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ORIGINAL ARTICLE

A female-biased gene expression signature of dominance in cooperatively breeding meerkats

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Abstract

Dominance is a primary determinant of social dynamics and resource access in social animals. Recent studies show that dominance is also reflected in the gene regulatory profiles of peripheral immune cells. However, the strength and direction of this relationship differs across the species and sex combinations investigated, potentially due to variation in the predictors and energetic consequences of dominance status. Here, we investigated the association between social status and gene expression in the blood of wild meerkats (*Suricata suricatta*; $n = 113$ individuals), including in response to lipopolysaccharide, Gardiquimod (an agonist of *TLR7*, which detects single-stranded RNA in vivo) and glucocorticoid stimulation. Meerkats are cooperatively breeding social carnivores in which breeding females physically outcompete other females to suppress reproduction, resulting in high reproductive skew. They therefore present an opportunity to disentangle the effects of social dominance from those of sex per se. We identify a sex-specific signature of dominance, including 1045 differentially expressed genes in females but none in males. Dominant females exhibit elevated activity in innate immune pathways and a larger fold-change response to LPS challenge. Based on these results and a preliminary comparison to other mammals, we speculate that the gene regulatory signature of social status in the immune system depends on the determinants and energetic costs of social dominance, such that it is most pronounced in hierarchies where physical competition is important and reproductive

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skew is large. Such a pattern has the potential to mediate life history trade-offs between investment in reproduction versus somatic maintenance.

KEYWORDS
cooperative breeding, gene expression, inflammation, reproductive skew, social dominance

1 | INTRODUCTION

In species that live in stable groups, social dominance often predicts access to food, mates and other monopolizable resources (Clutton-Brock, 1988, 2021; Krause & Ruxton, 2002; Rubenstein, 1978; Sterck et al., 1997; Wilson, 2000). However, there is substantial variation in how animals attain and maintain dominance, both between and within species (e.g., between sexes). While some social systems are shaped by nepotistic inheritance, such that individuals attain a rank position similar to their relatives (e.g., female Japanese macaques: Kawai (1958), Kawamura (1958); female yellow baboons: Hausfater et al. (1982); female spotted hyenas: Holekamp and Smale (1991)), others are based on individual characteristics such as physical condition or fighting ability (e.g., male red deer: Clutton-Brock et al. (1982); male bottlenose dolphins: Samuels and Gifford (1997)). Dominance status also varies in temporal stability and the behavioural expression of dominance. For example, in the macaque radiation, rhesus macaque females enforce dominance via regular harassment directed down a predictable linear hierarchy (Bernstein et al., 1974). In contrast, in closely related crested macaques, agonistic interactions are bidirectional, rarely involve physical threat or contact and are often followed by conciliatory behaviour (Duboscq et al., 2013). Consequently, while high status is generally fitness-enhancing, its physiological costs and benefits are expected to vary.

Variation in the costs and benefits of high status is well-supported by studies of the relationship between dominance and glucocorticoid levels, a hormonal marker of both energetic and psychosocial stress (Abbott et al., 2003; Beehner & Bergman, 2017; Cavigelli & Caruso, 2015; Creel, 2005). Although experimental studies in lab models generally link low status to high glucocorticoid levels and/or glucocorticoid resistance (e.g., Kohn et al. (2016), Razzoli et al. (2018), Willard and Shively (2012); reviewed in: Beehner and Bergman (2017), Cavigelli and Caruso (2015)), research across a wider range of species, including in natural populations, paints a more complex picture. Higher glucocorticoids correlate with low status in some cases, especially when dominance is aggressively enforced or opportunities for social support are lacking (Abbott et al., 2003). However, high glucocorticoid levels are linked to *high* status in other settings, potentially because of the high energetic demands of achieving high rank or investing in reproductive opportunities (Creel et al., 1997; Fichtel et al., 2007; Gesquiere et al., 2011; Muller et al., 2021; Muller & Wrangham, 2004; Schoof & Jack, 2013). In cases where high status is associated with high glucocorticoid levels, high status has also been linked to other, presumably costly, outcomes. For instance, in male baboons in the Amboseli study population, high status predicts high glucocorticoid levels, old-for-age epigenetic age and a moderately elevated mortality risk (Anderson et al., 2021; Campos et al., 2020, 2021).

Recent studies have also begun linking variation in social status to gene regulation, producing a novel molecular source of insight into the potential costs and benefits of dominance. While many such studies have focused on gene expression changes in the brain (e.g., in cichlid fish: Baran & Streelman, 2020, Renn & Schumer, 2013, Schumer et al., 2011; honeybees: Evans & Wheeler, 2000, Grozinger et al., 2003, Maruska et al., 2013; songbirds: Bentz et al., 2019, 2021), more recent work, centred in mammals, has sought to understand how the different experiences of high- versus low-status individuals translate to changes in gene regulation in peripheral immune cells (Bondar et al., 2018; Cole, 2014; Lea et al., 2018; Lee, Milewski, et al., 2022; Simons & Tung, 2019; Tung et al., 2012). Strong support for status-related effects comes from lab studies of mice, in which low-status animals and those subjected to repeated social defeat show substantially altered peripheral blood mononuclear cell (PBMC) gene expression (Lee, Milewski, et al., 2022; Pizarro et al., 2004; Powell et al., 2013). In primates, experimental manipulations of group hierarchies in rhesus macaques alter not only baseline gene expression but also the response to immune stimulation (Sanz et al., 2020; Snyder-Mackler et al., 2016, 2019). In general—and in agreement with correlational studies in humans (Cole, 2019; Miller et al., 2009; Murray et al., 2019; Powell et al., 2013)—these studies suggest that low social status is typically associated with elevated activity of pro-inflammatory pathways. Conversely, high status is frequently linked to increased activity of genes involved in interferon-induced antiviral defence.

