A Physiological Role for a Moonlighting Protein in Lipopolysaccharide-induced Endotoxemia

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Background and Hypothesis: The pathogenesis of Bronchopulmonary Dysplasia (BPD) is multifactorial leading to inflammation. In BPD, Endothelial-Monocyte Activating Polypeptide II (EMAP II, encoded by *Aimp1*), a moonlighting pro-inflammatory cytokine, is initially found in bronchiolar club cells followed by intra-alveolar GAL-3+ macrophages. Sustained EMAP II mimics BPD, invoking inflammation, alveolar simplification, and macrophage recruitment. Targeted ablation of EMAP II in the recruited macrophages may dampen innate immune response.

Experimental Design: Gender-matched, aged-matched littermate mice with myeloid-cell specific ablation of *Aimp1* (Lyz2-Cre;Aimp1$^{flox/flox}$, denoted as *Aimp1*$^{\Delta/\Delta}$) or without (control) were subjected to lipopolysaccharide (LPS)-endotoxemia. Survival rates of co-housed or singly housed mice were measured over 72 hours following a lethal dose (15 mg/kg). Clinical scores (0-6) based on the integrity of their locomotion, fur, and eyes were assigned every 2 hours. Blood and bone marrow smears, average bodyweights, spleen-weights to bodyweights and liver-weights to bodyweights were analyzed.

Results: There were no baseline differences in bodyweight, spleen weight:bodyweight, liver weight:bodyweight (p-val = 0.42, 0.46, 0.64). Representative bone marrow and blood smears showed no notable difference. *Aimp1*$^{\Delta/\Delta}$ male mice co-housed (dose 15 mg/kg) but not singly housed survived longer than their littermates (median survival: hours); *Aimp1*$^{\Delta/\Delta}$ female mice showed a survival advantage (median survival: hours) with lower clinical scores than their littermates. The kinetics of NFKBIA/IκB degradation was similar between *Aimp1*$^{\Delta/\Delta}$ and control peritoneal macrophages in response to LPS, although there was a higher basal amount in *Aimp1*$^{\Delta/\Delta}$.

Conclusion and Potential Impact: Aimp1/EMAP II does play a positive feedback role in innate immunity, potentially in a metabolically and gender-specific role of *Aimp1* which remain to be explored.