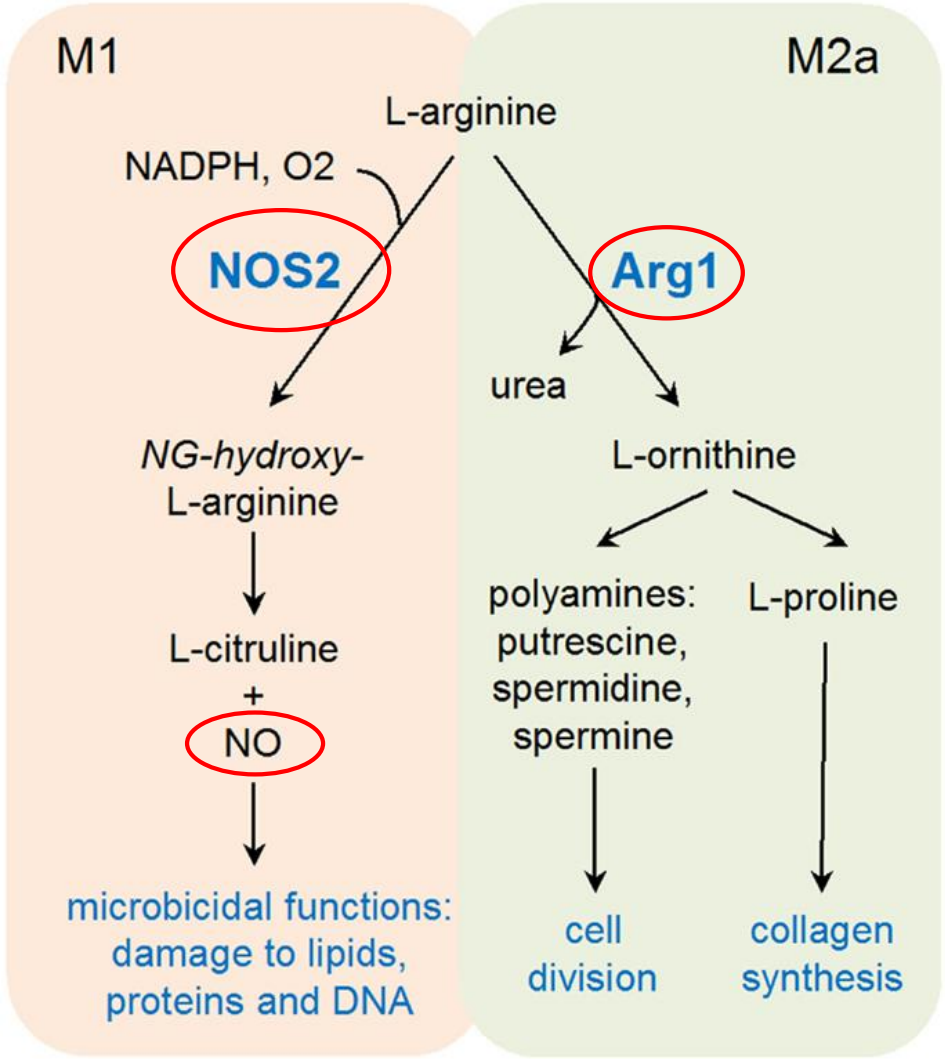
Macrophage polarization signaling pathways