However, the settings in which links between social status and immune gene regulation are most pronounced have not been systematically explored. Recent studies in wild baboons indicate that there may be substantial variation in the strength and direction of these effects (Anderson et al., 2022; Lea et al., 2018). For example, while low-ranking baboon females show a pattern of pro-inflammatory/antiviral polarization similar to that reported for socially stressed humans and captive rhesus macaques (Murray et al., 2019; Snyder-Mackler et al., 2016), this pattern is reversed for baboon males from the same study population (Anderson et al., 2022; Lea et al., 2018). One possible explanation for this contrast involves the distinct dynamics of status competition in male versus female baboons. While male baboons physically compete to establish dominance, young females typically insert into the status hierarchy directly below their mothers (Hausfater et al., 1982; Lea et al., 2014). Additionally, the reproductive skew is greater in males than in females (Alberts

et al., 2006; Lukas & Clutton-Brock, 2014), consistent with typical observations in polygynous or polygynandrous mammals (Clutton-Brock, 1988). In support of the importance of an underlying role for competition/skew, the more aggressive sex upregulates similar sets of brain-expressed genes in both *Julidochromis transcriptus* and *J. marlieri*; but in *J. transcriptus*, these are males, whereas in *J. marlieri*, they are females (Schumer et al., 2011). Differences in the level of competition for social dominance and status-related variance in reproductive investment may therefore also be important for understanding the gene regulatory signature of social status in immune cells.

Testing this hypothesis requires separating patterns of competition and reproductive investment from the effects of sex per se. Although in many mammals, males engage in more intense competition and energetic investment in mating opportunities than females, this pattern is reversed in some species (e.g., Clutton-Brock and Huchard (2013), Lukas and Clutton-Brock (2014); see also Emlen and Wrege (2004), Goymann et al. (2004), Oring and Lank (1986) for work outside of mammals). In cooperatively breeding meerkats (*Suricata suricatta*), for instance, reproduction is concentrated in one dominant breeding female per group, who defends her position via regular aggression directed at competitors (Clutton-Brock et al., 2001; Kutsukake & Clutton-Brock, 2006; Young et al., 2006). Because subordinates of both sexes assist in rearing young, dominant females can also breed multiple times a year. As a result, reproductive skew in female meerkats can be extreme: in one example, a successful dominant female reared 72 offspring during her lifetime, whereas most subordinates produce no surviving offspring (Clutton-Brock et al., 2006; Hodge et al., 2008). Dominance in males also leads to skewed reproduction, as dominant males father most pups born to the dominant female in their groups (Griffin et al., 2003; Hodge et al., 2008; Spong et al., 2008). However, because dominant males typically have shorter breeding lifespans, variance in lifetime breeding success is higher in females and competition for breeding opportunities is more frequent and more condition-dependent (Clutton-Brock et al., 2001, 2006; Clutton-Brock & Manser, 2016; Duncan et al., 2018, 2023; Hodge et al., 2008; Lukas & Clutton-Brock, 2014). Further, while dominance is associated with higher cortisol levels in both sexes (Carlson et al., 2004), female meerkats exhibit higher parasite load than males (Smyth & Drea, 2016), and dominant females (but not males) have higher androgen levels than their same-sex subordinates (Carlson et al., 2004; Drea et al., 2021; Drea & Davies, 2022).

The unusual pattern of sex differences in meerkats therefore provides an ideal test case for investigating the patterns responsible for associations between social status and immune gene expression. To do so here, we investigate the association between social status and gene regulation in wild meerkats of both sexes. We focus on gene expression patterns in circulating peripheral immune cells, which are accessible using minimally invasive methods and capture aspects of immune function that may trade-off against dominance-related investment in body condition or reproductive effort. First, we ask if dominance status predicts immune gene expression, and whether these signatures differ by sex. Second, we investigate whether social status is associated with the immune gene expression response to lipopolysaccharide (LPS), to model bacterial exposure; Gardiquimod (Gard), which activates Toll-like receptor 7 signalling (important in antiviral defence); and the synthetic glucocorticoid Dexamethasone (Dex), an important modulator of inflammation. Third, we assess whether status-related gene expression differences in females are explained by age, body mass, or reproductive state. Finally, we place our results for meerkats in context by performing a preliminary comparative analysis with the most comparable available data sets to date, on two non-cooperatively breeding primates (Anderson et al., 2022; Snyder-Mackler et al., 2016). Together, our work suggests how diverse social structures shape the gene regulatory signature of dominance and contribute to an emerging understanding of the processes that link social status to its molecular correlates.

2 | METHODS

2.1 | Field site and sampling

This study was conducted on 129 unique wild meerkats (69 males and 60 females), members of 15 study groups monitored by the Kalahari Meerkat Project at the Kalahari Research Centre, Northern Cape Province, South Africa, between August 2017 and September 2020 (Figue 1; Table S1). These groups were visited 3–7 days per week to collect demographic, life history and behavioural data, including agonistic interactions used to infer dominance status (Clutton-Brock et al., 1998). The majority of blood samples used in this study were collected cross-sectionally during scheduled biannual or annual draws ($n = 237$ blood samples from 129 unique individuals; because multiple gene expression samples were generated from the same draw, we use the term 'gene expression samples' to refer to unique individual-capture-culture condition combinations, as distinct from 'blood draw' or 'blood sample'). However, we also targeted newly dominant individuals for longitudinal blood sampling, with blood collected (i) as close to the date of their transition from subordinate to dominant status as possible, (ii) four weeks after their dominance transition and (iii) four months after their initial transition (assuming the animal retained dominant breeding status). We simultaneously collected blood samples from a subordinate member of the same group and a subordinate member of a different group for comparison, allowing us to control for temporal, seasonal and group effects. Ninety-eight total blood draws were collected based on this longitudinal design. The meerkats in the study population were habituated to humans and were captured by hand. Meerkats were anaesthetized using 4% isoflurane (Isofor, Safe Line Pharmaceuticals, Johannesburg, South Africa) mixed with oxygen administered via a gas mask attached to a portable vaporizer. After full sedation, isoflurane dosage was lowered to 1%–2% and a blood sample was obtained from the jugular vein using a 25 G needle and 2-mL

