Molecular origins and outcomes of status and stress in primates

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Social dominance hierarchies are common in human and nonhuman animals and profoundly affect the behavior, health, and well-being of every member of a community. Research on diverse species has expanded our understanding of how ecological and social forces shape interactions influencing social status, behavior, and the underlying biology (1, 2). Across vertebrates, repeated social subordination (equivalent to low status) has been shown to result in depression-like phenotypes (3–6). It has also been suggested that the gene modules controlling responses to repeated social defeat are evolutionarily conserved (7, 8). The use of a comparative framework combined with genome-scale approaches provides an unparalleled opportunity to examine the effects of social status on behavior and health. In PNAS, two new studies (9, 10) use advanced genomic methods to investigate the effects of social status on immunity and stress physiology by examining gene regulation in blood cells of two different primate species.

To uncover the molecular mechanisms involved in social status and stress, Snyder-Mackler et al. (9) examine social interactions in 45 captive, unrelated female rhesus macaques. Female rhesus macaques exhibit stable, linear social hierarchies (based on kin-directed nepotism). Low-ranking females receive increased harassment and decreased social support (e.g., grooming) and exhibit elevated levels of circulating glucocorticoids (GCs) (e.g., cortisol). Previous research by Snyder-Mackler et al. (11) demonstrated that low-ranking females exhibit a proinflammatory profile in their blood cells compared with high-ranking females (Fig. 1*A*). Importantly, when these animals received an immune challenge in the form of the bacterial stimulant of infection [lipopolysaccharide (LPS)], rank differences in gene expression were amplified (Fig. 1*B*). In their new study, Snyder-Mackler et al. (9) evaluate GC signaling using in vitro treatment with the synthetic GC dexamethasone (Dex). Peripheral blood mononuclear cells collected from individual rhesus macaques were incubated with or without Dex. The authors then examined gene expression with RNA sequencing (RNA-seq), and chromatin accessibility with the assay for transposase-accessible chromatin using sequencing (ATAC-seq). They observed the expected status differences in gene expression, in which low-ranking females exhibit a more proinflammatory profile than high-ranking females (Fig. 1*A*). Importantly, anti-inflammatory treatment using Dex attenuated social status effects on gene expression by 75% but did not affect overall status effects on chromatin accessibility (Fig. 1*B*). Subsequent analyses revealed that in low-ranking females, transcription factor binding sites involved in the inflammatory response became more accessible after Dex treatment, whereas regions of the chromatin that open after Dex treatment were enriched for many of the same transcription factor binding motifs that were more accessible in high-ranking females (Fig. 1*A*). These findings suggest that chromatin accessibility may be crucial in mediating rank effects on GCs and immune-related gene expression (Fig. 1*A*).

To further explore the relationship between social status and immune regulation, Lea et al. (10) examine social interactions in wild yellow baboons (monitored by the Amboseli Baboon Research Project), where males and females exhibit different types of status hierarchies. Males of this species form highly dynamic, competition-based hierarchies by aggressively fighting for social dominance, while females form relatively stable, nepotistic (e.g., kin-based) hierarchies. The authors evaluate the effect of status on gene expression in male and female baboons and evaluate the effect of an immune challenge using ex vivo treatment with a bacterial stimulant of infection, LPS. Blood samples were collected from 35 males and 26 females and incubated with or without LPS. Serum cytokines involved in inflammatory signaling pathways were up-regulated by LPS in both males and females. To examine the effects of rank on gene expression, the authors isolated white blood cells from the samples and measured gene expression using RNA-seq. Remarkably, rank-based differences in gene expression