- M1 – TLR4/IFNg signal
- M2 – IL4/IL13 – STAT6 signal

Introduction

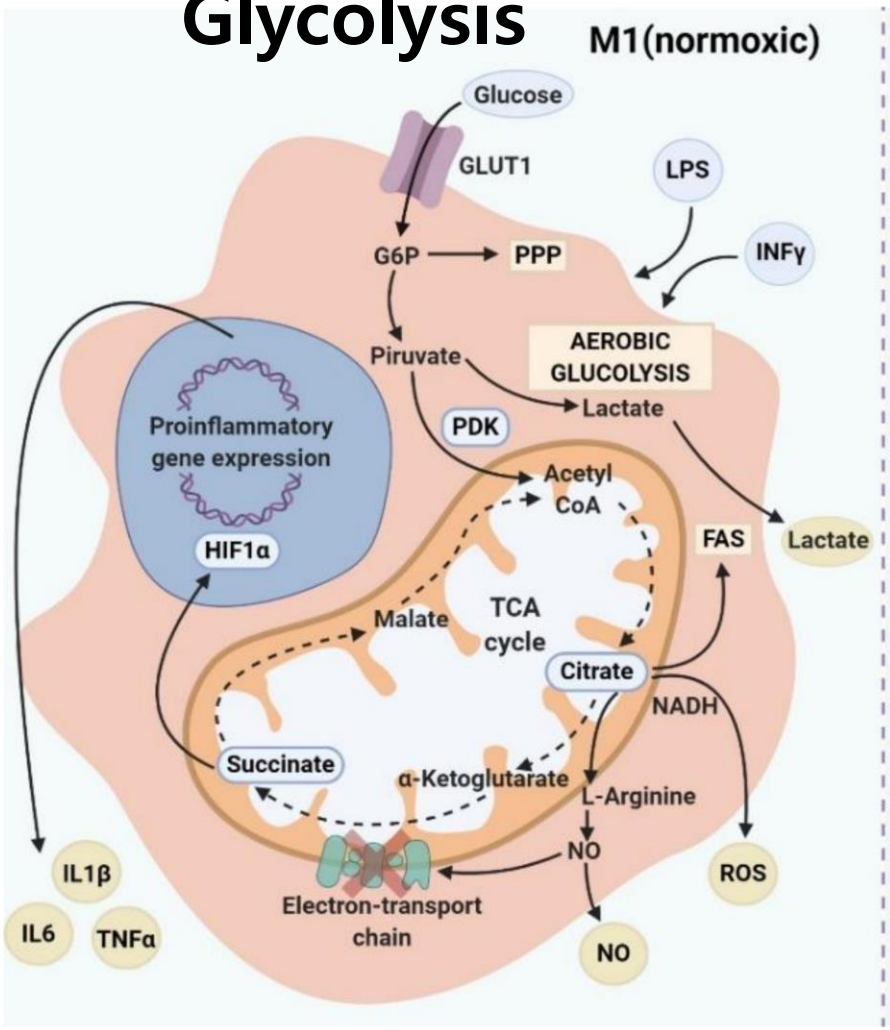
Arginine metabolism of macrophages



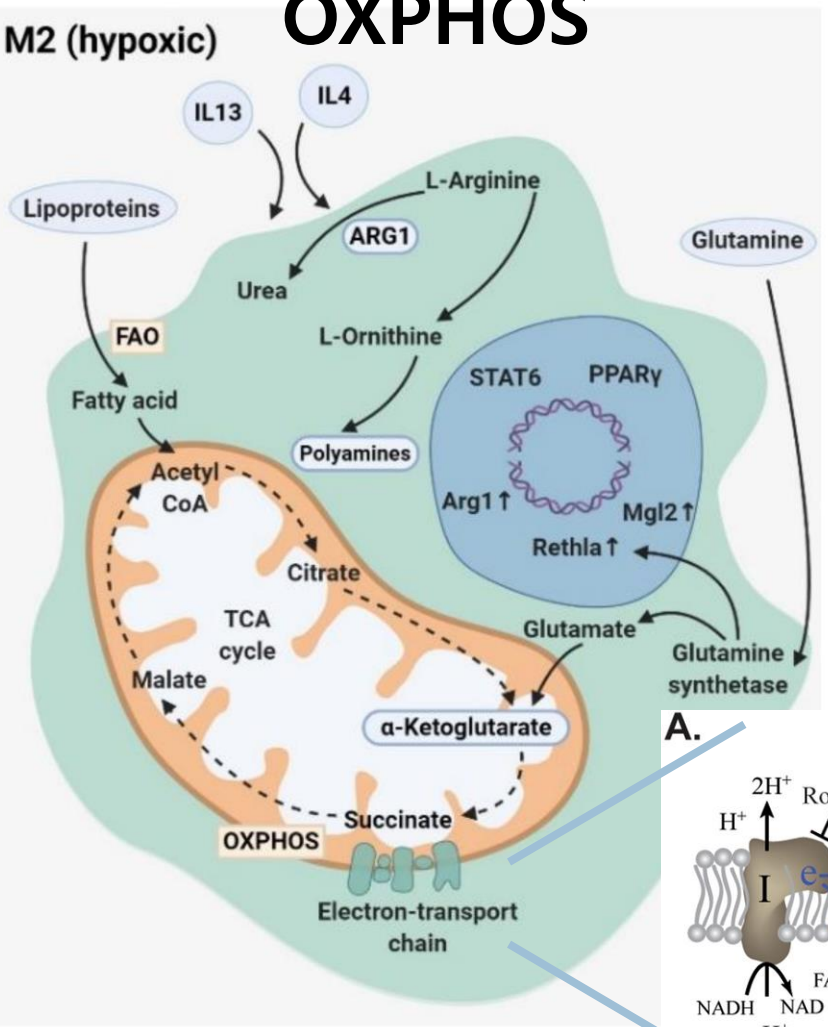
Introduction

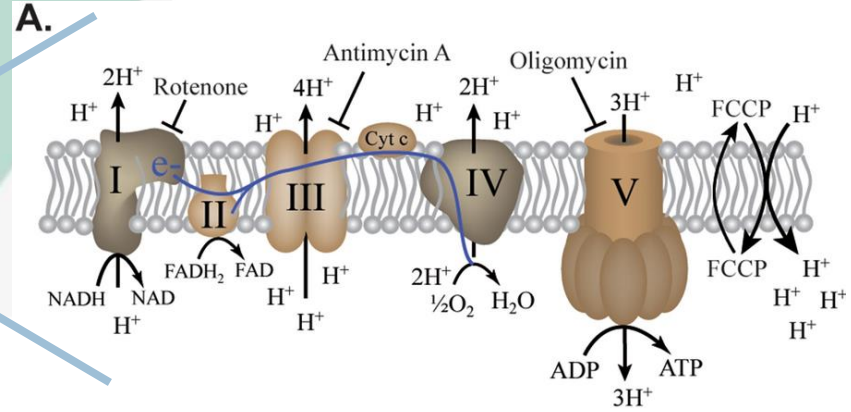
Difference in metabolism of macrophages

Glycolysis



OXPHOS





Introduction

Macrophage repolarization

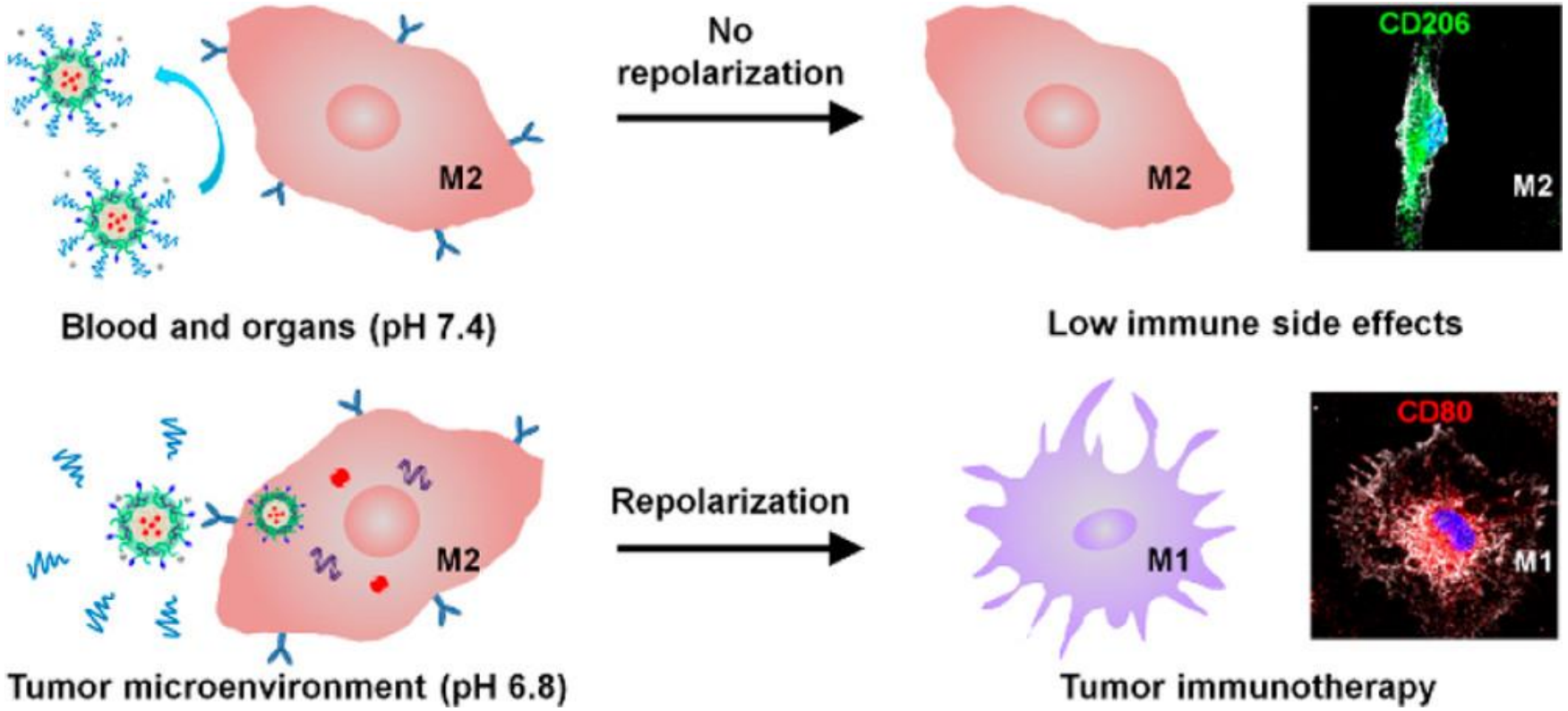
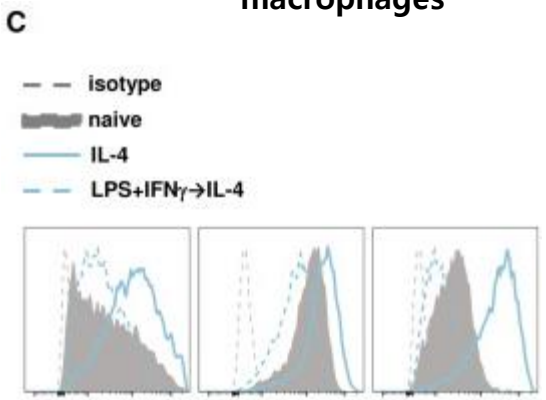
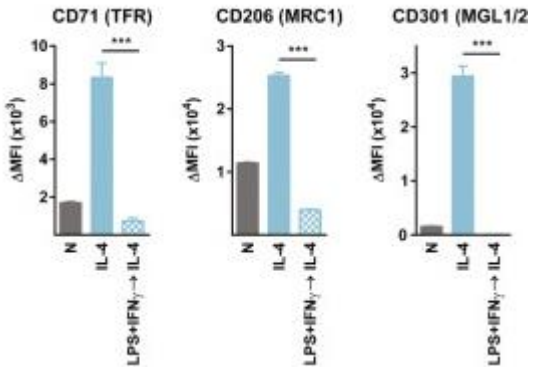


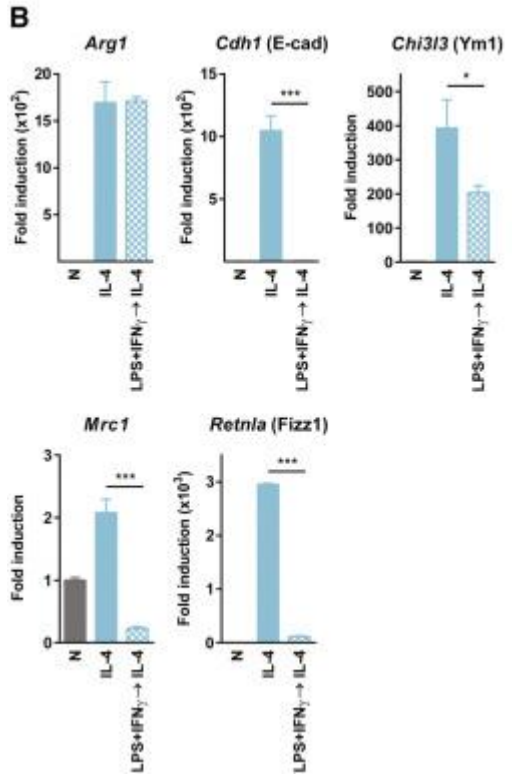
Figure 1.