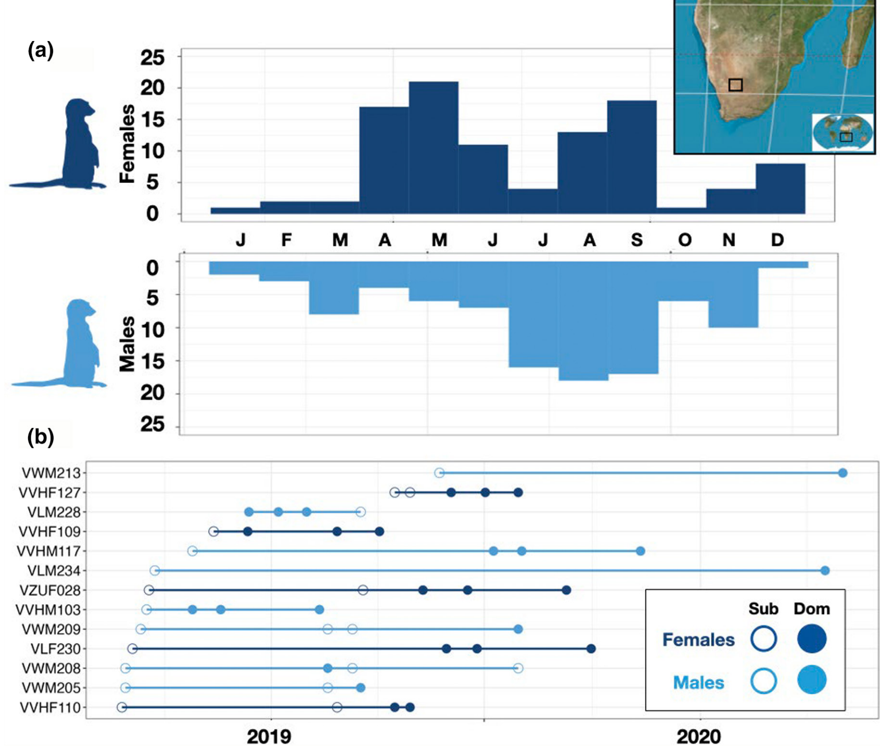

FIGURE 1 Blood sampling strategy. (a) Blood samples collected by calendar month across the study, broken down by month and sex (females dark blue, males light blue). Inset map shows the location of the study population (b) Longitudinal blood sampling for the subset of males and females sampled as both dominants and subordinates. Each line represents one individual, and the horizontal axis shows time across multiple years of blood sample collection. Empty circles represent blood samples collected when the animal was subordinate and filled circles represent samples collected when the animal was dominant.

syringe (as in Carlson et al., 2004; Dantzer, Bennett, & Clutton-Brock, 2017; Drea et al., 2021). This procedure is highly standardized and typically takes no longer than 20–30 min from capture to release.

To assess dominance status as well as pregnancy we drew on regular behavioural and demographic observations, as described in Clutton-Brock et al. (1998). Dominant animals routinely displace subordinates, scent-mark more often and are typically older and, in the case of females, heavier than their groupmates (Figure S1). They are also more likely to be reproductively active, although not exclusively so. Pregnancy was assessed via observations of physical expansion of the abdomen, which becomes visually obvious roughly halfway through the 70-day gestation period (Clutton-Brock et al., 1998). Fifteen blood draws were conducted when females were likely pregnant (13% of the 119 samples). Because we avoided blood draws on visibly pregnant female meerkats, 93% of draws were collected in the first half of pregnancy (11–39 days gestation). Nine of these 15 blood draws were collected from dominant females and 6 were from subordinate individuals, but consistent with high reproductive skew in female meerkats, only one pregnancy from a subordinate female resulted in live offspring that survived more than one week.

Finally, to assess body mass, study subjects were weighed non-invasively multiple times daily using electronic balances (members of the study population are habituated to standing on portable scales: see Clutton-Brock et al. (1998)). To determine weight at the time of capture and blood draw, we averaged all of a subject's weight measurements collected within 30 days of its capture date, excluding 2.3% of measurements identified as outliers (Grubbs outlier test of 10 consecutive weights, $p < .05$). Age at blood draw (mean = 2.1 ± 1.44 years; range = 0.96–10.4 years; Table S1) was based on long-term observations and was known to be within a few days' error for 97% of individuals in the field sample.

2.2 | Cell challenge and RNA-seq data generation

We purified PBMCs from ~1 mL of blood per blood draw via density gradient centrifugation, within 3–4 h of the original blood draw. For each blood sample, we plated 200,000 PBMCs in a 200 µL cell suspension into each of four tissue culture wells containing 20 µL cell culture media (RPMI; 10% FBS; 1% penicillin–streptomycin), for a total volume of 220 µL. Purified PBMCs from each blood sample were cultured for 4 h in (i) media only (control condition), (ii) media with 10 ng/mL lipopolysaccharide (LPS from the *E. coli* O111:B4 strain), to mimic bacterial exposure; (iii) media plus 1.0 µg/mL Gardiquimod (Gard), which activates Toll-like receptor 7 signalling or (iv) media plus 1.0 µM Dexamethasone (Dex), a synthetic glucocorticoid. Dex is a synthetic glucocorticoid often used in studies of glucocorticoid regulation of gene expression (John et al., 2011; Reddy et al., 2009). Notably, while ex vivo stimulation does not directly model endogenous cortisol exposure, the response to Dex in isolated lymphocytes predicts the response to glucocorticoid therapy in humans, suggesting that it contains information about how whole organisms respond to in vivo glucocorticoid exposure (Corrigan et al., 1996; Hakonarson et al., 2005; Hearing et al., 1999; Maranville et al., 2013). For all treatments, cells were incubated in parallel for 4 h (37°C and 5% CO_2), washed with 1× PBS, lysed and stored immediately at −80°C until library preparation.

We prepared RNA-sequencing libraries for each gene expression sample (control, Dex-challenged, Gard-challenged, LPS-challenged)

by purifying mRNA using the miRNeasy Mini Kit (Qiagen). Libraries were generated following the Transposase Mediated 3′ RNAseq (TM3′seq) protocol (Pallares et al., 2020) with an input of 50 ng total RNA. This protocol generates 3′ tags to represent transcripts as opposed to conventional full transcript RNA-seq, reducing the read depth required to represent the transcriptome (Pallares et al., 2020). All libraries were sequenced on an Illumina NovaSeq 6000 at the University of Chicago's Genomics Facility using 100 bp single-end reads.

2.3 | Data analysis

TM-3′-seq data were first filtered with trimmomatic (version 0.38, Bolger et al., 2014) and then mapped to the meerkat genome (GCF_006229205.1, https://www.ncbi.nlm.nih.gov/datasets/genome/GCF_006229205.1/) using the STAR two-pass method (version 2.7.10ac, Dobin et al., 2013). Mapped reads were aggregated to the gene level using HTseq (version 2.0, Putri et al., 2022) based on overlap with annotated gene exons. As expected based on the library preparation method we used, mapped reads were highly biased towards the 3′ end of genes (Figure S2). We excluded 199 libraries from further analysis because the number of genes with non-zero read count was low (<10,000, compared to mean = 11,690); typically, these libraries also were shallowly sequenced overall. We also removed 11 gene expression samples where the distribution of gene expression levels (logCPM) was systematically lower for most genes than observed on average.

