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## Reduced Gravity Contributes to Neutrophil to Lymphocyte Ratio Shifting and Promotion of the Oxidative Stress Response

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# REDUCED GRAVITY CONTRIBUTES TO NEUTROPHIL TO LYMPHOCYTE RATIO SHIFTING AND PROMOTION OF THE OXIDATIVE STRESS RESPONSE

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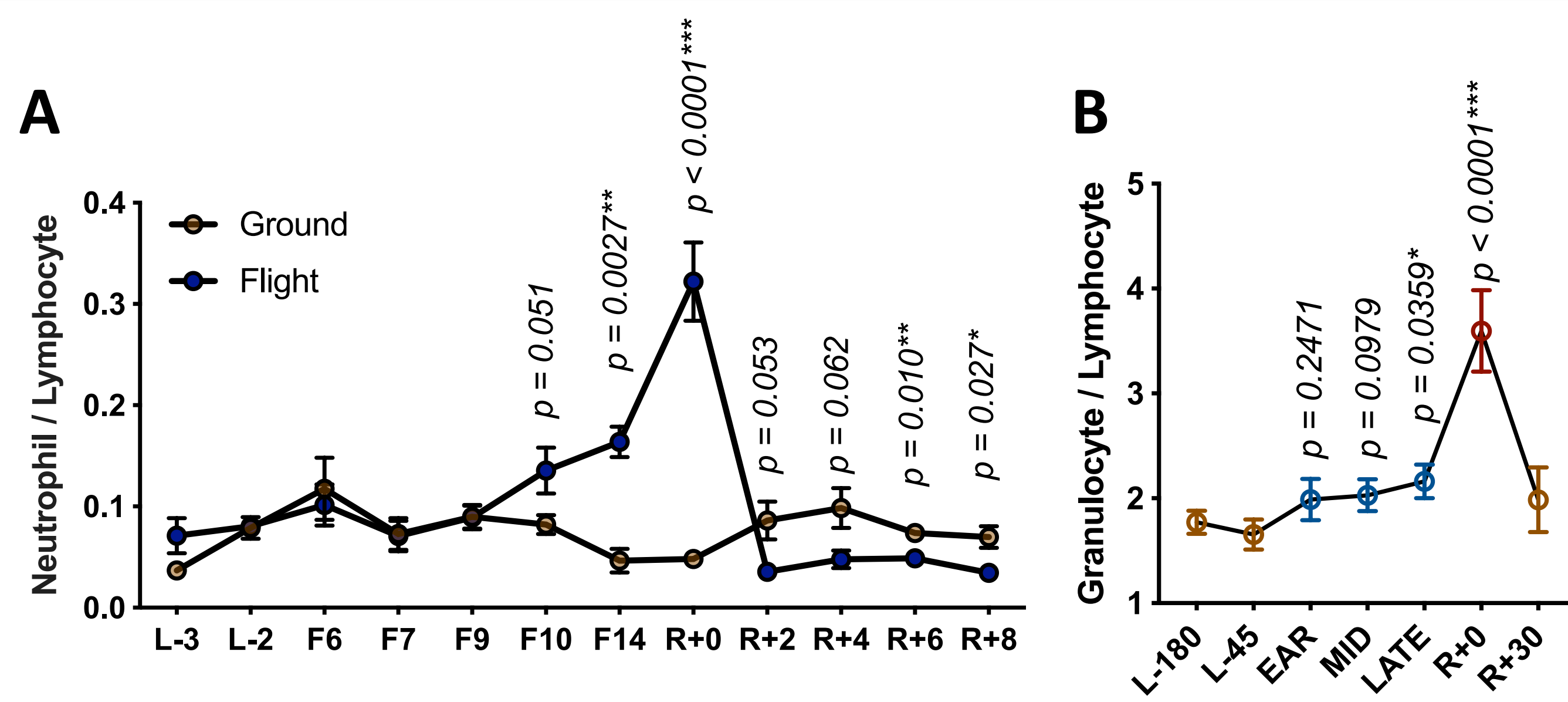
## Introduction