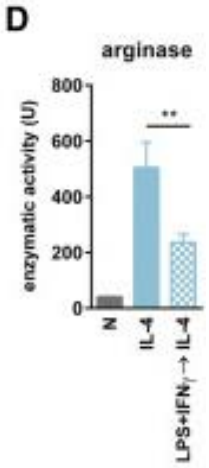
Mouse M1 macrophages fail to repolarize to M2 upon IL-4 restimulation in vitro



M2 macrophage markers



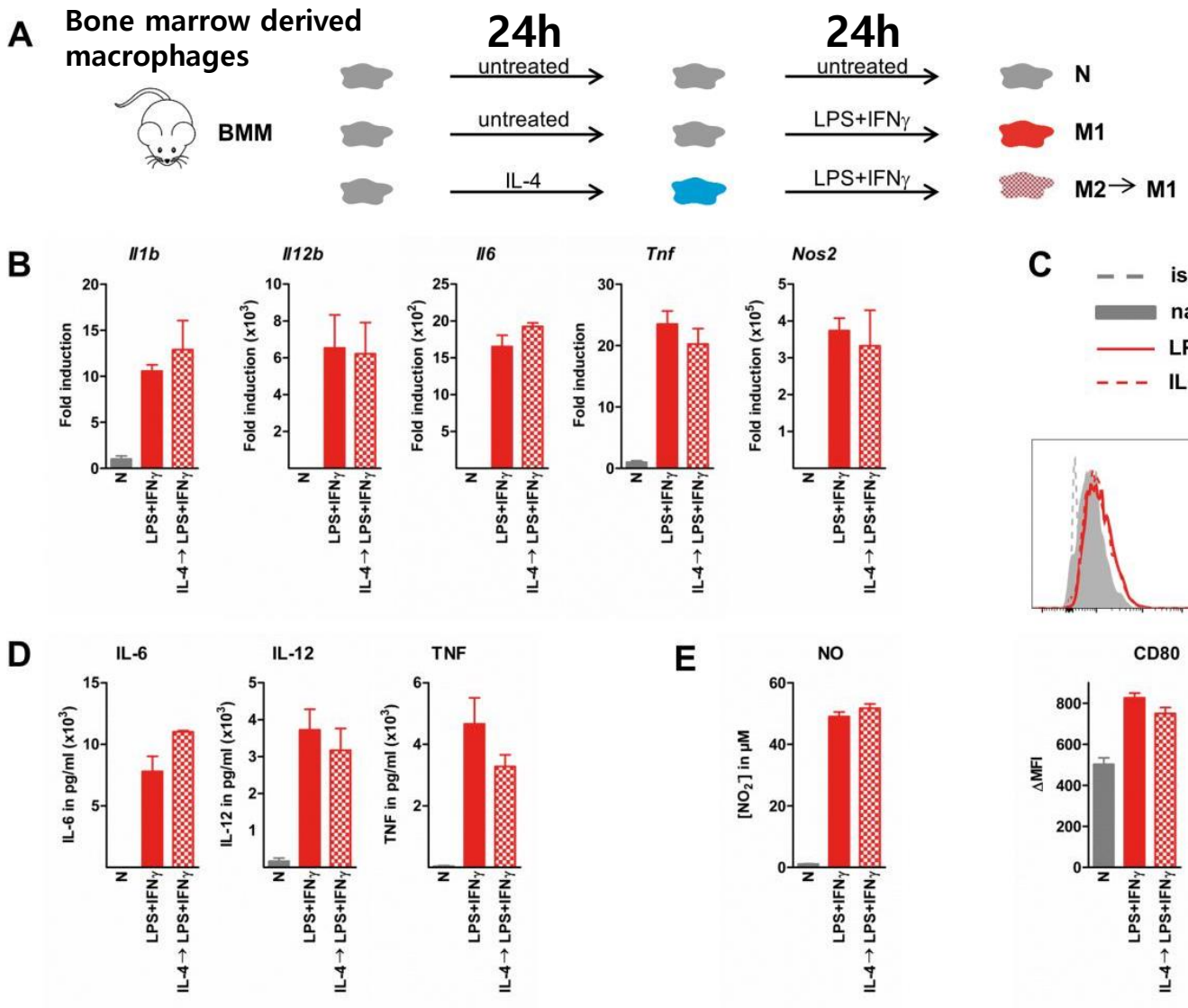




✓ Mouse M1 macrophages didn't response to M2 signal

Figure S3.

IL-4-induced M2 macrophages respond to LPS+IFNγ-stimulation

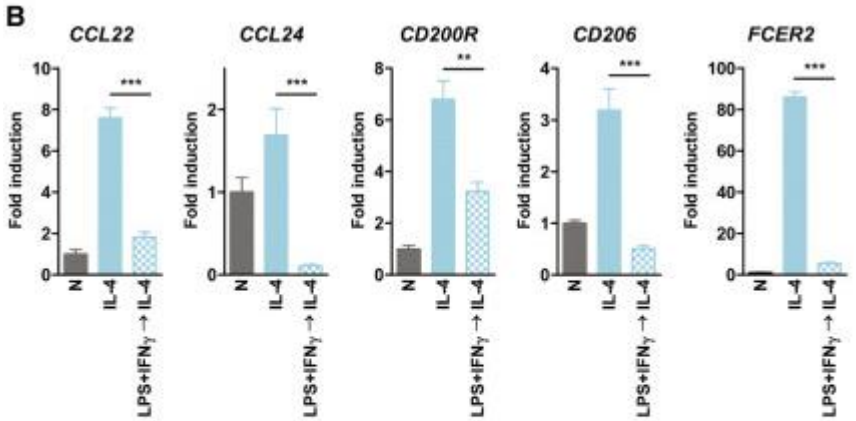


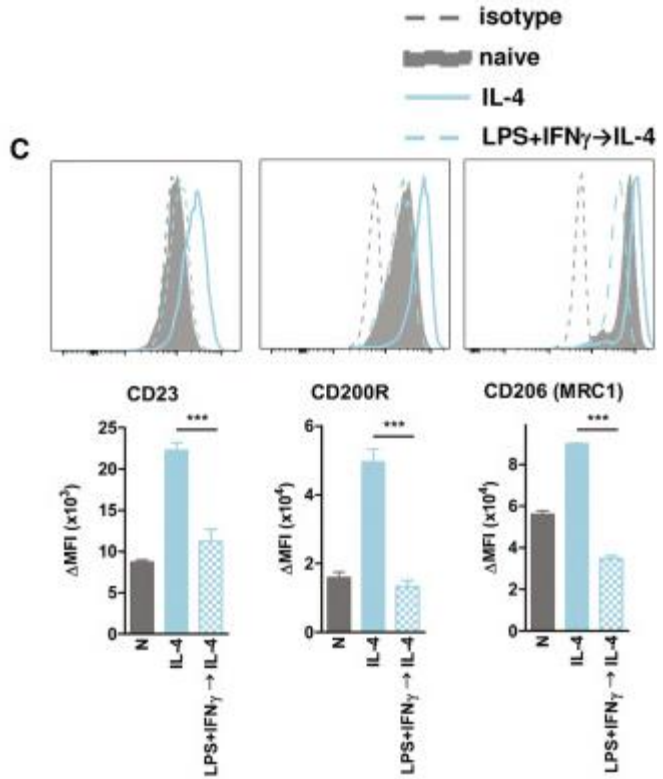
✓ M2 macrophages could repolarize to M1 macrophages

Figure 2.

