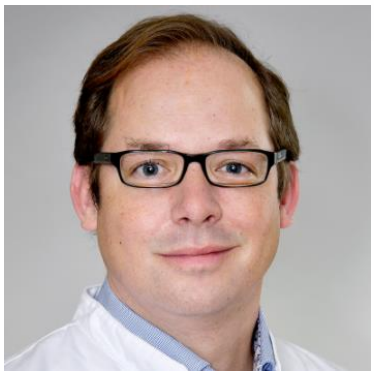
DEPARTMENT OF BIOMEDICINE
HEALTH
AARHUS UNIVERISTY

MEMBRANES Seminar with Prof. Andreas Linkermann

Monday, February 28, 2022 | 12.00-13.00 | Lille Anatomisk auditorium (building 1231, room 424)



Prof. Andreas Linkermann

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Talk title
Getting closer to dying - how glucocorticoids sensitize to ferroptosis

Host
Ina Maria Schiessl

Abstract. In this presentation, I will introduce the major forms of regulated cell death, mainly ferroptosis and necroptosis, and discuss novel data on the regulation of inflammation by necrotic cells (necroinflammation). In addition, immunosuppressive agents, such as dexamethasone, may directly affect cell death. Dexamethasone is widely used as an immunosuppressive therapy and recently as COVID-19 treatment. Here, we demonstrate that dexamethasone sensitizes to ferroptosis, a form of iron-catalysed necrosis, previously suggested to contribute to diseases such as acute kidney injury, myocardial infarction and stroke, all of which are triggered by glutathione (GSH) depletion. GSH levels were significantly decreased by dexamethasone. Mechanistically, we identified that dexamethasone upregulated the GSH metabolism regulating protein dipeptidase-1 (DPEP1) in a glucocorticoid receptor (GR)-dependent manner. DPEP1-knockdown reversed the phenotype of dexamethasone-induced ferroptosis sensitization. Ferroptosis-inhibitors, the DPEP1 inhibitor cilastatin, or genetic DPEP1 inactivation reversed the dexamethasone-induced increase in tubular necrosis in freshly-isolated renal tubules. Our data indicate that dexamethasone sensitizes to ferroptosis by a GR-mediated increase of DPEP1-expression and GSH-depletion. Together, we identified a novel mechanism of glucocorticoid-mediated sensitization to ferroptosis bearing clinical and therapeutic implications.

On behalf of the organizer,
Søren Brandt Poulsen
Administrative Research Theme Coordinator
MEMBRANES

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