Research Institute for
Farm Animal Biology

Immunometabolic responses of porcine blood immune cells to endotoxin and glucocorticoid stimulation

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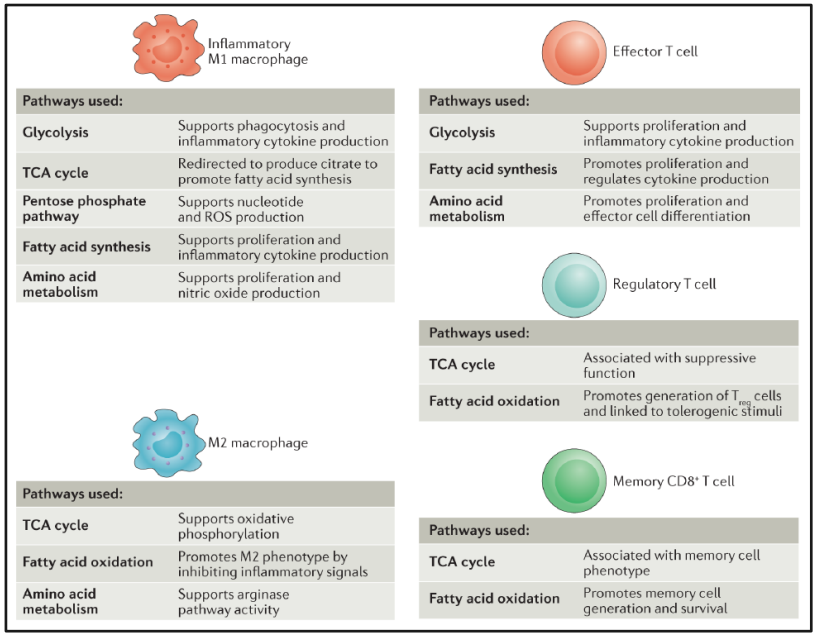
Background and objectives

- **Immunometabolism**: Immune response and metabolic pathways are mutually connected
- This connection is largely unexplored in farm animals
- There are species-specific differences in immunometabolism =>
  discover mechanisms acting in farm animals (pigs)



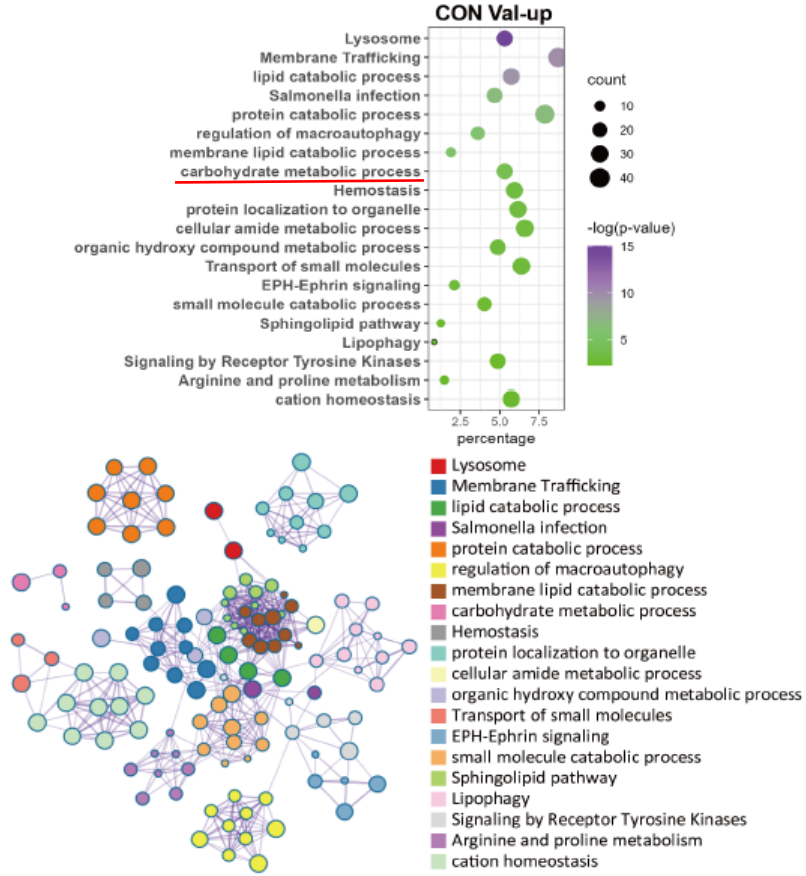
A guide to immunometabolism for immunologists
PMID: 27396447