Human inflammatory macrophages do not repolarize to M2 in vitro

M2 macrophage mRNA markers

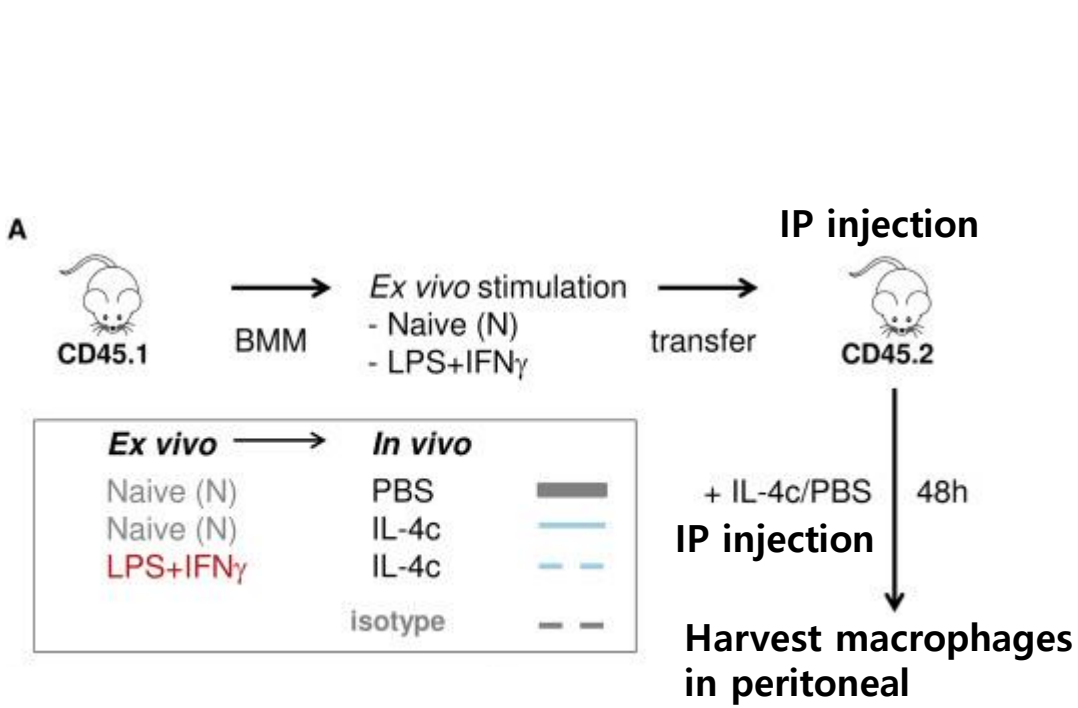


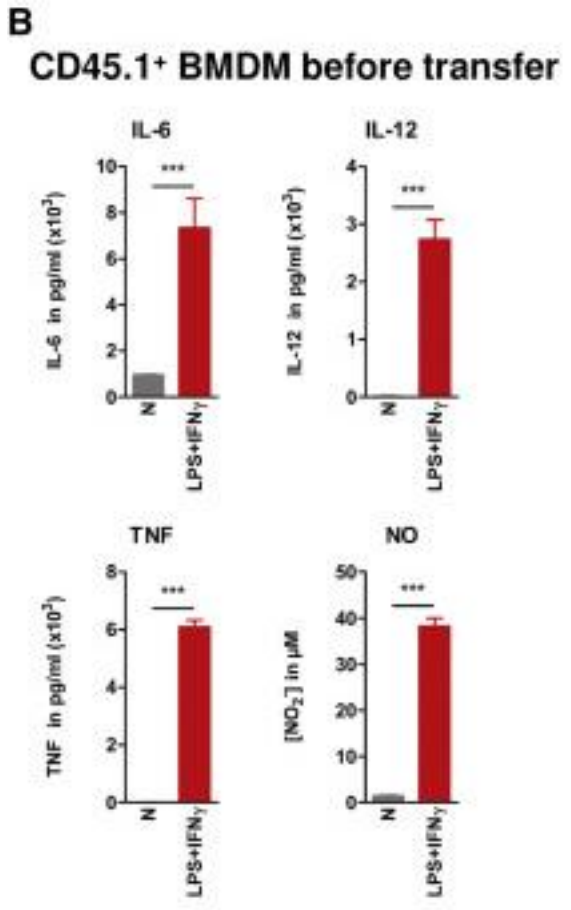


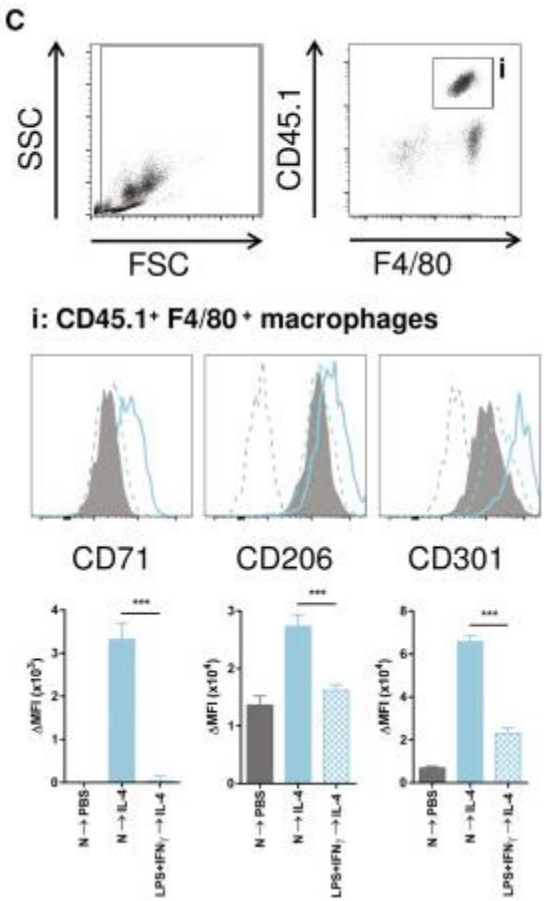
✓ Human M1 macrophages also couldn't repolarize to M2

Figure 3.

Inflammatory macrophages fail to repolarize to M2 in vivo





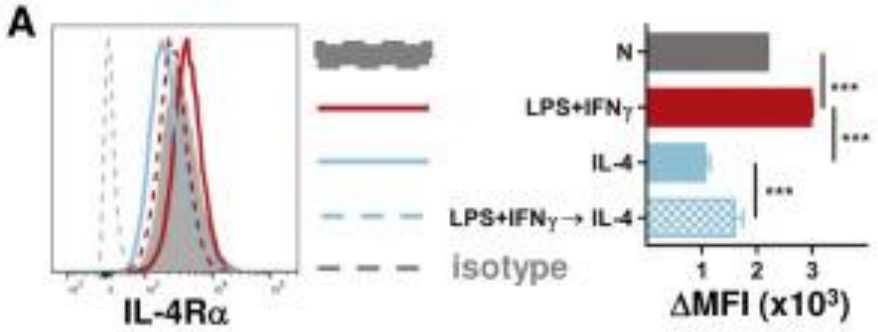


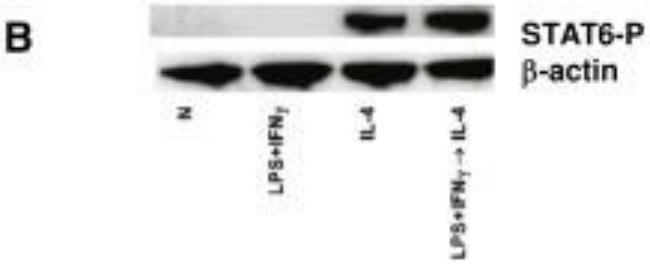
✓ M1 macrophages didn't respond to M2 signal in vivo

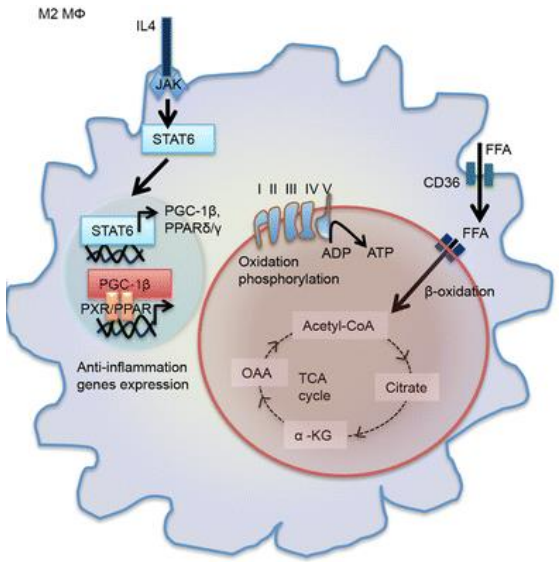
Figure 4.

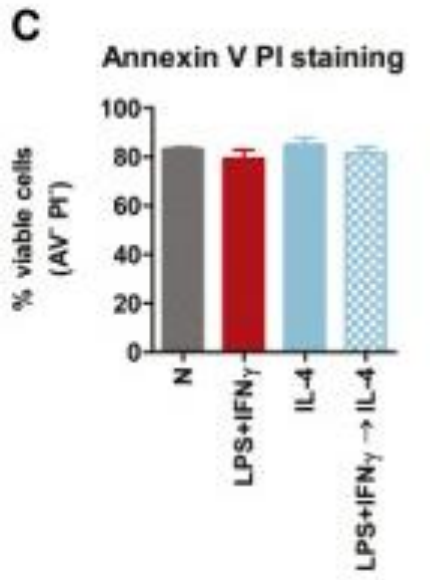
LPS+IFNγ treatment blunts mitochondrial oxidative respiration in mouse macrophages