To investigate the gene expression signature of treatment (LPS, Gard and Dex compared to control gene expression samples) and dominance status, we focused on genes that were moderately to highly expressed in meerkat PBMCs, based on mean expression across samples ($n = 6012$–6932 genes with mean log(CPM) >5, depending on sex-culture condition combination; Table S3). To control for differences in sequencing depth and technical effects of library quality and batch, we normalized the gene count matrix using the function *voom* from the R package limma (version 3.54.1, 2015; Ritchie et al., 2015) and regressed out library batch, number of unique genes, percent of reads in feature, and percent of reads mapped to the genome. We first explored the effect of LPS, Gard and Dex stimulation in both sexes and in models for males and females separately (see 'Treatment-control' models in the Supplementary Methods). Here, we controlled for mean-centred body mass, mean-centred age at blood draw, dominance status (represented as a binary variable for dominant versus subordinate), and pregnancy status (represented as a binary variable, in females only) as fixed effect covariates.

These initial models pointed to shared effects of stimulation in both sexes but indicated that dominance status effects were only detectable in females. To test this possibility further, we fit sex-specific models considering data from all treatment conditions together (including condition as a fixed effect in addition to body mass, age, pregnancy status and dominance status; see 'All conditions, sex-specific' model in the Supplementary Methods). Because the results of these analyses again indicated that dominance status effects are detectable only in females, we ran subsequent models for female meerkats only ('Condition-specific, female-only' model in the Supplementary Methods). Finally, for the subset of genes with evidence for gene expression-dominance status associations ($n = 735$, 10% FDR in any condition), we tested for a link between dominance status and the response to challenge by modelling data from the control condition and the relevant stimulated condition(s), nesting the binary dominance status variable within the condition ('Status × treatment interactions, female-only' model in the Supplementary Methods). We again controlled for body mass, age and pregnancy status, and included a fixed effect of the condition itself. We then compared the estimated effect sizes for dominance status within the control condition and the stimulated condition.

All models controlled for relatedness within the data set (R package: EMMREML version 3.1, Akdemir & Okeke, 2015). To control for multiple hypothesis testing, we calculated false discovery rates based on a comparison of the observed p-value distributions to empirical null distributions generated via permutation (Storey & Tibshirani, 2003). To create the empirical null, we permuted dominance status (or other predictor variables of interest, such as treatment) across blood draws, with gene expression samples from the same draw treated as a block. We then fit the same model as in the real data.

For females followed longitudinally across a dominance transition ($n = 5$ who transitioned, plus $n = 5$ controls sampled at the same time, who did not transition), we focused on 514 genes identified as dominance-associated in the full data set (after removing blood samples from multiple capture dates for the longitudinally followed individuals: see Supplementary Methods). For each of the 514 genes, for each of the five females, we calculated the within-individual log-fold change of the difference in gene expression levels between blood samples collected when the female was dominant versus subordinate. If multiple blood samples were collected from a given individual when she was subordinate or dominant, we randomly chose a single blood sample to represent each dominance category. Because pregnancy also may affect gene expression (Figure S3), we also required that both the 'subordinate' and 'dominant' blood samples for the same individual be matched for reproductive status: either both blood draws must have occurred when the female was pregnant ($n = 1$), or both blood draws must have occurred when the female was not pregnant ($n = 4$).

To test for enrichment of pathways and gene sets within dominance-associated genes, we conducted gene set enrichment analysis (GSEA) using the Molecular Signatures Database Hallmark Gene Sets (Liberzon et al., 2015) against the background set of all genes included in our analyses, with the p-value for enrichment estimated based on comparison to GSEA test statistics derived from permuting observed effect sizes across genes. In addition, based on prior work indicating social status-associated polarization of TLR4 signalling pathways (Cole, 2011; Lea et al., 2018; Slavich & Cole, 2013; Snyder-Mackler et al., 2016), we annotated a custom set of MyD88- and TRIF-dependent genes (Ramsey et al., 2008)

(Supplementary Methods). The MyD88 and TRIF pathways are crucial components of the mammalian innate immune response and represent alternative signalling pathways downstream of Toll-like receptor pathogen detection that stimulate NFkB-mediated and Type I interferon transcriptional cascades.

Finally, to perform a preliminary comparison of the gene expression signature of dominance status across female meerkats and nonhuman primates, we drew on previously published results from male and female baboons (Anderson et al., 2022) and female rhesus macaques (Snyder-Mackler et al., 2016). We extracted standardized effect sizes for the effect of dominance rank/social status, as reported in each original analysis, and then tested for pathway/gene set enrichment against the background set of genes analysed for the same sex-species combination. For all data sets, effect sizes are coded so that positive values correspond to genes in which expression levels are higher in dominant/higher status individuals, and vice-versa.

Statistical analyses were conducted in R (v4.1.2, R Development Core Team, 2021). All analysis code and necessary files are available at https://github.com/cryancampbell/meerkatPaper.

3 | RESULTS

3.1 | A sex-specific signature of breeding status in peripheral blood gene expression patterns

Following quality control, our final data set included RNA-seq profiles from 113 meerkats in the Kalahari study population (740 total gene expression samples from 52 females and 61 males in 15 social groups, obtained across 200 blood draws; Figure 1; Table S1; mean = 5.87 million ± 5.06 million s.d. reads; Table S2). Fifty-nine animals were dominant at the time of capture (31 females and 28 males) and 141 were subordinate at the time of capture. Forty individuals were sampled in multiple blood draws, 15 of whom are represented in our data set as both subordinates and dominants. We focus on 5 of these individuals for our longitudinal analysis below, based on the set of blood samples from females for whom both subordinate and dominant blood draws were collected in the same pregnancy state.

We observed a strong gene regulatory response to stimulation in our data set. For all three stimulants (LPS, Gard and Dex: Figure 2a), control gene expression samples separate from stimulated samples along the first and/or second principal component of variation in overall gene expression levels ($r_{\text{PC1-treatment condition}} = -.91$, $p = 7.80 \times 10^{-139}$ for LPS, $n = 6470$ genes; $r_{\text{PC2-treatment condition}} = -.78$, $p = 3.12 \times 10^{-78}$ for Gard, $n = 6381$ genes; $r_{\text{PC1-treatment condition}} = .66$, $p = 4.46 \times 10^{-48}$ and $r_{\text{PC2-treatment condition}} = .64$, $p = 2.04 \times 10^{-44}$ for Dex, $n = 6725$ genes; Figure 2b). Responses to all stimulants are highly consistent between males and females (Figure 2c; Figure S4; Table S3), and responsive genes for all three stimulants are strongly enriched in pathways related to innate immunity (e.g., TNFα signalling via NFkB, all $p_{adj} < 5 \times 10^{-4}$; inflammatory response, all $p_{adj} < 5 \times 10^{-4}$). As expected, stimulation with LPS and Gard, but not Dex, strongly increased the activity of multiple innate immune defence pathways, including IL6 signalling, interferon signalling and the pro-inflammatory response (Figure 2d).