Background and objectives

- The $GR_{Ala610Val}$ variant enhancing endotoxin sensitivity in pigs changes many metabolic pathways in Primary Blood Mononuclear Cells (PMID: 36505401)

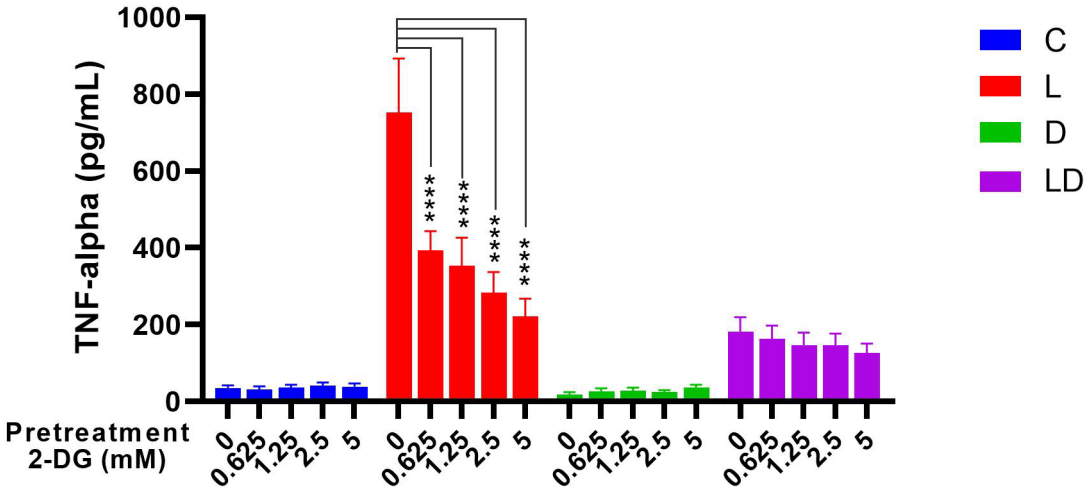
- Involvement of glucocorticoids in immunometabolism recognized only very recently

- To explore the function of $GR_{Ala610Val}$ => **better understand the role of glucocorticoids in immune metabolism**