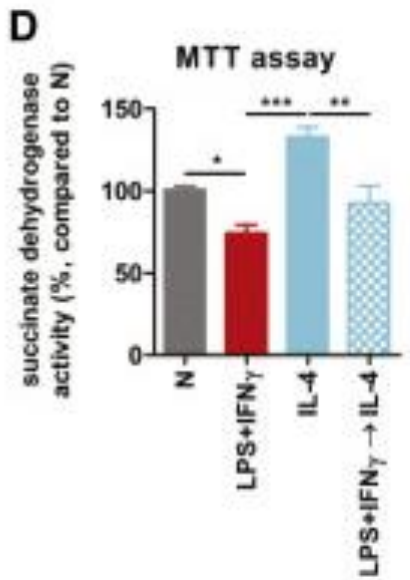
IL-4 receptor expression

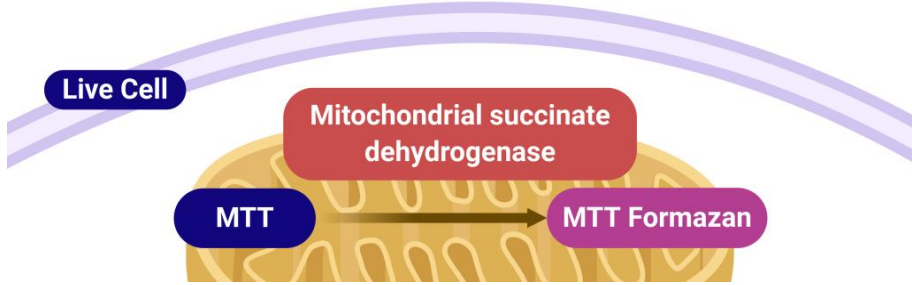








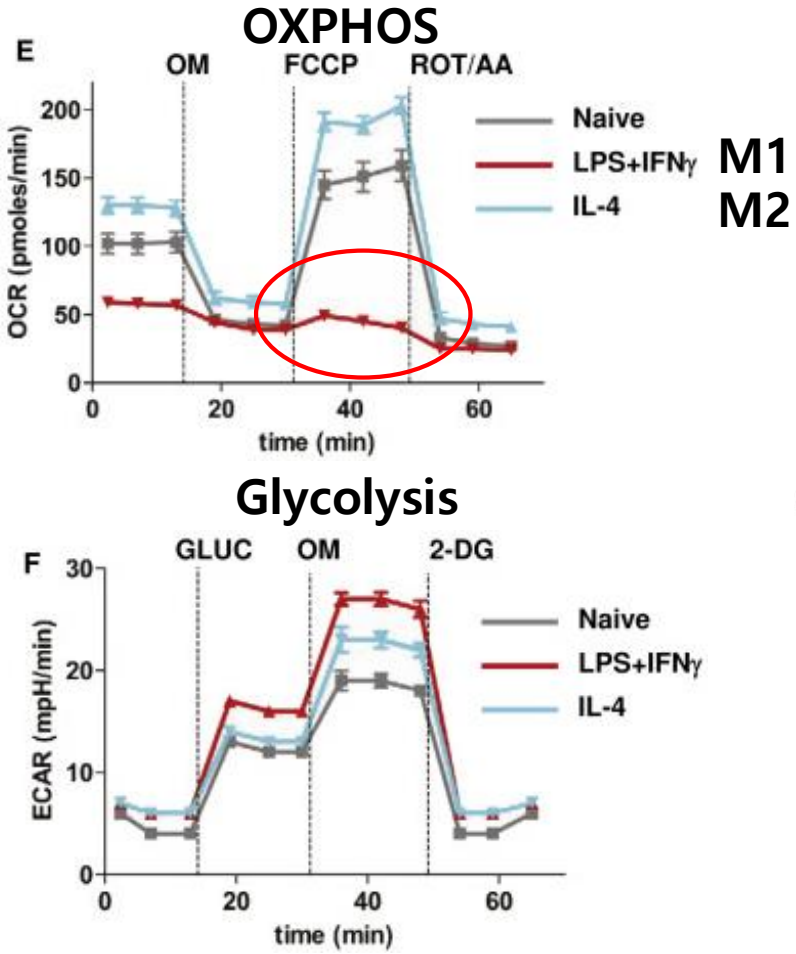


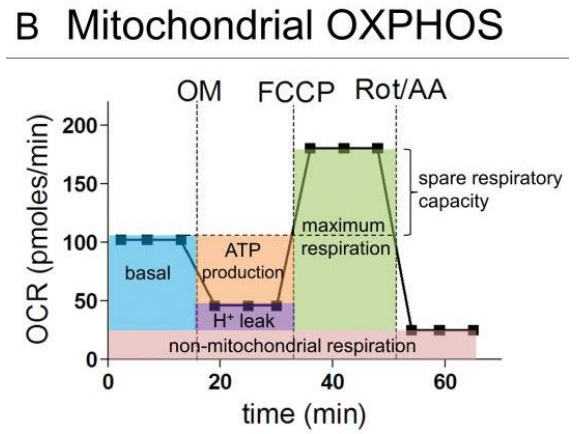


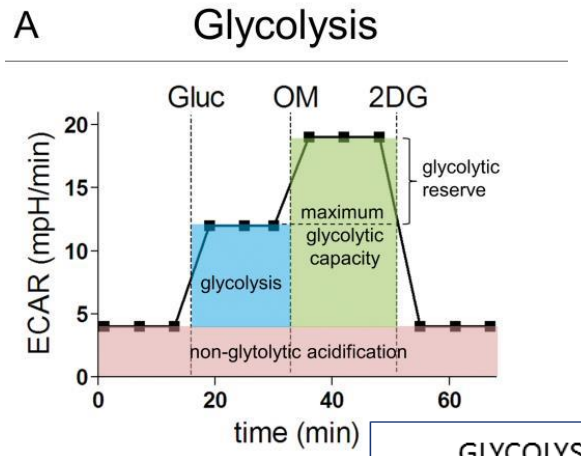
✓ M1 signals didn't impede IL-4/STAT6 pathway, but influenced on mitochondrial activity

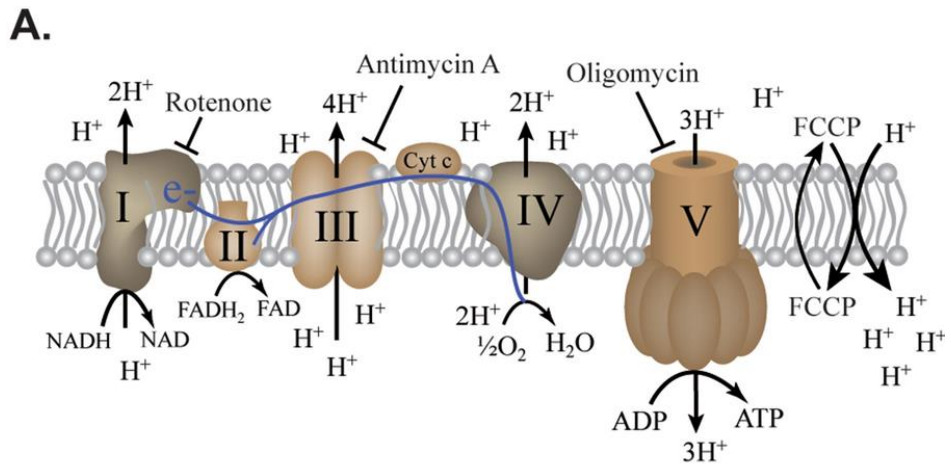
Figure 4.

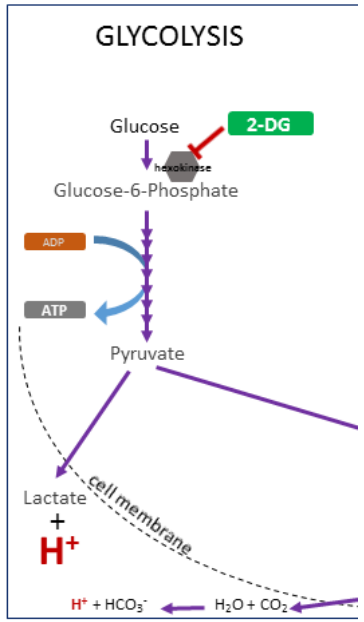
LPS+IFNγ treatment blunts mitochondrial oxidative respiration in mouse macrophages











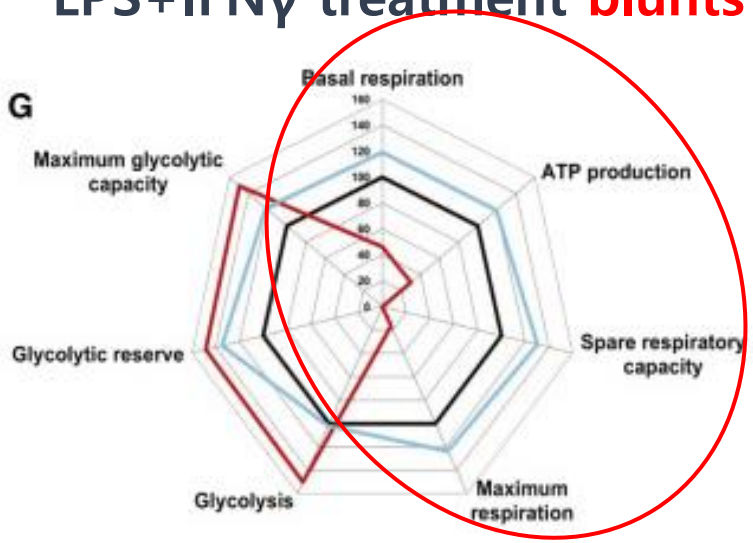
OCR: oxygen consumption rate, OXPHOS parameter
OM: oligomycin, block mitochondrial ATP synthase activity

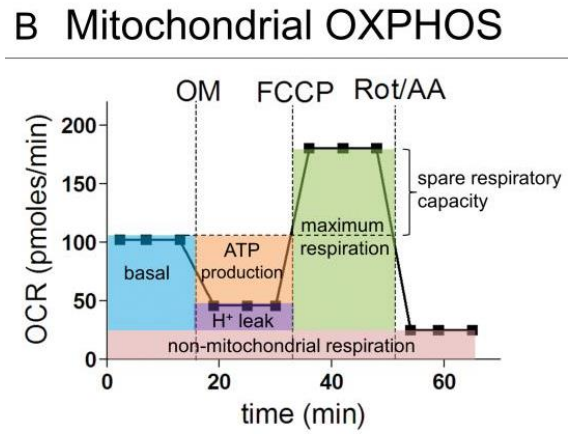
ECAR: extracellular acidification rate, Glycolysis parameter
OM: oligomycin
2-DG: 2-deoxyglucose

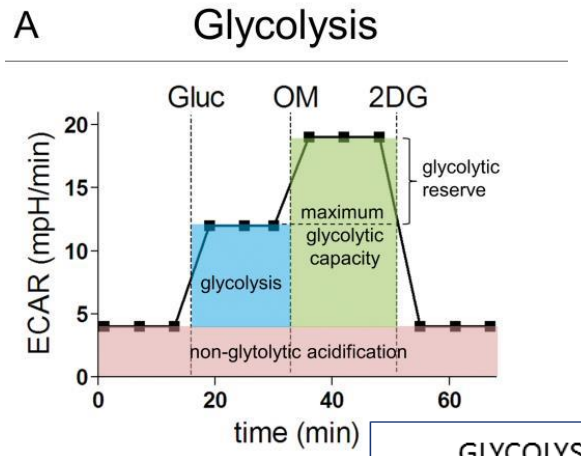
✓ **M1 signals blunts mitochondrial oxidative respiration**

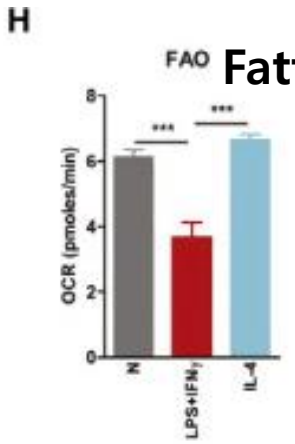
Figure 4.