Short- and long-term spaceflight missions can cause immune system dysfunction in astronauts. Studies indicate elevated white blood cells (WBC) and polymorphonuclear neutrophils (PMN) in astronaut blood, along with unchanged or reduced lymphocyte counts, and reduced T cell function, during spaceflight. A high PMN to lymphocyte ratio (NLR) can act as a strong predictor of poor prognosis in cancer, and as a biomarker for subclinical inflammation in humans and chronic stress in mouse models, however, the NLR has not yet been identified as a predictor of astronaut health during spaceflight. For this, complete blood cell count data collected from astronauts and rodents that have flown for short- and long-term missions on board the International Space Station (ISS) was repurposed to determine the NLR and granulocyte to lymphocyte ratio (GLR) pre-, in-, and post-flight. Collectively, these results suggest a disrupted NLR/GLR profile in spaceflight, which may further disrupt immune homeostasis. Under the hypothesis that spaceflight induces a higher NLR due to aberrant oxidative stress response, this study aimed to: **1: determine the NLR and GLR of astronauts and rodents during short- and long-term missions, and 2: determine the contributing role of reactive oxygen species (ROS) in this immune profile shifting.** For this, the ground-based microgravity analog, hindlimb unloading (HU) mouse model and the high-aspect rotating wall vessel cell culture system (HARV-RWV) were utilized to determine the effects of microgravity on the generation of ROS and resulting effects on the maturation and function of PMNs in human blood samples.