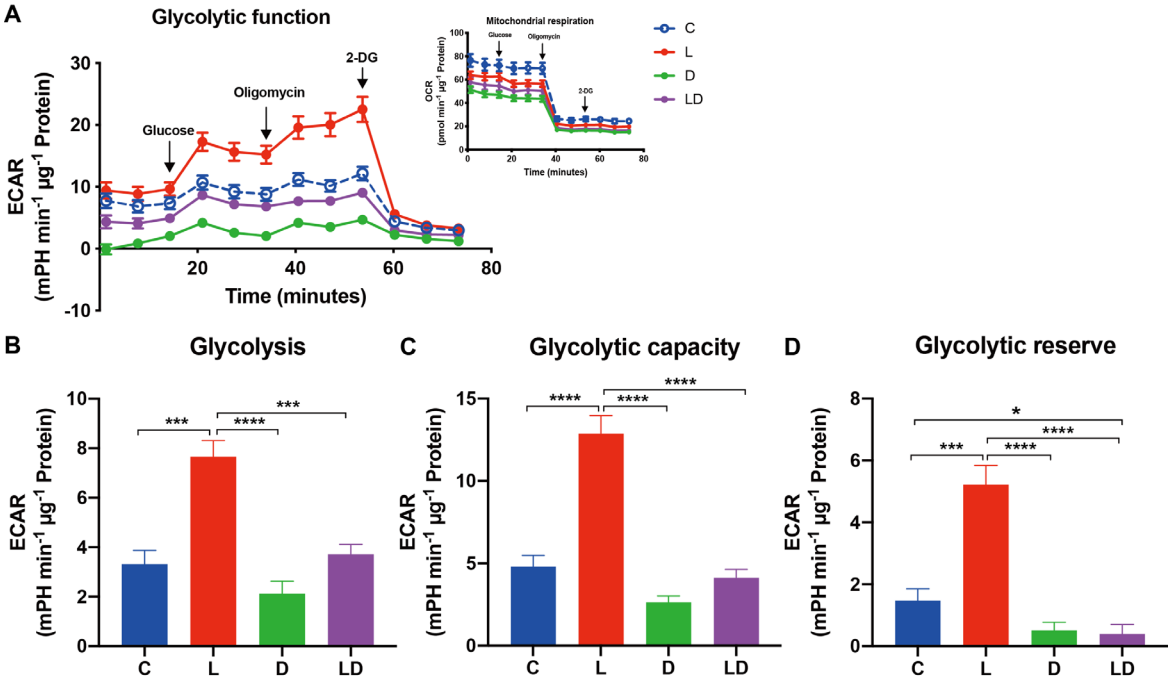
Glycolysis vs. inflammatory response

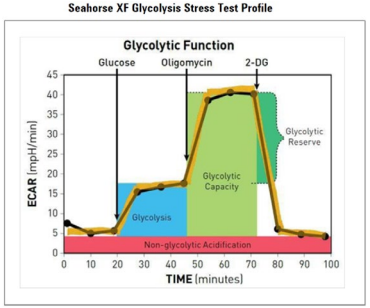
- Inhibition of glycolysis by 2-deoxy D-glucose (2-DG) reduces inflammatory response of PBMC to LPS



Inflammatory status vs. glycolysis

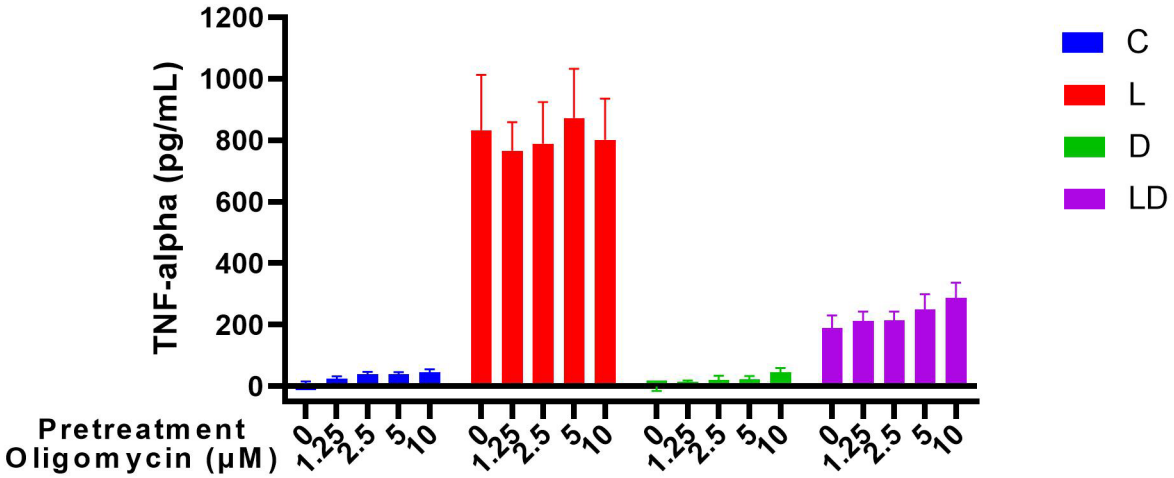
- 24h exposure to LPS enhances glycolysis ← this effect is effectively abolished by DEX