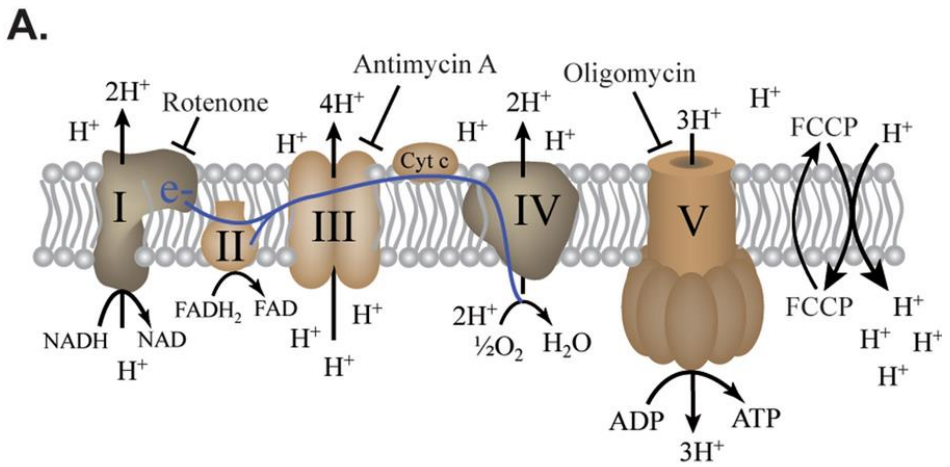
LPS+IFNγ treatment blunts mitochondrial oxidative respiration in mouse macrophages

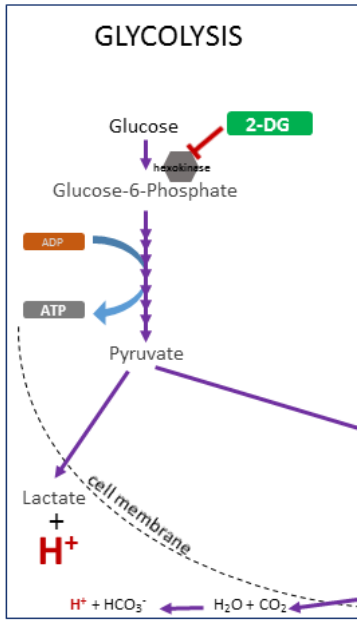












OCR: oxygen consumption rate, OXPHOS parameter
OM: oligomycin, block mitochondrial ATP synthase activity

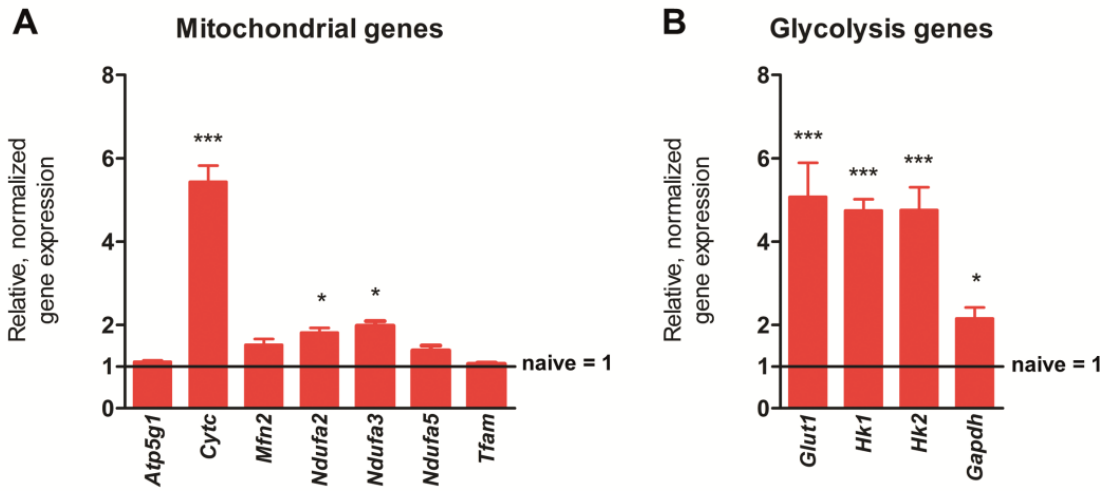
ECAR: extracellular acidification rate, Glycolysis parameter
OM: oligomycin
2-DG: 2-deoxyglucose

✓ **M1 signals blunts mitochondrial oxidative respiration and fatty acid oxidation**

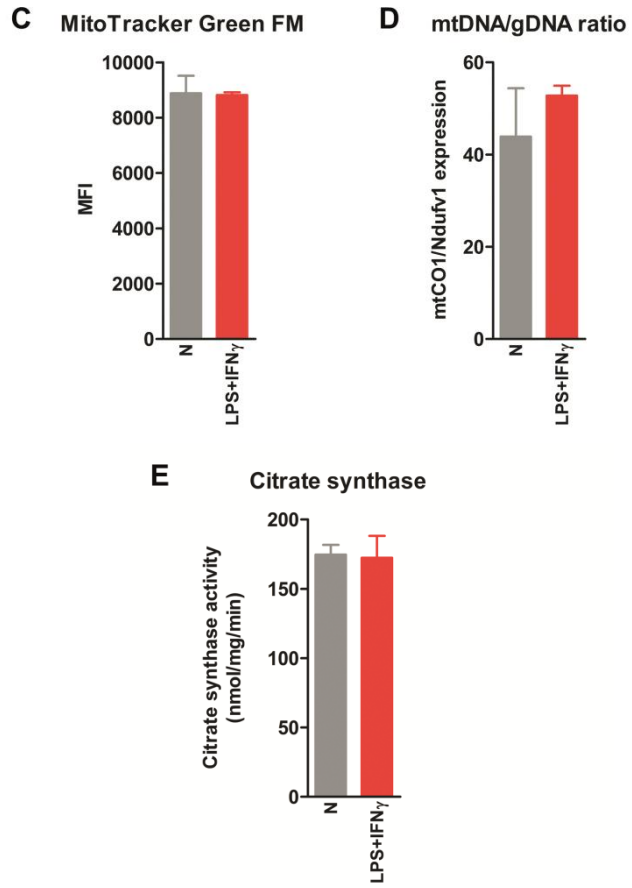
Figure S6.

Suppressed OXPHOS in M1 cells is not caused by mitochondrial problem nor by reduced citrate synthase activity