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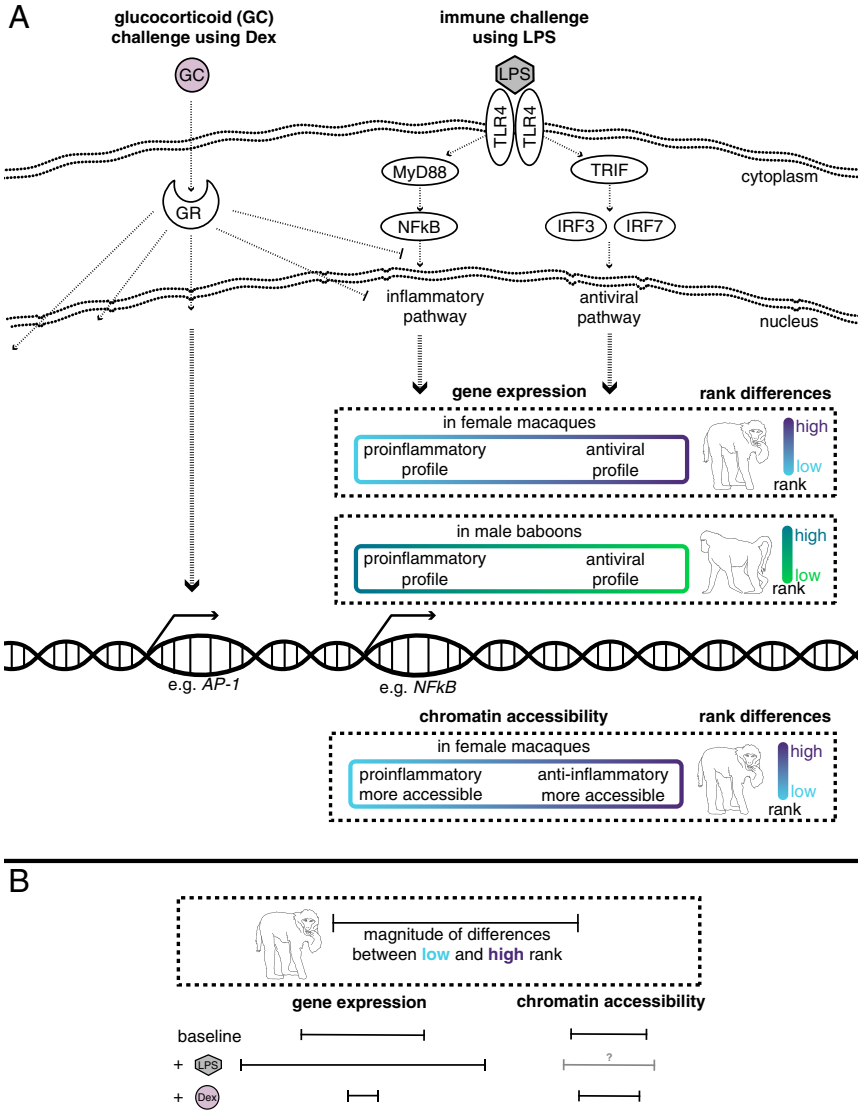

Fig. 1. Effects of social rank on blood cell gene expression and regulation vary by species and treatment according to two new studies in PNAS (9, 10). (*A*) The Toll-like receptor 4 (TLR4) is activated by bacterial LPS, which induces a MyD88-dependent proinflammatory pathway and a Toll/IL-1 receptor domain-containing adaptor-inducing IFN-β (TRIF)-dependent antiviral pathway. Also shown is the GC hormone-induced GC receptor (GR) pathway to highlight interactions across LPS and GC treatment. Social rank-mediated effects on gene expression in response to LPS are represented for female macaques and male baboons, while rank-mediated effects on chromatin accessibility are represented for female macaques. (*B*) Overview of the relative scale of rank-mediated differences in gene expression and chromatin accessibility in female macaques in response to LPS and GC (Dex) treatment. IRF, interferon regulatory factor.

were highly sex specific, with social rank predicting the expression of almost 100 times more genes in males (2,277) than in females (25)! Interestingly, high-ranking males showed increased expression of genes involved in innate immunity and the proinflammatory NF-κB–mediated pathway, while no strong rank differences were observed in females. This pattern of gene expression in male baboons, with high-ranking individuals exhibiting a more proinflammatory profile than low-ranking individuals, stands in stark contrast to the pattern observed in female rhesus macaques (Fig. 1*A*). The authors suggest that this might be a direct consequence of the sex differences in how dominance hierarchies are established and the extent to which social buffering can protect low-ranking individuals.