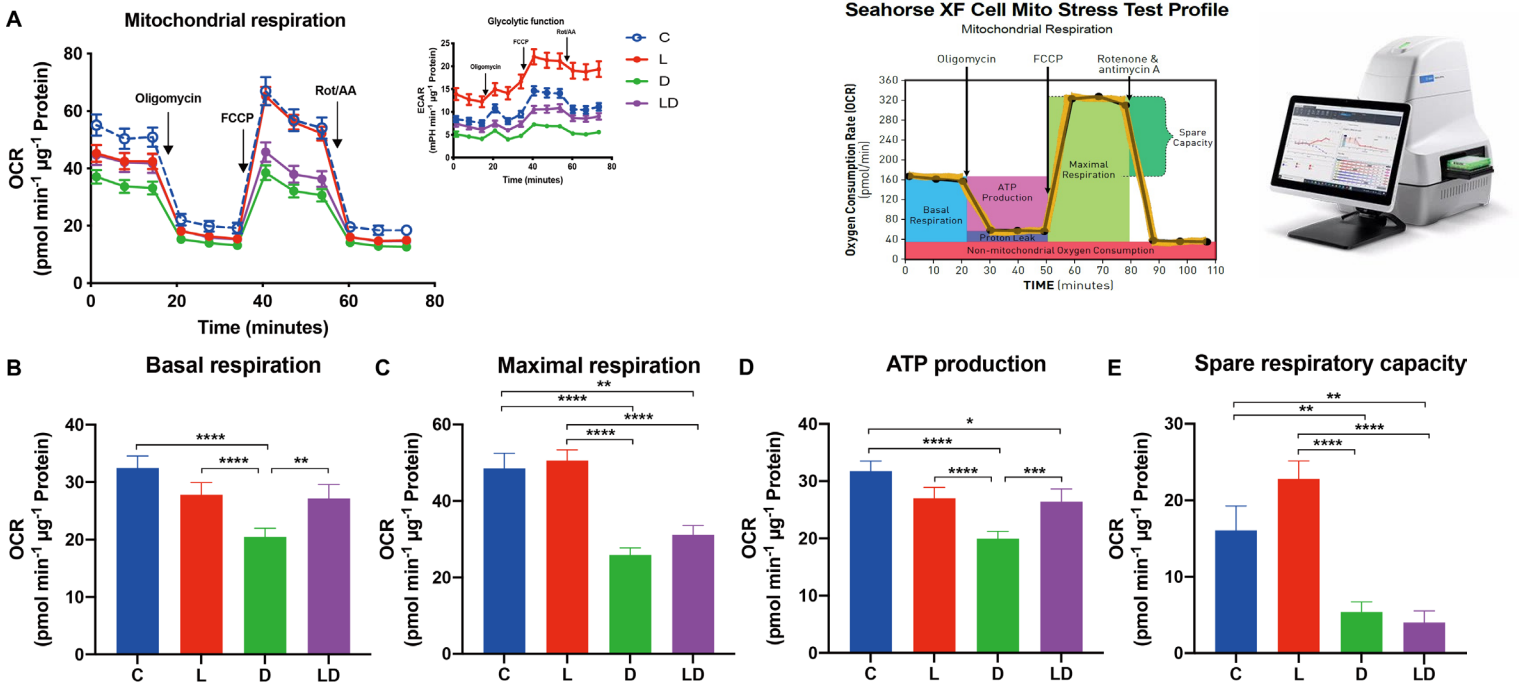
Mitochondrial respiration vs. inflammatory response

- Inhibition of ATP production (at complex V) by oligomycin does not influence the inflammatory response of PBMC



