Published in final edited form as:

Trends Cogn Sci. 2019 September ; 23(9): 722–725. doi:10.1016/j.tics.2019.06.003.

Social Status and Gene Regulation: Conservation and Context Dependence in Primates

Noah D. Simons¹, Jenny Tung^{1,2,3,4,*}

¹Department of Evolutionary Anthropology, Duke University, Durham, NC 27708, USA

²Department of Biology, Duke University, Durham, NC 27708, USA

³Duke Population Research Institute, Duke University, Durham, NC 27708, USA

⁴Institute of Primate Research, National Museums of Kenya, 00502 Nairobi, Kenya

Abstract

Current models suggest that low social status affects immune function by increasing inflammation and compromising antiviral defense. While this pattern appears to be somewhat conserved, recent studies argue that the gene regulatory signature of social status also depends on the local environment and the nature of social hierarchies.

Low social status is a frequent (although not universal) source of socially induced stress that can have profoundly negative consequences for health and mortality risk in humans and other social animals. Recent estimates show that, in the USA, the expected lifespan of adults at the bottom of the socioeconomic scale is up to a decade shorter than those at the top [1]. This pattern generalizes to other species: for example, socially subordinate male mice experience substantially elevated rates of atherosclerosis and tumorigenesis compared to dominant mice, even in controlled laboratory environments [2]. The health effects of low social status are thought to arise in part from the physiological effects of chronic social stress. This model proposes that socially induced changes in the central nervous system (CNS) lead to downstream changes in hypothalamic–pituitary–adrenal (HPA) axis and autonomic nervous system functioning, which in turn compromise health.

In the periphery, these effects are thought to be mediated in part through tissue-specific changes in gene regulation which, thus far, have been best studied in the peripheral blood [3]. Indeed, studies across species suggest that the gene expression signature of low social status has remained somewhat conserved over evolutionary time, consistent with work on shared gene regulatory responses to social challenge (e.g., territorial intrusion in species as distinct as honey bees, fish, and mice [4]). However, recent studies argue that the effects of low status-induced social stress can also be exaggerated, attenuated, or even reversed in different contexts.

Signatures of social adversity in peripheral blood gene expression have been detected in both correlative studies in humans and experimental studies in animal models, particularly the

*Correspondence: jt5@duke.edu (J. Tung).

rhesus macaque (*Macaca mulatta*) [3,5,6]. Together, the animal model studies demonstrate that social status and other forms of social adversity can causally alter immune gene regulation, even in the absence of other environmental confounds (e.g., diet, exercise, or health care access). Meanwhile, the parallelism between these results and observations in humans, which extend to the level of specific genes and pathways, argue for their ethological relevance to human health and disease.

This parallelism has led researchers to emphasize shared, potentially conserved, transcriptional signatures of social adversity in peripheral blood immune cells (primarily at the level of broad biological processes) [3]. For example, in both humans and rhesus macaques, genes involved in inflammation tend to be more highly expressed in low status individuals compared to high status individuals. In contrast, genes involved in the innate immune response to virus, especially type I interferon (IFN) signaling, tend to be more highly expressed with high status (Figure 1A). These differences have in turn been linked to changes in the activity of transcription factors that respond to neuroendocrine signals of stress, such as the glucocorticoid receptor (GR) and nuclear factor (NF)- κ B, a master regulator of immune defense against infection. Indeed, experimental evidence from rhesus macaques shows that low social status leads to increased chromatin accessibility in regions of the genome that contain NF- κ B binding sites, but reduced accessibility to binding sites for the GR cofactor AP-1 [7].