In analyses across both sexes ('Treatment-control Models'), nesting dominance status (dominant breeder versus subordinate helper) within sex, our data suggested a strong signature of dominance in female meerkats but not male meerkats (Table S3). In support of this possibility, a subsequent analysis in females only, across all culture conditions, identified 1045 dominance status-associated genes (FDR <10%; 15% of 6932 analysed genes, Figure 3a; Table S4), compared to 0 status-associated genes in males. Dominant females tend to upregulate genes involved in the inflammatory response and NFkB signalling (TNFα signalling via NFkB, enrichment $p_{adj} < 5 \times 10^{-4}$ in the LPS challenge condition; inflammatory response, $p_{adj} < 5 \times 10^{-4}$ in the LPS challenge condition, Figure 5a) relative to subordinate female helpers. Sex differences are unlikely to result from differences in power, as our sample size for males ($n = 61$ unique males) exceeds our sample size for females ($n = 52$ unique females). Further, estimates for the dominance effect in males versus females are not well correlated (Pearson's $r = -.07$, $p = 1.20 \times 10^{-9}$, Figure S5). Our results, therefore, support highly sex-specific effects of dominance on meerkat gene regulation, consistent with previous findings in wild baboon blood cells (analogous to the sample type used here: Anderson et al. (2022), Lea et al. (2018)), cichlid brain (Burmeister et al., 2005), and mouse brain, liver and spleen (Lee, Dwortz, et al., 2022; Lee, Milewski, et al., 2022).

3.2 | Treatment condition-dependent effects of female dominance

To identify the conditions in which the dominance signature is most pronounced in females, we modelled gene expression levels as a function of dominance status in control, LPS-challenged, Gard-challenged and Dex-challenged gene expression samples separately (again controlling for body mass, age and pregnancy status; control: $n = 96$ gene expression samples and 6230 genes with log(CPM) >5; LPS: $n = 91$ gene expression samples, 6012 genes; Gard: $n = 98$ gene expression samples, 6119 genes; Dex: $n = 96$ gene expression samples, 6416 genes; Table S5). Our results indicate that the overall signature of dominance is driven by immune-challenged cells (Figure 3a). While only 4 genes are significantly associated with dominance in the control condition (10% FDR) and no dominance-associated genes are detectable in the Dex-challenged condition, 47 genes and 709 genes are dominance-associated in the Gard and LPS conditions, respectively. Consequently, many dominance-associated genes are only detectable in the LPS and, to a lesser degree, in Gard data sets (Figure 3c,d). We caution against a direct comparison between challenge conditions here, however, as we only examined a single dosage and incubation time for each stimulant.

The significant effect of dominance in the Gard and LPS conditions suggests that stimulation of the pro-inflammatory innate