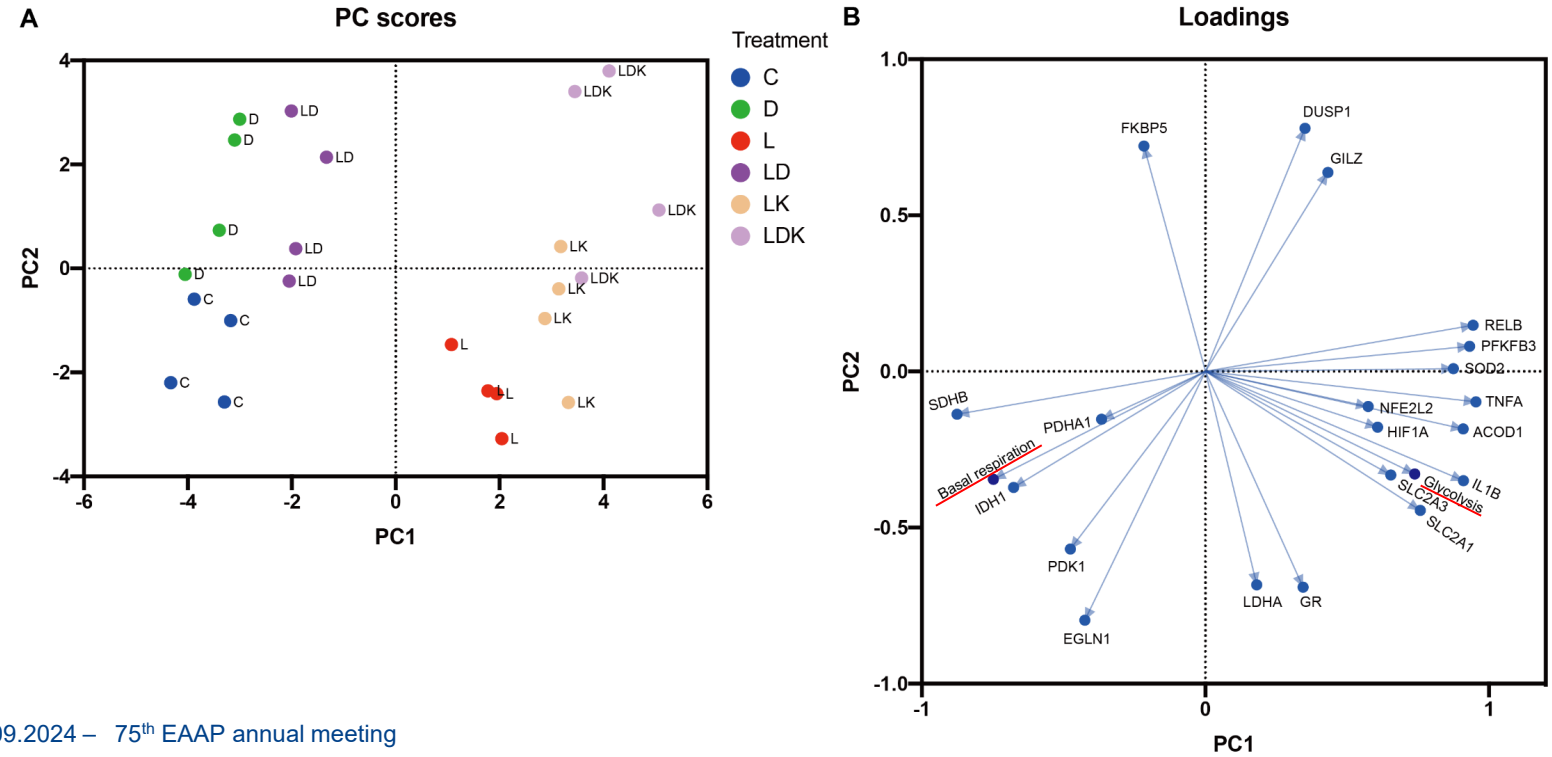
Inflammatory status vs. mitochondrial respiration

- Eposure to DEX - but not to LPS - reduces mitochondrial respiration of PBMC (!?)



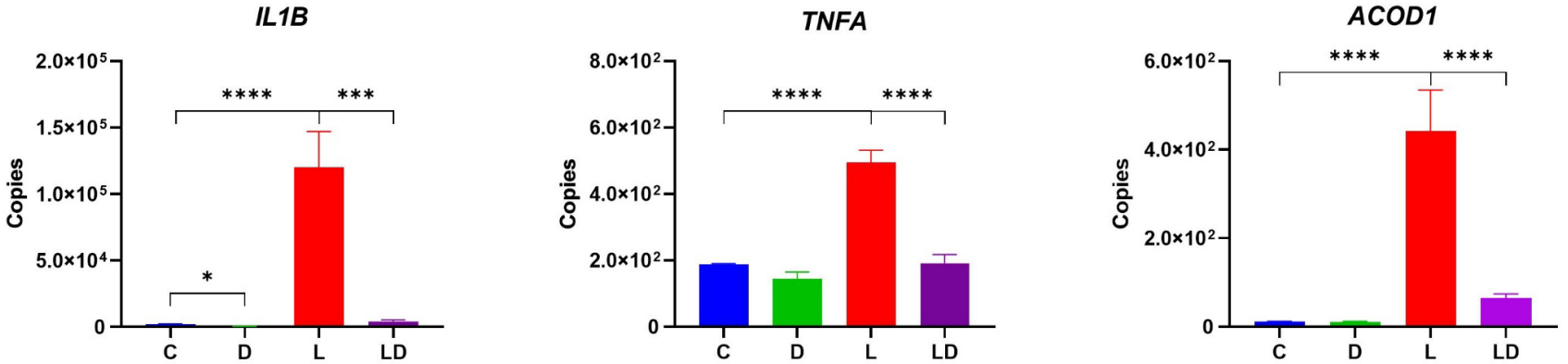
Gene expression links metabolism to immune phenotype