No decrease in M1 cells



No differences between normal and M1

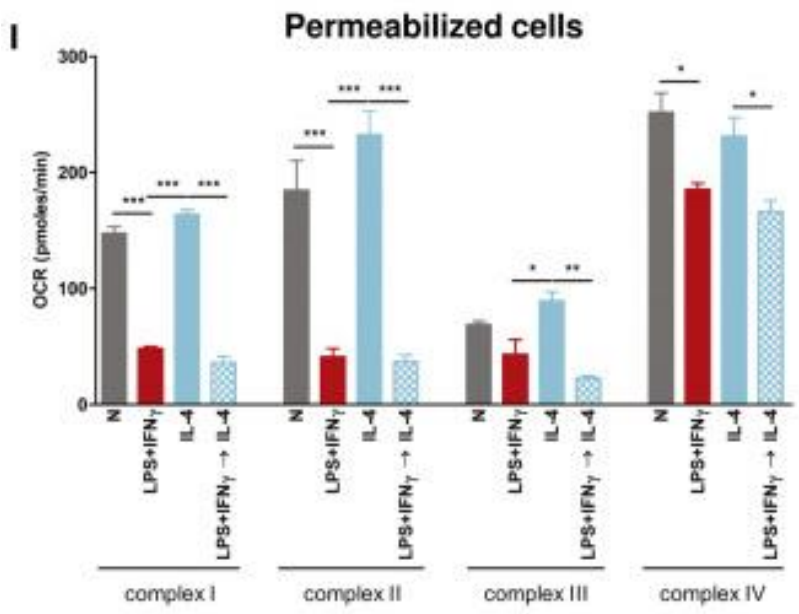


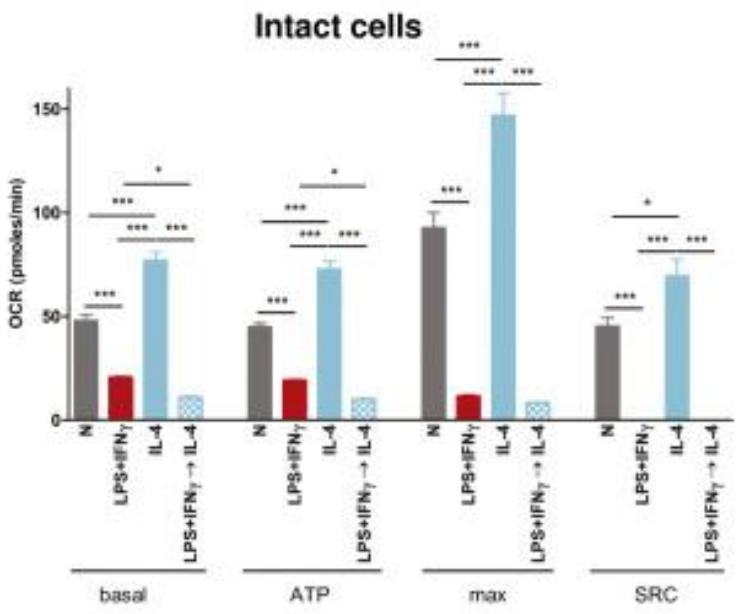
✓ OXPHOS suppression was not caused by mitochondrial problem

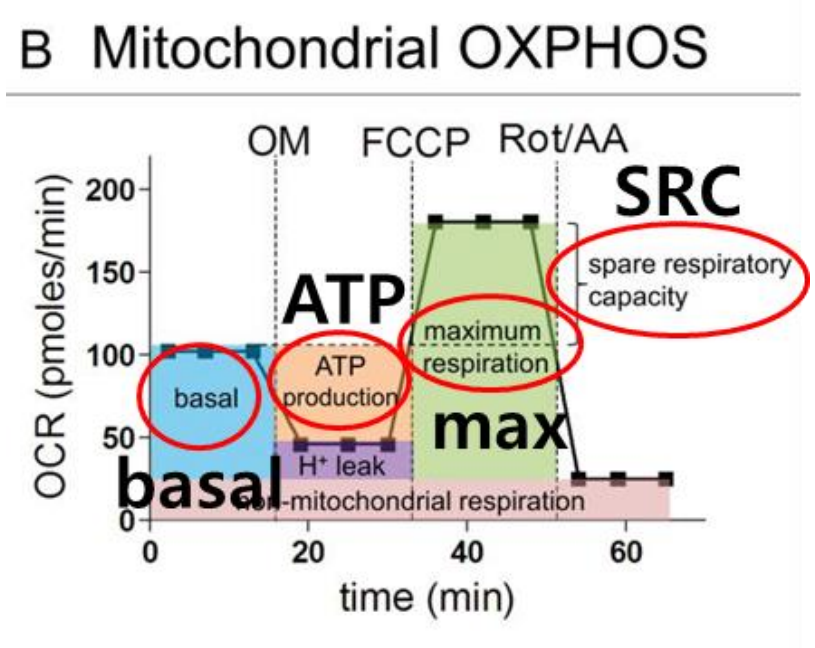
Figure 4.

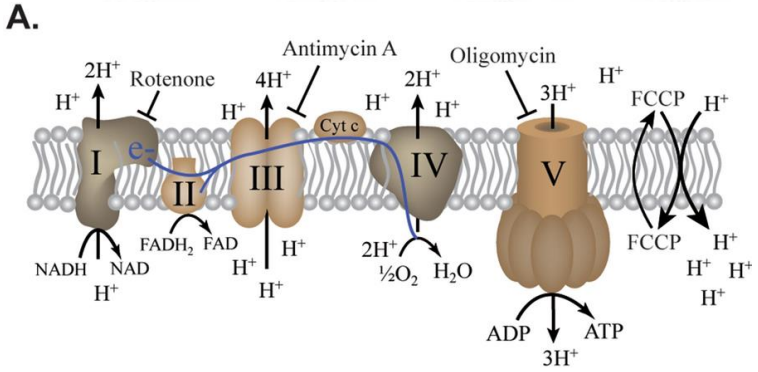
LPS+IFNγ treatment blunts mitochondrial oxidative respiration in mouse macrophages

Naive M1 M2 M1→M2







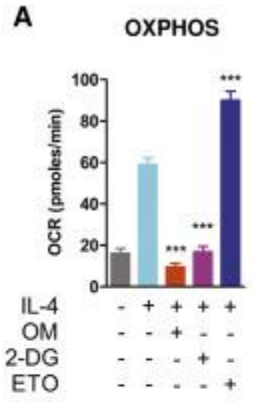


- ✓ M1 signals blunts OXPHOS complex 1, 2 hardly, and complex 3,4 moderately
- ✓ IL4 couldn't restore OXPHOS impairment

Figure 5.

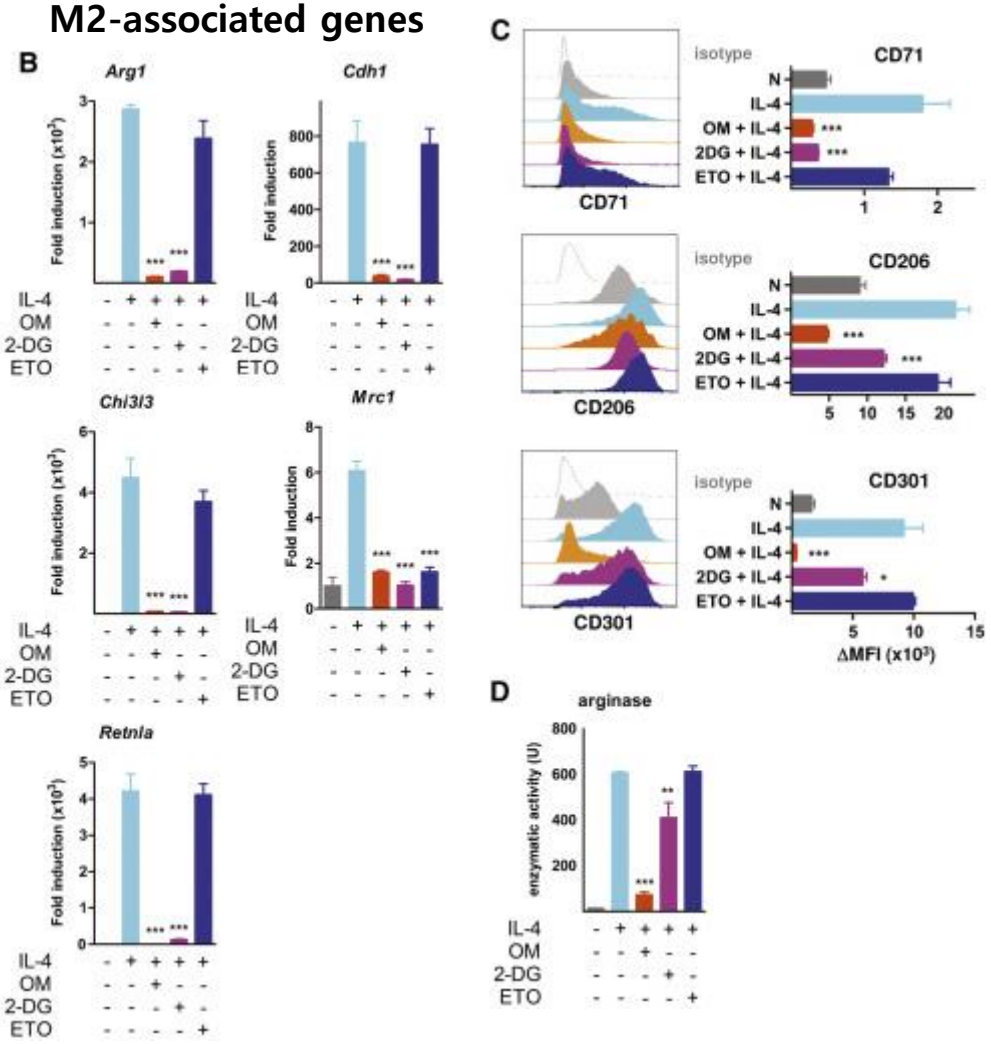
Mitochondrial function is required for the induction of an M2 phenotype