However, a major priority in studying the biology of social gradients lies in understanding heterogeneity in the response to social stressors, especially who is most likely to be affected, and under what conditions. Implicit in this idea is the argument that gene regulatory signatures of social adversity should not always be conserved. Indeed, evidence for such heterogeneity is beginning to accrue. For example, the effects of social status on gene expression differ in female macaques when their cells are challenged with a bacterial endotoxin (lipopolysaccharide; LPS) versus a viral mimic (gardiquimod, which simulates infection by a single-stranded RNA virus) [8]. In an LPS-challenged state, genes in proinflammatory pathways are upregulated in low status individuals. However, although high status predicts higher expression of viral defense genes at baseline, low status predicts higher expression of both viral defense genes and inflammation-related genes in gardiquimod-challenged cells. Remarkably, key genes involved in viral restriction (e.g., *STAT1*, *MX1*, and *viperin*) actually show directionally reversed effects of social status between gardiquimod and LPS-challenged cells (Figure 1B). More work is necessary to understand the mechanistic basis of these differences, but differences in the receptors responsible for detecting virus versus bacteria or in the regulatory elements that coordinate these responses, could be responsible. The immediate environment that cells experience (e.g., signals of bacterial infection or viral attack) is therefore an important determinant of both the magnitude and the direction of social gradients in gene regulation.

Superficially similar measures of social status can also mask underlying heterogeneity, especially when high status is achieved in different ways. This pattern has previously been highlighted by studies of social stress and HPA axis function, which show that social subordination is most closely associated with high glucocorticoid levels in hierarchies where subordination is linked to regular harassment or high levels of social uncertainty [9]. Such

variation also applies at the level of peripheral blood gene expression. For example, a remarkably similar set of genes and pathways are associated with social status in both wild male baboons and captive female macaques. However, the direction of these relationships is inverted: genes that tend to be more highly expressed in low-ranking female macaques tend to be more highly expressed in high-ranking male baboons (Figure 1C) [10]. A likely explanation for this difference is that, in female macaques, social status is relatively stable and largely dependent on kin relationships, not fighting ability. In contrast, in male baboons, social hierarchies are established and maintained via direct physical competition. Elevated expression of inflammation-related genes (as observed in high-ranking male baboons) could potentially be beneficial in social contexts that increase the likelihood of physical injury – a scenario that is does not apply to high status female macaques (or, in most cases, high status humans).

In summary, the idea that social status-related variation in gene regulation is partially conserved is reasonable, and studies of the evolutionary origins of these conserved patterns promise to be of great interest. At the same time, however, gene regulatory responses to social status-induced stress can deviate from those conserved patterns depending on individual characteristics (e.g., age, sex, and genotype), social context (e.g., how status is attained and maintained, as well as the steepness or stability of social hierarchies), subjective experience/interpretation (see [11] for an extended discussion of perception and subjectivity in studies of social stress/adversity), and other environmental factors (e.g., pathogen exposure and resource availability). Because understanding heterogeneity in the social adversity–gene regulation relationship is important for both prediction and intervention, a careful dissection of how social status interacts with these variables is therefore an important research priority. In addition, given the known association between neuroinflammation and neurodegenerative disease, extending functional genomic studies of social stress to other tissues –especially the brain and other neural tissues – should be another high priority [12]. Such studies have the potential to shed light on the role of immunity in mediating the relationship between social stress, cognitive function, and cognitive decline. Notably, by avoiding an *a priori* focus on conserved effects, researchers can take advantage of a strength of genomic data sets: an unbiased view of gene regulation from across the entire genome (Box 1).

Acknowledgments

We thank Luis Barreiro, Amanda Lea, and three anonymous reviewers for constructive feedback on earlier versions of this manuscript. This work was supported by NIH Grants R01-GM102562, R01-AG057235, and F32-AG062120.