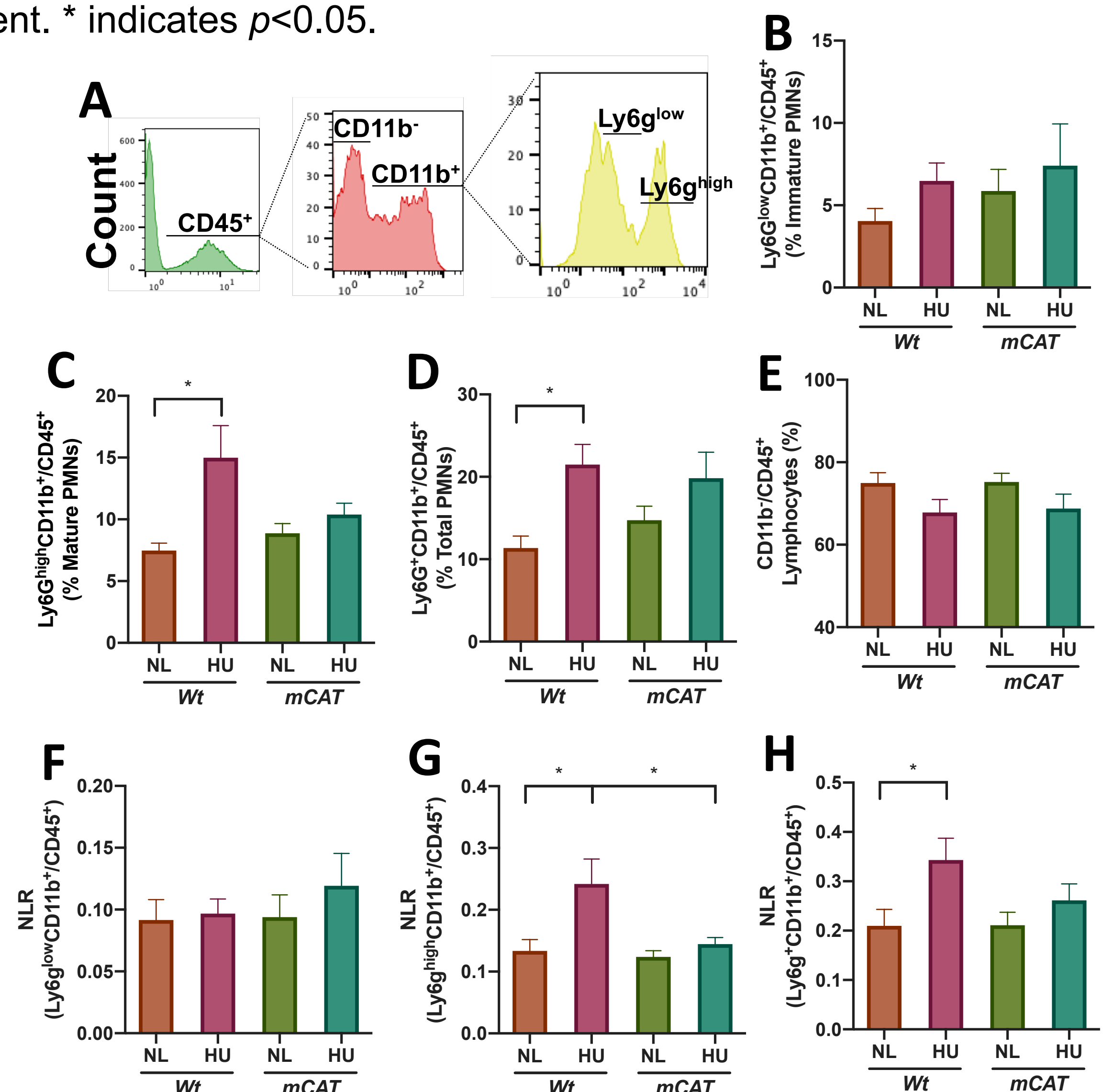
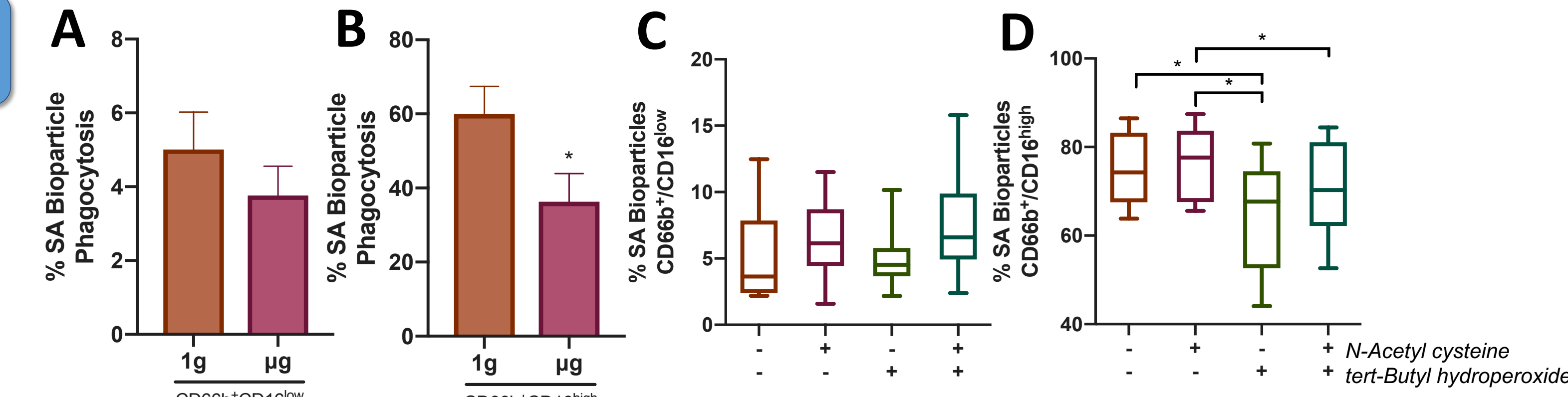