Although we may expect social rank and the associated gene expression profiles to be a direct consequence of nepotism in wild populations of female baboons (i.e., the female relatives of high-ranking females inherit their high rank), the causal relationship between rank and gene expression is much less clear in males that fight for social dominance. Using genotyping and a sophisticated statistical technique rooted in epidemiology, Lea et al. (10) conclude that the gene expression signature observed in high-ranking male baboons likely precedes their attainment of high rank. The authors conjecture that a proinflammatory transcriptomic state may be an indicator of high condition and/or may be needed for success and recovery in response to physical competition. Together, these two studies add to the growing realization that social context is critical for understanding the relationship between social status and immune function.

Both Snyder-Mackler et al. (9) and Lea et al. (10) explore the effects of social status and stress on behavior and gene expression at the level of the transcriptome and epigenome. These studies considerably advance our understanding of interactions across

stress, status, and health using a comparative approach, and convincingly demonstrate the importance of context. Factors of particular importance for comparisons across species include sex differences, social hierarchies, and social support. Lea et al. (10) demonstrate strong sex differences in the effect of rank and immune challenge on gene expression in mixed sex groups. While this demonstrates the significance of examining sex differences, it also highlights the importance of considering the role of social hierarchy dynamics (e.g., merit based or nepotistic) on rank effects independent of sex. In female rhesus macaques, social dominance hierarchies are nepotism driven, and low-status females exhibit an up-regulation of MyD88-dependent proinflammatory pathway genes (consistent with social subordination-driven proinflammatory activity) (11). In contrast, in male baboons, social rank is attained by fighting, and the same proinflammatory pathway is up-regulated in high-ranking males (10). It would be informative to examine rank-based differences on chromatin accessibility in species in which the social hierarchy is fighting based (e.g., male baboons). The lack of rank-based differences in gene expression in wild female baboons (10) also suggests that—at least in wild communities—social support plays a likely role in buffering context-dependent effects of status on immune-related gene expression. Low rank is strongly associated with proinflammatory gene expression in societies with strict hierarchy enforcement (e.g., harassment or displacements), in which social support for low-ranking individuals is often absent. While both low-ranking baboons (10) and macaques (11) are harassed more than their high-ranking counterparts, low-ranking wild female baboons may have access to social support that captive rhesus macaques do not. The possible role of social support as a buffer is further bolstered by previous research (11) that demonstrated that grooming was a stronger predictor than harassment of the rank effects on gene expression in cells of female macaques that were most sensitive to status (e.g., natural killer cells). This suggests that a lack of positive social interactions may be more important in shaping rank effects on gene expression than the harassment received as a low-ranking individual.

Can we apply these new results beyond the two primate species examined in these studies? The discovery that gene expression levels and epigenetic states can be socially modulated by variation in chromatin accessibility provides a key step toward resolving the apparent paradox that chronic stress can predispose toward inflammation while high levels of GCs can simultaneously enact strong anti-inflammatory effects. Snyder-Mackler et al. (9) speculate that, at baseline, increased accessibility to binding sites of GC receptor cofactors in high-ranking animals could drive more efficient GC negative feedback, resulting in tighter control of the inflammatory response. Given the role of GCs as signaling molecules involved in regulating stress physiology, there is plausible support for the hypothesis that GCs contribute to the integration of the processing of social experiences with the downstream pathways involved in divergent molecular pathways. Future studies can improve our understanding of the possible fitness consequences of stress and status by exploring how these factors interact with chromatin accessibility over the course of an individual's lifetime. It will also be informative to explore the importance of the social group and integration within it to further investigate the influence of social support on rank-mediated effects on gene expression and chromatin accessibility across diverse species. Whatever the outcomes of such future studies, they will provide important insight into the mechanisms by which social rank affects health and well-being and how these mechanisms might have come about in social evolution.

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