block mitochondrial ATP synthase activity
block glycolytic flux
block FAO



***inhibitors treated 30 mins before Macrophage activation**

M2-associated genes

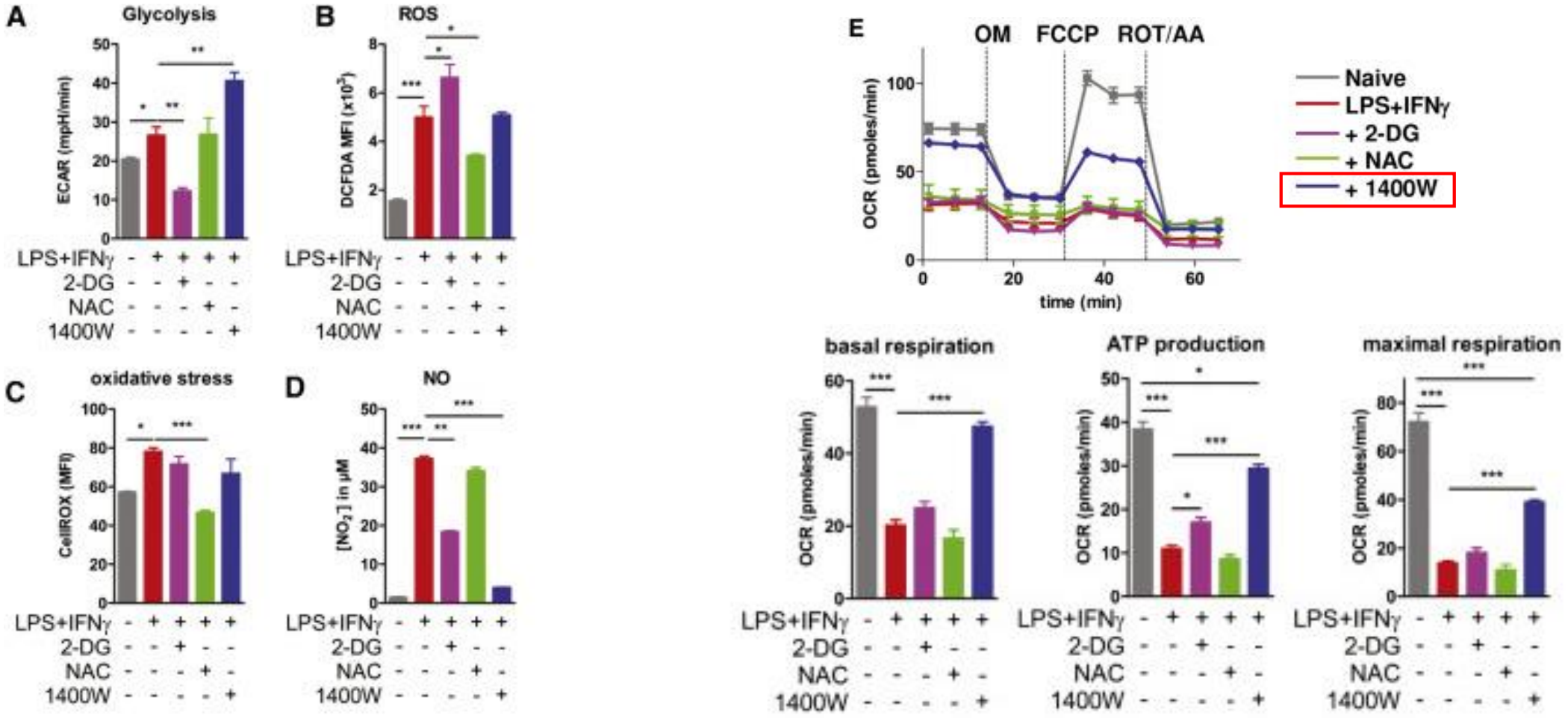


OM: oligomycin, block mitochondrial ATP synthase activity
2-DG: 2-deoxyglucose, block glycolytic flux
ETO: etomoxir, block FAO

- ✓ **OXPHOS function is required for M2 induction**
- ✓ **cf) FAO didn't decrease OXPHOS activity**

Figure 6.

Nitric Oxide blunts mitochondrial respiration and prevents plasticity in M1 macrophages

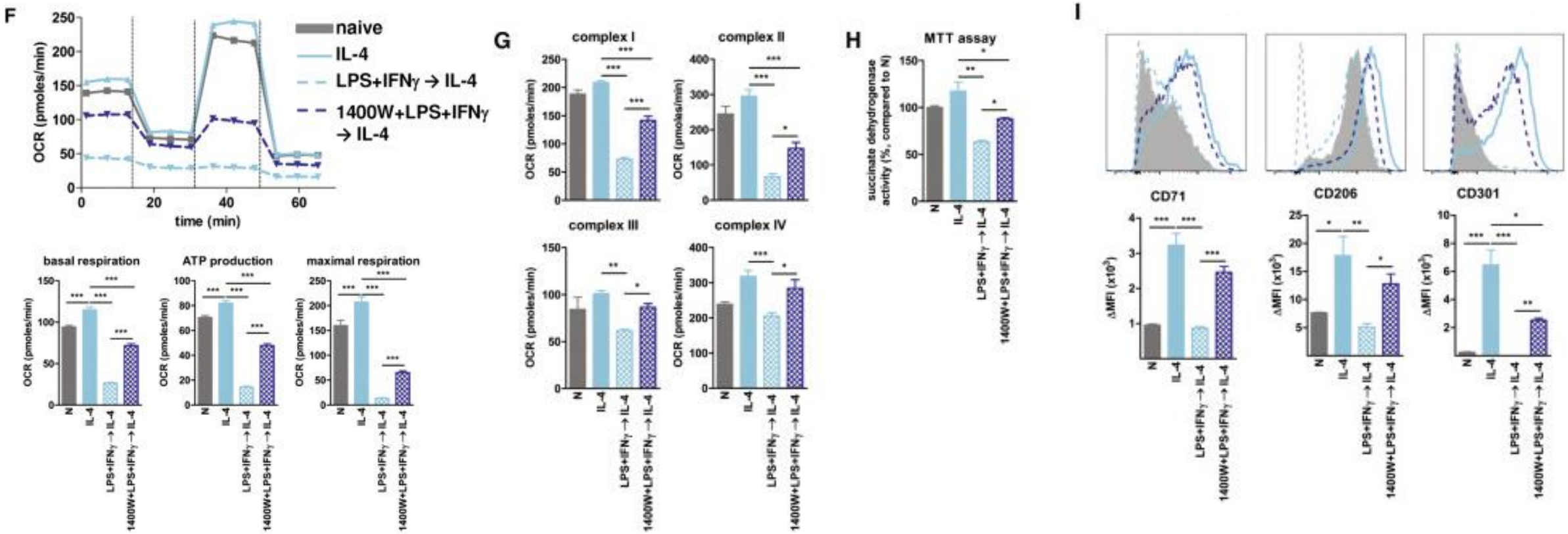


2-DG: 2-deoxyglucose, block glycolytic flux
NAC: ROS scavenger
1400W: iNOS inhibitor (NO inhibitor)

- ✓ **Inhibiting glycolysis and ROS didn't restore OXPHOS activity**
- ✓ **Inhibiting NO restored OXPHOS activity (not fully)**

Figure 6.

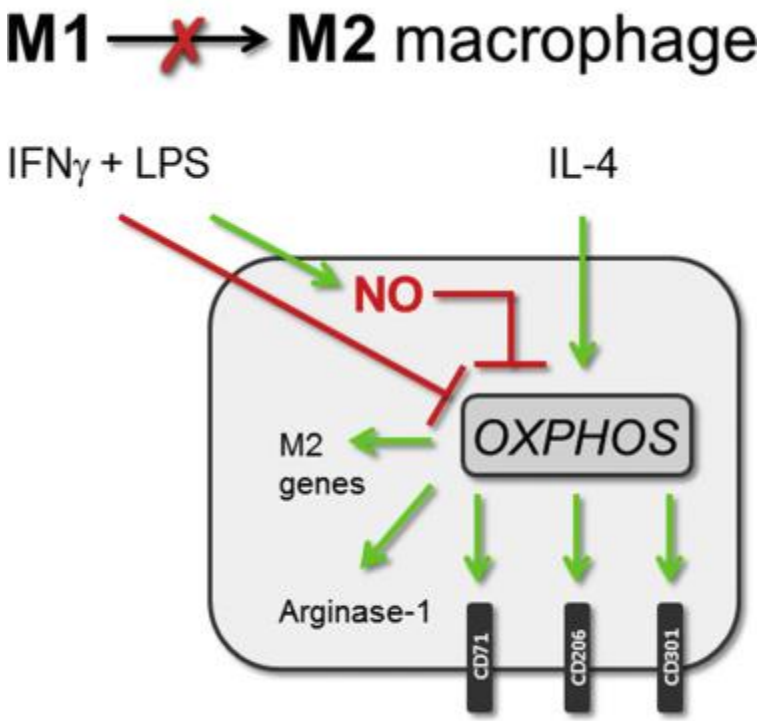
NO blunts mitochondrial respiration and prevents plasticity in M1 macrophages



✓ **Inhibiting NO production prevents OXPHOS damage**

1400W: iNOS inhibitor

Summary



- ✓ M1 signal impede M2 repolarization
- ✓ M2 macrophages could repolarize to M1 macrophages
- ✓ M2 polarization needs mitochondrial OXPHOS system
- ✓ M1 signal blunt OXPHOS system
- ✓ NO made damage to OXPHOS system (maybe via ROS, damage to complexes)