How social status causally changes the immune system: experimental evidence from rhesus macaques

Luis Barreiro[*]

lbbarreiro@gmail.com;luis.barreiro@umontreal.ca

In hierarchically organized species, social status can strongly influence fertility, survival, and other fitness-related traits, and in humans, status is one of the best predictors of disease susceptibility. To understand its effects at the molecular level, we used sequential manipulations of social status in female rhesus macaques to (i) establish that social status causally changes gene regulation in immune cells; (ii) localize these effects to specific cell types and signaling pathways; and (iii) investigate how they shape the response to pathogen infection.

To do so, we constructed 9 social groups ($n = 5$ females per group) using a well-established paradigm in which order of introduction predicts dominance rank: earlier introduced animals attain higher status. After monitoring these status hierarchies for a year (Phase 1), we reorganized group composition to maximize changes in rank, and then monitored the new hierarchies for a second year (Phase 1-Phase 2 rank $r = 0.063, p = 0.68$). Using RNA-seq, we profiled gene expression from all females in both phases, in five FACS-sorted immune cell populations. Both independent and meta-analytic approaches revealed highly heterogeneous responses to rank, concentrated in Natural Killer cells and helper T cells (1128 and 451 rank-responsive genes, respectively), but weak or absent in the other three cell types (monocytes, cytotoxic T, and B cells). Our results were highly concordant across Phases, indicating a substantial degree of plasticity upon changes in the social hierarchy.

To test how social status influences the response to pathogens, we used an ex vivo lipopolysaccharide (LPS) stimulation experiment. Gene expression data from paired control and LPS-stimulated samples clearly separated samples by condition (PC1: $r = 0.86, p < 10^{-15}$) and, within conditions, by dominance rank (PC2: $r = 0.59$, $p < 10^{-8}$). Rank x condition interactions were most robust for genes that were more strongly upregulated by LPS in low status females, including NFKB1, a master regulator of inflammation. In contrast, high

[*]Département de pédiatrie, Université de Montréal, C.P. 6128, succ. Centre-ville, Montréal, QC H3C 3J7, CANADA

status females expressed antiviral and type I interferon-related genes more highly, suggesting that social status polarizes the use of alternative arms of the LPS-responsive TLR4 signaling pathway. Together, our results provide novel insight into the molecular basis of social gradients in fitness and health, and the evolution of social hierarchies more broadly.