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POSTER ABSTRACTS

102.IRON HOMEOSTASIS AND BIOLOGY

Differential Effect of Transferrin Lobe Iron Occupancy on a Murine Model of Inflammation

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Introduction: Iron status is both affected by and a determinant of the inflammatory response. Several lines of evidence support a role for transferrin as a signaling as well as an iron delivery molecule. We previously demonstrated that mice with transferrin mutations that prevent iron binding to the C-lobe of transferrin (C-blocked) have increased red cell production relative to erythropoietin and increased hepcidin expression relative to iron status compared to mice with transferrin mutations that prevent iron binding to the N-lobe of transferrin (N-blocked). Based on these observations, we hypothesize that two forms of transferrin would differentially modulate the hematopoietic and iron distribution changes that occur with inflammation. We explored this hypothesis by comparing the effects of lipopolysaccharide (LPS) administered either acutely or in repeated doses to wild-type, N-lobe blocked, or C-lobe blocked transferrin mutant mice.
Methods: For a model of acute inflammation, 14 day old wild-type (wt), N-blocked and C-blocked Tf mutant mice were treated with 1mg/kg LPS or carrier i.p. and sacrificed 6 hours later. Repeated LPS dosing, seven daily i.p. injections of 0.3 mg/kg LPS or carrier beginning at seven days of age, served as a model of chronic inflammation.
Results: While wild-type and C-blocked mice had the expected hypoferremia in response to acute LPS administration, there was no effect on serum iron in the N-blocked mice. These mice moreover demonstrated an unanticipated increase in liver iron concentrations with LPS. All strains manifested expected increases in liver hepcidin expression; however, these were attenuated in the N-blocked mice relative to the C-blocked. Moreover, N-blocked mice have higher serum C reactive protein concentrations compared to C-blocked and wt mice following acute LPS administration. The elevated Hamp1 expression was not sustained in the chronic model. Although serum iron returned to baseline in wt and C-blocked mice, it remained elevated in N-blocked mice. Hemoglobin concentrations were decreased in all strains after repeated endotoxin dosing; however, C-blocked mice demonstrated higher neutrophil to lymphocyte ratios than wt or N-blocked mice, and increased circulating RBC count relative to WBCs.
Conclusions: We conclude that the specificity of transferrin lobe iron occupancy is an important modulator of the inflammatory response and speculate that this modulation includes an effect on hematopoietic cell lineage determination.

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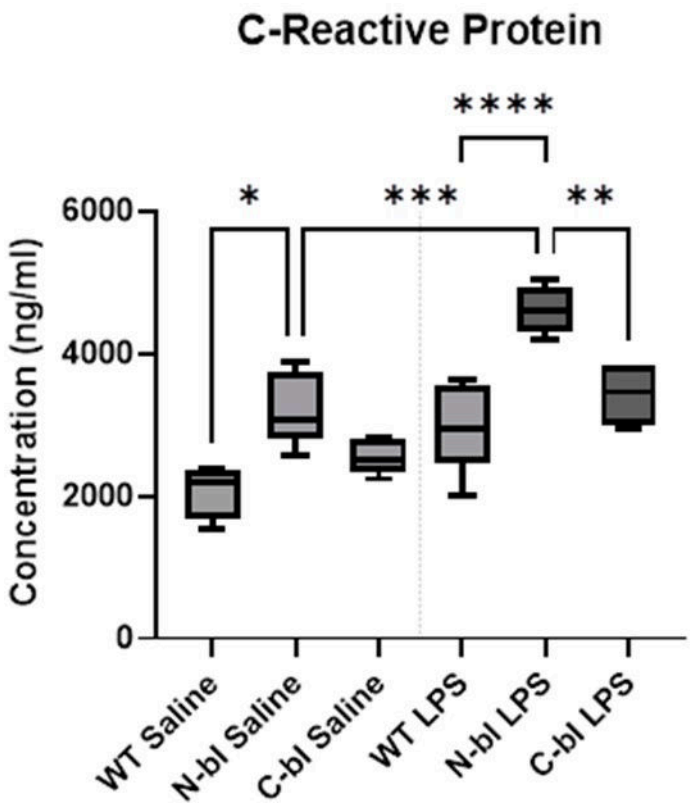

Figure 1

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