- **PC1** - inflammatory status **PC2** - glucocorticoid response



LPS and DEX treatment induced the expected responses

- LPS-induced Itaconate synthesis is suppressed by DEX



Article

Metabolic rewiring promotes anti-inflammatory effects of glucocorticoids

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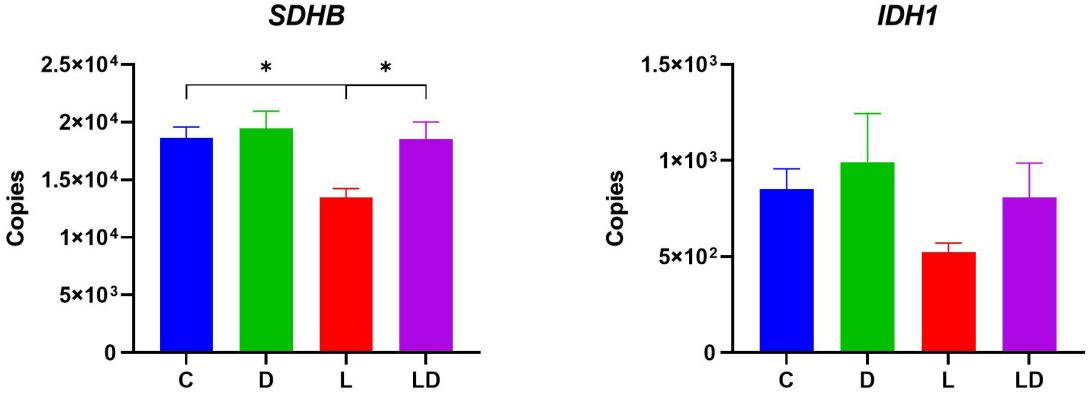
Jean-Philippe Auger[1,2], Max Zimmermann[1,2], Maria Faas[1,2], Ulrich Stifel[1], David Chambers[1,2], Brenda Krishnacoumar[4,5], R. Verena Taudte[4,7], Charlotte Grund[1,2], Gitta Erdmann[6], Carina Scholtysek[1,2], Stefan Uderhardt[2,8,9], Oumaima Ben Brahim[1,2,9], Mónica Pascual Maté[1,2], Cornelia Stoll[1,2], Martin Böttcher[2,10], Katrin Palumbo-Zerr[1,2], Matthew S. J. Mangan[11], Maria Dzamukova[12], Markus Kieler[13,14], Melanie Hofmann[13,14], Stephan Blüml[15], Gernot Schabbauer[13,14], Dimitrios Mougiakakos[5,16], Uwe Sonnewald[16], Fabian Hartmann[1,2], David Simon[1,2,9], Arnd Kleyer[1,2,9], Anika Grüneboom[6], Susetta Finotto[12], Eicke Latz[8,10], Jörg Hofmann[15], Georg Schett[1,2], Jan Tuckermann[3] & Gerhard Krönke[1,2,8,10,17]