References

1. Chetty R. et al. (2016) The association between income and life expectancy in the United States, 2001–2014. *JAMA* 315, 1750–1766 [PubMed: 27063997]
2. Razzoli M. et al. (2018) Social stress shortens lifespan in mice. *Aging Cell* 17, e12778 [PubMed: 29806171]
3. Cole SW. (2019) The conserved transcriptional response to adversity. *Curr. Opin. Behav. Sci* 28, 31–37 [PubMed: 31592179]

4. Rittschof CC. et al. (2014) Neuromolecular responses to social challenge: common mechanisms across mouse, stickleback fish, and honey bee. *Proc. Natl. Acad. Sci. U. S. A* 111, 17929–17934 [PubMed: 25453090]
5. Cole SW. et al. (2012) Transcriptional modulation of the developing immune system by early life social adversity. *Proc. Natl. Acad. Sci. U. S. A* 109, 20578–20583 [PubMed: 23184974]
6. Snyder-Mackler N. et al. (2016) Social status alters immune regulation and response to infection in macaques. *Science* 354, 1041–1045 [PubMed: 27885030]
7. Snyder-Mackler N. et al. (2019) Social status alters chromatin accessibility and the gene regulatory response to glucocorticoid stimulation in rhesus macaques. *Proc. Natl. Acad. Sci. U. S. A* 116, 1219–1228 [PubMed: 30538209]
8. Sanz J. et al. (2019) Social history and exposure to pathogen signals modulate social status effects on gene regulation in rhesus macaques. *bioRxiv* Published online February 18, 2019 10.1101/552356
9. Beehner JC and Bergman TJ. (2017) The next step for stress research in primates: To identify relationships between glucocorticoid secretion and fitness. *Horm. Behav* 91, 68–83 [PubMed: 28284709]
10. Lea AJ. et al. (2018) Dominance rank-associated gene expression is widespread, sex-specific, and a precursor to high social status in wild male baboons. *Proc. Natl. Acad. Sci. U. S. A* 115, E12163–E12171 [PubMed: 30538194]
11. Cacioppo JT and Hawkley LC. (2009) Perceived social isolation and cognition. *Trends Cogn. Sci* 13, 447–454 [PubMed: 19726219]
12. Ransohoff RM. (2016) How neuroinflammation contributes to neurodegeneration. *Science* 353, 777–783 [PubMed: 27540165]

Box 1.**Genomic Approaches to Studying Social Status and Gene Regulation**

Because of the expense of generating genomic data, studies of gene regulation and social stress have historically been power limited. Some researchers have therefore focused on analyzing an *a priori*-defined gene set, even if genome-wide data were collected. This approach minimizes the multiple testing burden, and has been argued to increase the power and replicability of socially sensitive genes across studies.

However, the costs of genomic analyses are rapidly falling. Consequently, as is the case for other genetic/genomic analyses (e.g., genotype–phenotype mapping), genome-wide analyses are therefore positioned to generate the most reliable results, while also leaving the door open to new discovery. Furthermore, pathway/process-level enrichment analyses require this scale of analysis, as the null for enrichment is determined by the background set of genes analyzed. Importantly, genome-wide approaches do not preclude the ability to test for consistency across studies, since the hypothesis that previously discovered genes/pathways are enriched in a new data set can readily be tested. Thus, while it remains important to recognize that the absence of evidence is not evidence of absence (i.e., false negatives will occur because almost all studies are power limited), we argue that genome-wide analyses should be the standard approach in sociogenomic research.

Figure 1. Conserved and Context-Dependent Relationships between Social Status and Immune Gene Regulation.

(A) In both humans and female rhesus macaques, low social status is linked to lower expression of genes involved in antiviral defense (left) and higher expression of genes involved in proinflammatory pathways (right). (B) Genes involved in antiviral defense are also more highly expressed in high status macaque females in a lipopolysaccharide (bacterial)-challenged state. However, this pattern is reversed in a gardiquimod (viral)-challenged state. An example of this context-dependent relationship is shown for *viperin*, a key gene in viral restriction (data from [8]). (C) In both bacterial-challenged and baseline (not shown) states, genes involved in proinflammatory pathways are more highly expressed in low status female macaques, but this pattern is reversed for baboon males. White arrows depict the direction of enrichment.