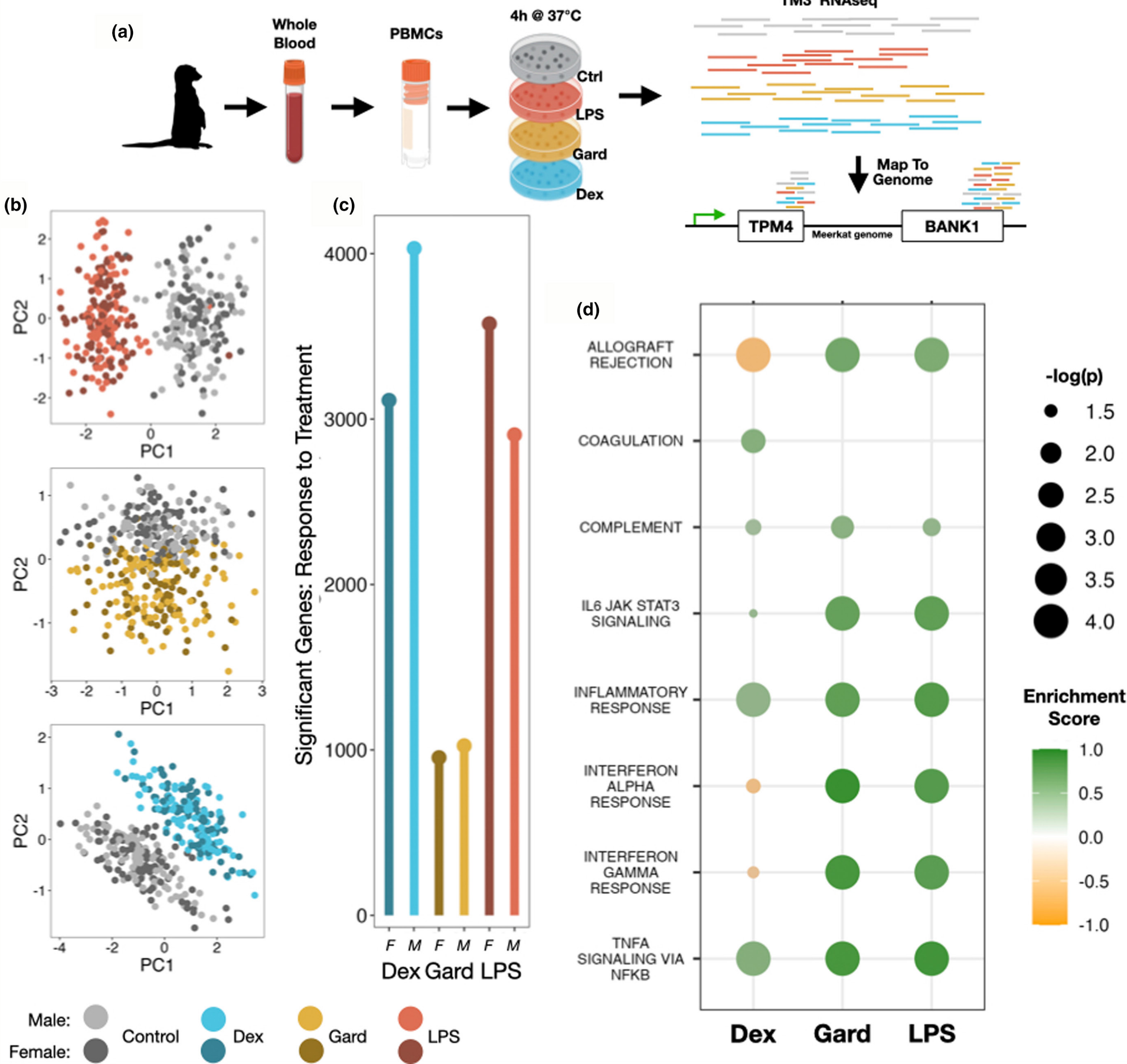

FIGURE 2 Strong gene expression responses to ex vivo stimulation in meerkat PBMCs. (a) PBMCs were purified from blood samples obtained during each capture, aliquoted into wells with culture media and cultured for 4 h at 37°C under control, LPS-challenged, Gard-challenged, or Dex-challenged conditions. TM-3′seq libraries were prepared from each capture-culture condition combination. (b) The top principal components of the gene expression data separate each treatment condition (LPS, Gard and Dex) from the control condition, in both sexes, as supported by (c) the large number of genes that show a significant response to stimulation (relative to the control condition) for all three conditions, in both males and females. Dark shades = females; light shades = males. (d) Strong enrichment for genes involved in innate immunity among treatment-responsive genes, especially for LPS and Gard-responsive genes. Circle size is scaled by *p*-value for enrichment (all plotted points are significant at a nominal $p < .05$) and colour represents the enrichment score: Green circles are more highly expressed in the treatment condition and orange circles are more highly expressed in the control condition.

immune response may magnify differences between dominant and subordinate meerkats (glucocorticoid stimulation may also attenuate them, although the evidence here is less clear: Figure S6). In support of this possibility, dominance status also significantly predicts the *magnitude* of the gene regulatory response to LPS (i.e., the fold-change difference between LPS-challenged and control gene expression samples for the same individual) for 26 genes (10% FDR, Table S6). These genes include endothelin-1 (*EDN1*, Figure 3f), which is a key component of wound healing and inflammation (Khimji & Rockey, 2010); COMM Domain-containing genes *COMMD1* and *COMMD5* (Figure 3g), which regulate the transcription factor NF-κB (Maine & Burstein, 2007); and the protein kinase *AKT1* (Figure 3h) which regulates the response of macrophages to LPS (Androulidaki et al., 2009).

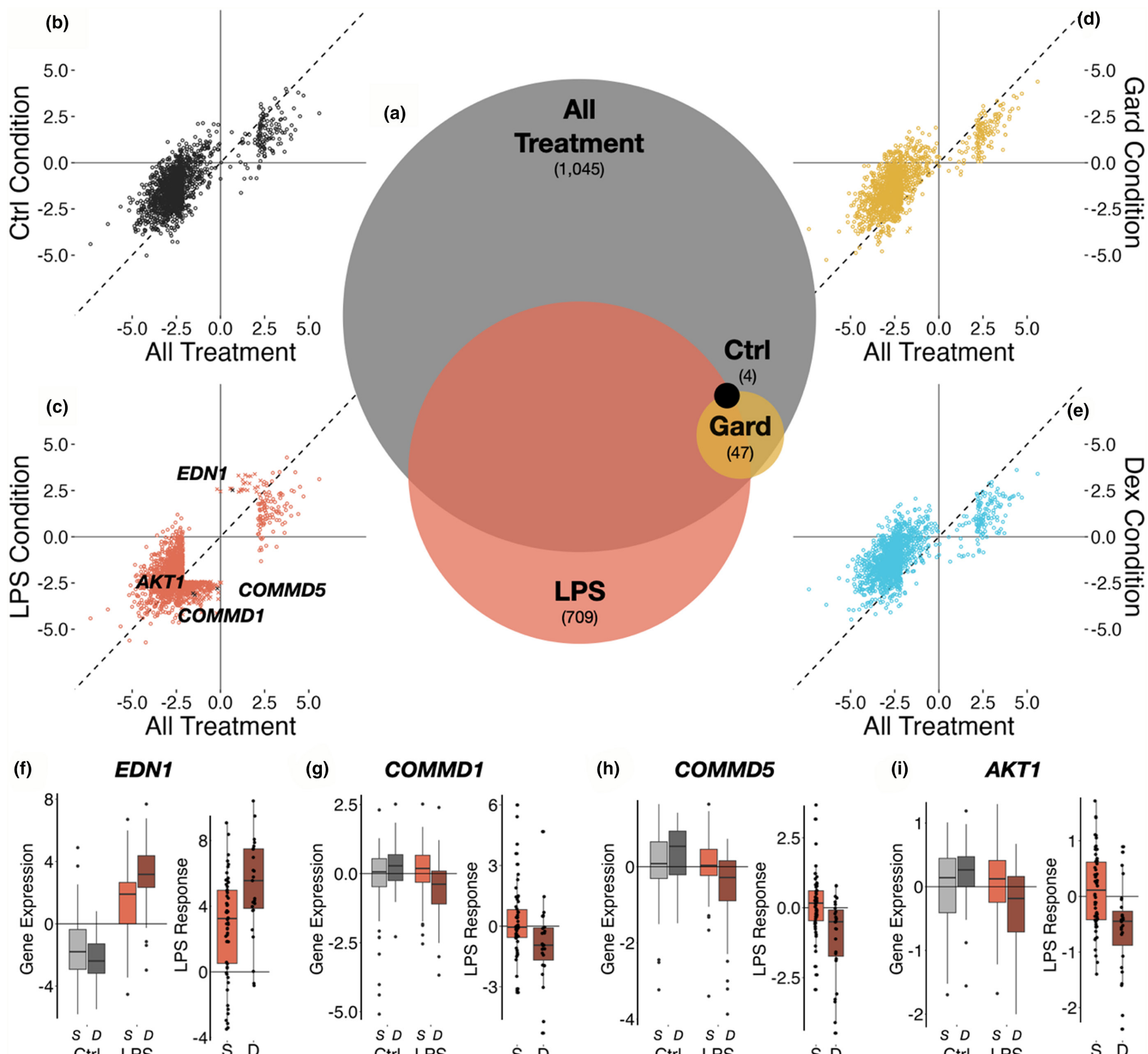

FIGURE 3 The gene expression signature of dominance status in female meerkats. (a) Venn diagram of status-associated genes (FDR <0.10) across each condition-specific model in females, relative to a model including data from all conditions. Dex is not shown because no genes pass a 10% FDR cut-off in the Dex-specific model. (b–e) Scatterplot of standardized effect sizes for dominance status in a model including data from single treatment conditions (*y*-axis; b: Control; c: LPS; d: Gard; e: Dex) versus all data (*x*-axis). Genes that are only detectably status-associated in a given condition are plotted with an 'x;' the remaining dots correspond to the union set of all genes identified as status-associated in any condition or the model including all data. (f–i) Gene expression levels for subordinate (S) and dominant (D) female meerkats in the control condition versus the LPS condition for four immune-related genes (left plot for each panel) in which the response to LPS stimulation systematically differs by social status. Variation in the within-individual response to LPS (i.e., using paired samples) is shown in the right-hand plot for each panel. The difference in response was modelled as an effect of dominance status on within-individual log-foldchange in gene expression after stimulation (EDN1: $q = 4.0 \times 10^{-2}$; COMMD1: $q = 4.7 \times 10^{-2}$; COMMD5: $q = 4.7 \times 10^{-2}$; AKT1: $q = 4.7 \times 10^{-2}$).