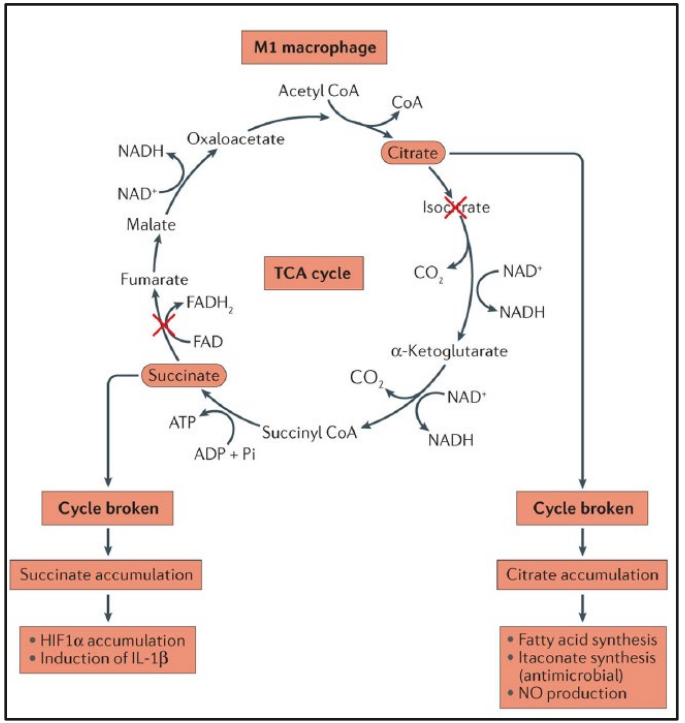
LPS and DEX treatment induced the expected responses

- LPS-induced TCA cycle impairment is prevented by DEX



Glucocorticoids coordinate macrophage metabolism through the regulation of the tricarboxylic acid cycle

Ulrich Stifel [1], Eva-Maria Wolfschmitt [2], Josef Vogt [2], Ulrich Wachter [2], Sabine Vettorazzi [1], Daniel Tews [3], Melanie Hogg [2], Fabian Zink [2], Nora Maria Koll [4], Sandra Winning [4], Rémi Mounier [5], Bénédicte Chazaud [5], Peter Radermacher [2], Pamela Fischer-Posovszky [6], Giorgio Caratti [1,*,7], Jan Tuckermann [1,*,7]



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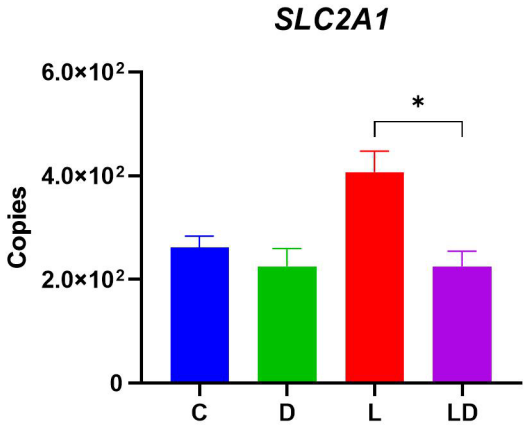
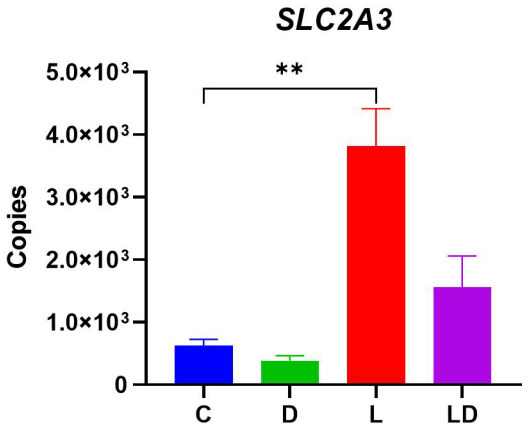
LPS and DEX treatment induced the expected responses

- Expression profile of glucose transporters, particularly ***SLC2A3*** **(GLUT3)**, explains the opposing metabolic action of LPS and DEX