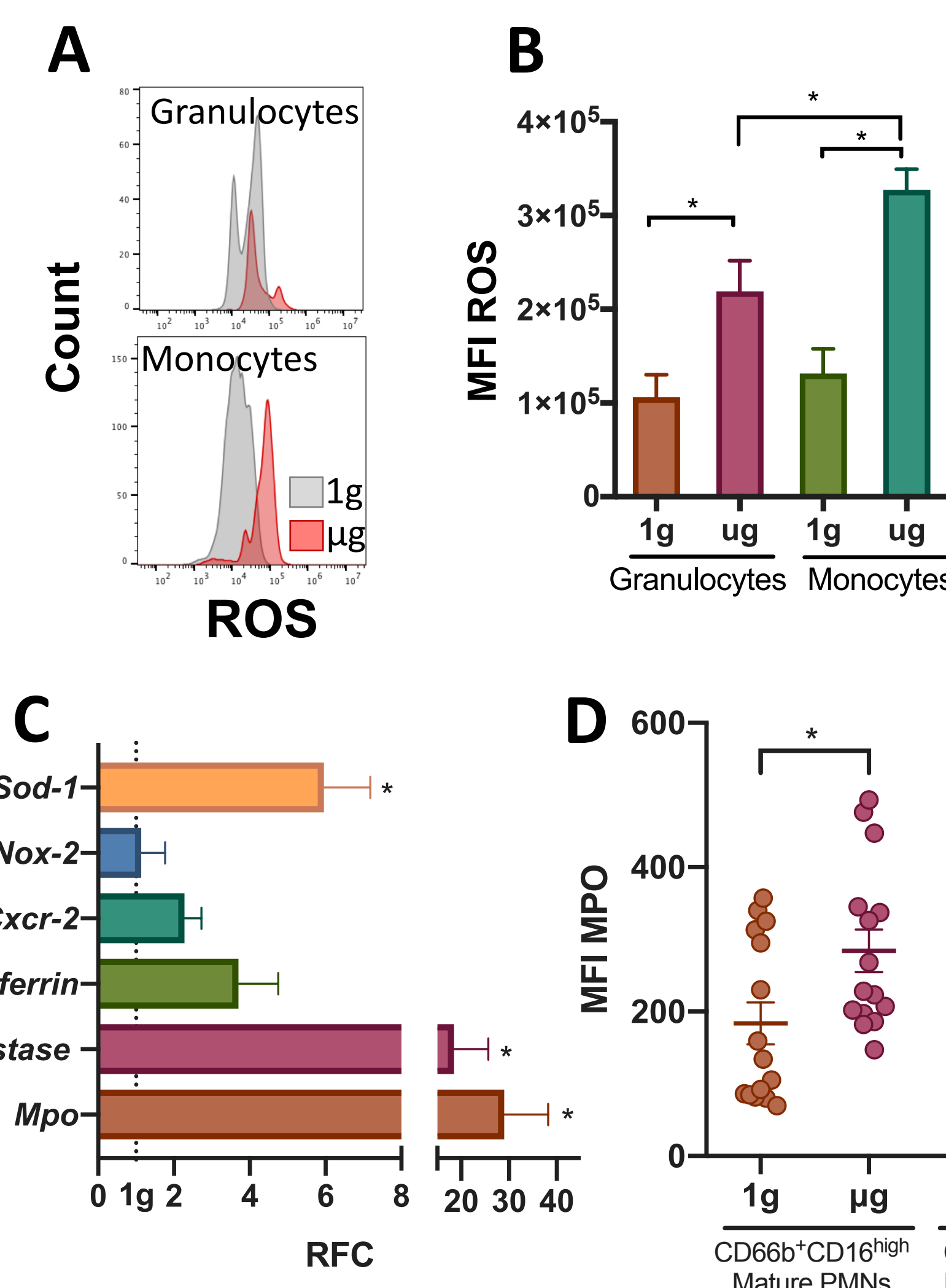
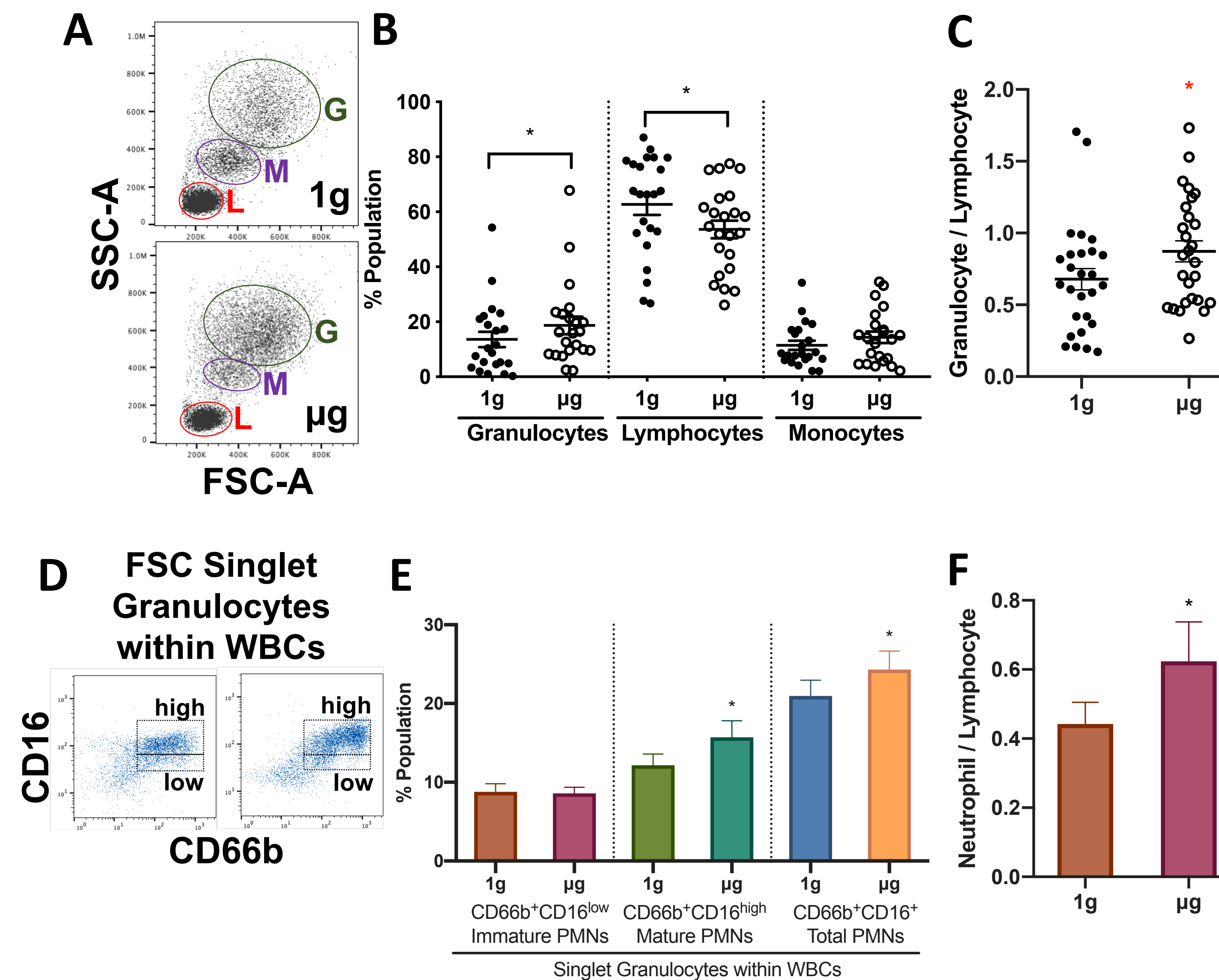
## Methods