3.3 | Validation of dominance status-related gene expression in longitudinal blood samples

If females differ in PBMC gene expression because of their dominance status, then females who were sampled first as subordinates and later as dominants should show shifts in gene expression levels that are congruent with our findings above. To test this prediction, we focused on five females who were sampled longitudinally across a transition to dominance. As a control for technical effects of sampling and/or ecological and demographic differences across the elapsed time between blood draws, we also compared longitudinal differences in gene expression for five matched subordinate females

sampled at the same time (±1 day), but who did *not* undergo a transition (i.e., remained subordinate throughout the same period).

For the 514 gene-condition combinations we identified as status-associated in the cross-sectional analysis (this number reflects a reduction in power after removing samples from the longitudinally sampled females; FDR < 10%; 489 unique genes, as 25 genes were dominance-associated in multiple conditions), 454 (88%) exhibited directionally consistent changes in mean expression levels across the dominance transition (Table S7). In other words, genes that were more highly expressed in dominant animals in the cross-sectional analysis also were more highly expressed in females that transitioned to dominant breeder status during the study, relative to the same females when they were subordinates. In comparison, in the control (matched blood draw date) set, significantly fewer genes (60%) exhibited directionally consistent shifts (two-sample proportion test, $p = 5.5 \times 10^{-24}$). Further, 95 of the 454 directionally consistent genes (21%) also exhibited large enough shifts to be identified as significant within-individual changes ($p < .05$, paired *t*-test) and the dominance status effect size in the cross-sectional analysis is strongly correlated with the *t*-statistic from the longitudinal blood draws (Pearson $r = .494$, $p = 6.88 \times 10^{-33}$; Figure 4a). In the control set, only 17 (4%) of the same genes showed significant within-individual changes, consistent with the expected number of false positives across 454 tests ($p < .05$, paired *t*-test). In addition, while there is a significant correlation between the dominance effect size from the cross-sectional analysis and the longitudinal blood sample *t*-statistic in the control set, it is much weaker than for females who transitioned to a dominant role (Pearson $r = .133$, $p = 2.42 \times 10^{-3}$; Figure 4b).

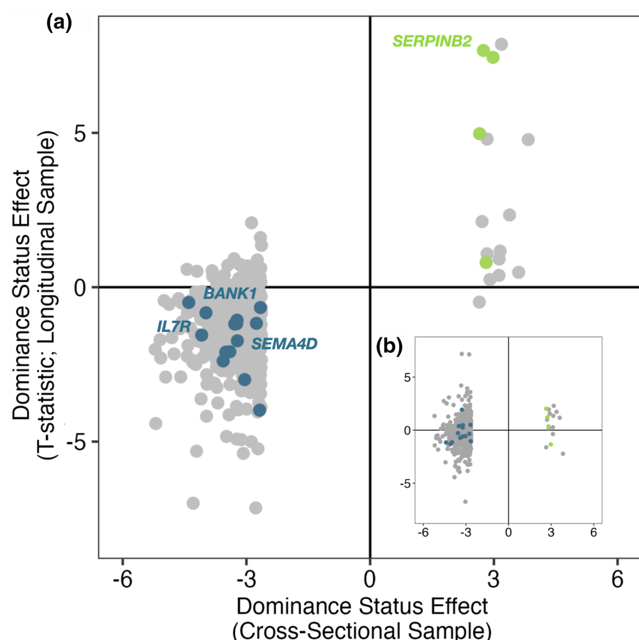

FIGURE 4 Status effects estimated from cross-sectional data are congruent with changes in gene expression in longitudinal transitions from subordinate to dominant. (a) Standardized effect size of dominance status in females from cross-sectional analysis (*x*-axis: Data from the LPS condition, where status effects are most apparent, are shown, based on analyses where only one sample was included from each set of longitudinal blood draws) are positively correlated with paired *t*-statistic values for the difference in gene expression between female meerkats when they transitioned from subordinate to dominant status (*y*-axis). Highlighted genes are members of key innate immune function gene sets enriched among status-associated genes. (b) This strong positive correlation is not observed when calculating the parallel *t*-statistics for control meerkats for whom blood draws occurred at the same time (*x* and *y* axes are as in a).

3.4 | Cell composition and demographic correlates of female dominance do not explain the gene expression signature of breeding status

Dominant female meerkats are distinct from subordinate females in several key respects that do not define dominance per se. Dominant females tend to be heavier (this study: dominant mean = 709.1 g ± 89.2 s.d.; subordinate mean = 626.5 g ± 81.6 s.d., Figure S1) and older (dominant mean = 3.13 years ± 1.54 s.d.; subordinate mean = 1.61 years ± 0.60 s.d., Figure S1; see also Clutton-Brock et al. (2006); Kutsukake and Clutton-Brock (2005)). They are also more likely to be sampled when pregnant: 9 of 15 captures of pregnant females were dominants. Further, only one of the pregnancies from subordinate captures resulted in live offspring, compared to 7 of 9 in dominants. In addition to controlling for pregnancy, body mass and age in our main model, post hoc analyses showed that regressing out each of these variables from the gene expression data did not alter our findings for dominance status (*r* for dominance effect betas in the original model versus after first removing body mass, pregnancy and age effects >.99, Figure S7).