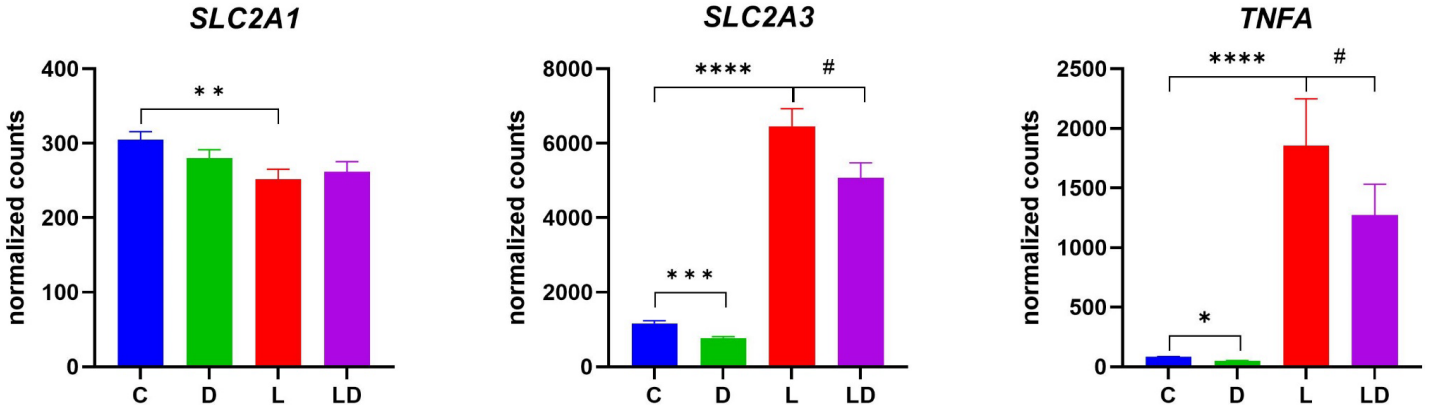


The glucocorticoid dexamethasone inhibits HIF-1α stabilization and metabolic reprogramming in lipopolysaccharide-stimulated primary macrophages

Sally A. Clayton[1,2,*,‡], Chloe Lockwood[1,‡], John D. O'Neil[1], Kalbinder K. Daley[1], Sofia Hain[1,3], Dina Abdelmottaleb[1,4], Oliwia O. Bolimowska[1], Daniel A. Tennant[2] and Andrew R. Clark[1]

LPS and DEX treatment induced the expected responses

- ***SLC2A3* (GLUT3)**, but not ***SLC2A1* (GLUT1)** is responding to LPS and DEX signaling already in the early phase of the treatment (at 2h)



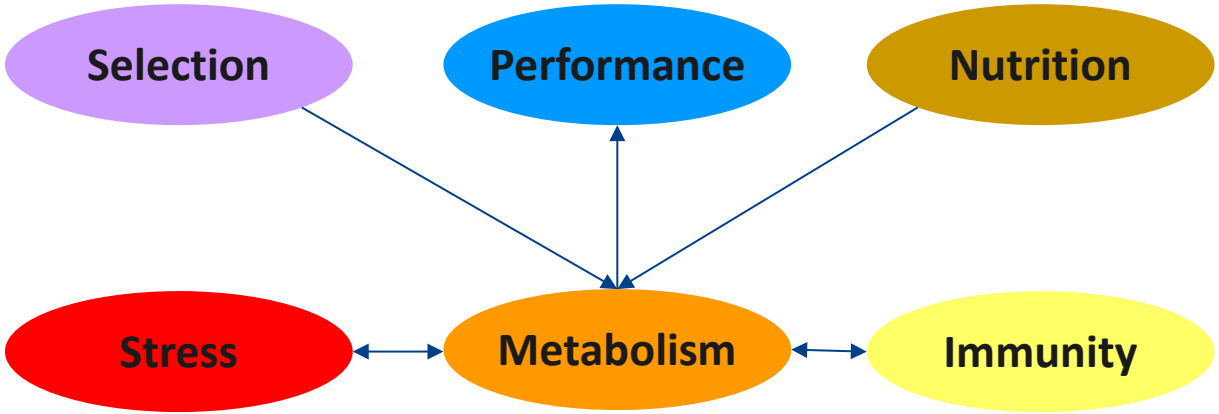
Summary

- ✓LPS-induced pro-inflammatory response in porcine PBMC is connected to oxidative glycolysis
- ✓LPS influences the TCA cycle in PBMC to supply immunoregulatory metabolites, but this does not impair mitochondrial respiration
- ✓Glucocorticoids (DEX) oppose the metabolic reprogramming of PBMC induced by LPS
- ✓Glucose transporters play an important role in the LPS/DEX antagonism
- ✓Glucocorticoids (stress?) induce low energetic state of PBMC (consequence?)

Conclusions

➢ Why care about immunometabolism?

- a new factor in the trade-off between animal health/welfare vs. performance?



- Cellular models allow deep diving into **G2P** mechanisms

Thank you for your attention!

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