- Cell Culture:** Human whole blood was separated into cell types using ficoll- and histo-paque. Similarly, mouse blood was collected and separated. RBCs were lysed and WBCs were cultured in complete RPMI media.
- Phagocytosis assay:** Isolated blood cells were cultured with pHrodo red/green bioparticles. Cells were fixed, washed and analyzed by flow cytometry.
- Simulated microgravity:** 3D high-aspect rotating wall vessels (HARV-RWV, Synthecon) were used to simulate microgravity. Cells were suspended at  $5 \times 10^5$  cells/ml in 10 ml and rotated at 20 RPM ( $\mu g$ ) for 20 hr. Upright flasks were used as 1g controls. Following incubation cells were collected for appropriate assays.
- Hindlimb unloaded mice:** Female, 4-month old mice were subjected to tail restrained hindlimb unloading for 30-days.
- qPCR:** Total RNA was extracted from sorted granulocytes. qRT-PCR was performed using iQ SYBR green supermix.  $\beta$ -Actin, normalizing gene was used for calculating relative fold change (RFC).

## Spaceflight



## Simulated microgravity models



## Conclusions

- Progressive increased in GLR (humans) and NLR (rodents) in spaceflight and at post-flight return.
- Increased GLR, NLR and ROS in human blood under simulated microgravity, resulting in dysfunctional phagocytosis and robust MPO expression.
- Increased NLR in hindlimb unloaded mice.

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