Another possibility is that dominant and subordinate females differ in the composition of their peripheral blood mononuclear cells: that is, the signature of dominance is primarily a signature of compositional differences in the peripheral blood. We estimated the composition of B cells, T cells and monocytes in our sample based on the gene expression deconvolution method implemented in CIBERSORT (Newman et al., 2015, see Supplementary Methods). We found that dominant females tend to have slightly lower estimated fractions of T cells (*t*-test *T* statistic = 2.09, $p = .04$) and somewhat higher estimated fractions of B cells ($T = -2.25$, $p = .03$). However, including the T cell and B cell estimates in our differential expression models did not quantitatively alter our findings for social status (Figure S8, Pearson *r*, status effect sizes with and without T cell and B cell estimates, $r = .98$–$.99$, $p < .001$ across four challenge datasets). Further, while marker genes for T cells and B cells are enriched among genes that are associated with social status in female meerkats (FET adjusted $p_{Tcell} = 5.08 \times 10^{-7}$; $p_{Bcell} = 1.7 \times 10^{-3}$), genes in these marker sets (i.e., those for which high expression is a marker of a given cell type) are not more likely to be systematically upregulated or downregulated with dominant status (FET adjusted $p_{Tcell} = 1$; $p_{earlyBcell} = 1$; $p_{lateBcell} = 1$). Consequently, while we cannot rule out a contribution of

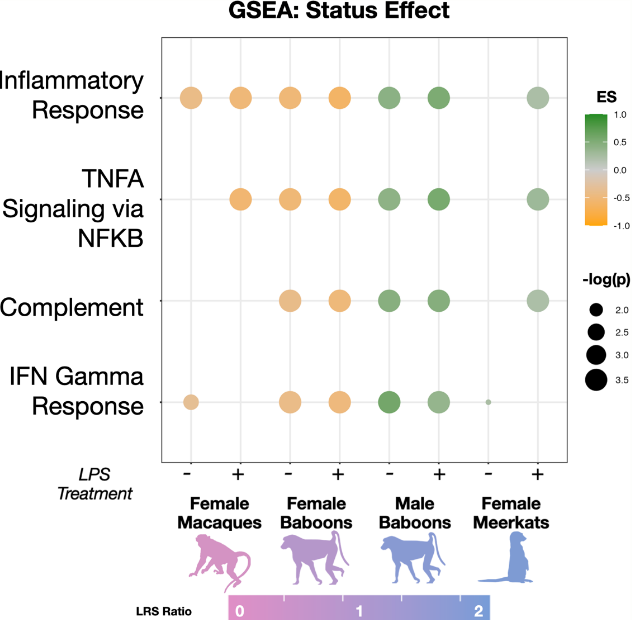

FIGURE 5 The gene regulatory signature of dominance in three social mammals. Gene set enrichment for immune pathways significantly enriched for dominance status effects in female meerkats (adjusted *p*-value <.05), across data sets. Green colours show pathways enriched among genes more highly expressed in high-status individuals; orange colours show pathways enriched among genes more highly expressed in low-status individuals. *p*-values are adjusted using Bonferroni correction based on running 27 total tests (all Hallmark gene sets in the immune, signalling and pathways categories). One possible explanation for this difference relates to the intensity of investment in reproduction: Colours for the silhouettes correspond to a bias towards a greater reproductive skew in the focal sex than the opposite sex (purple), or a greater reproductive skew in the opposite sex than the focal sex (pink), based on estimates in Lukas and Clutton-Brock (2014).

status-related differences in cell composition to our results, they do not appear to make a major contribution to the signature of social status in our sample.

3.5 | A preliminary analysis of social status and gene regulation in social mammals

Gene expression signatures of social status in comparable control and LPS-challenged conditions and cell types have been generated for two other social mammals: wild baboons (male and female, Anderson et al. (2022)) and captive female rhesus macaques (*Macaca mulatta*: Snyder-Mackler et al. (2016)). In both of these cases, as for female meerkats, genes associated with social status are enriched in innate immune pathways (Figure 5, Table S8). However, the signature of social status in meerkat females more closely resembles the pattern for baboon males than the pattern in either female-centred data set (Figure 5). Specifically, like high-ranking male baboons, high-status female meerkats tend to upregulate genes involved in TNFA signalling via NFkB and the interferon-gamma response. In contrast, genes in the same pathways tend to be downregulated in high-ranking female macaques and female baboons (Table S8). Consequently, the gene-level effect sizes of dominance status are positively correlated between female meerkats and male baboons for genes involved in the inflammatory response, in an LPS-stimulated condition (Pearson $r=.261$, $p=1.72\times10^{-2}$). Further, genes significantly associated with both dominance in female meerkats and dominance rank in male baboons tend to be directionally concordant (FET $p=3.26\times10^{-5}$; the odds ratio cannot be calculated because no genes are dominance-associated in both cases and directionally discordant). Finally, in support of the possibility that polarized TLR4 signalling after LPS challenge may be a hallmark of social status-related signatures, MyD88-dependent genes are strongly enriched among genes that are expressed more highly in dominant meerkat females (FET $\log2(OR)=3.42$, $p=4.75\times10^{-3}$), a resemblance shared with male, but not female, baboons.

4 | DISCUSSION

Our results demonstrate a strong signature of social status in immune cell gene expression in wild meerkats. This pattern extends previous findings in primates, in two species where males compete more intensely than females (Anderson et al., 2022; Lea et al., 2018; Snyder-Mackler et al., 2016), to a cooperatively breeding carnivore in which females compete more intensely than males (Clutton-Brock et al., 2001, 2006; Clutton-Brock & Manser, 2016). Despite the substantial evolutionary distance between carnivores and primates, several of the same pathways are associated with social status across lineages. These results suggest that a core set of genes is sensitive to differences in dominance status in the peripheral blood of social mammals—a finding consistent with the use of core gene expression modules in the brains of dominant fish (Renn et al., 2016).

However, we also observe substantial differences by sex. Dominant female meerkats exhibit increased expression of innate immune defence genes and polarize the expression of genes in the TLR4 response pathway towards an NFkB-mediated pro-inflammatory response. In contrast, we detected no measurable gene expression signature of dominance in meerkat males. Unlike in female meerkats, body mass does not predict the likelihood that male meerkats will attain dominant breeding status. Instead, group size and composition are the primary predictors of reproductive success (Spong et al., 2008). Dominance in male meerkats is also not regularly reinforced by targeted harassment of subordinates, a common feature of nonhuman primate hierarchies. Instead, subordinate meerkat males voluntarily seek out reproductive opportunities outside their natal groups and are seldom evicted (Stephens et al., 2005). The lack of strongly rank-structured physical competition and received aggression (as well as evidence that dominant and helper males are undifferentiated by testosterone levels) may explain why they are also undifferentiable from the perspective of gene expression. In cooperatively breeding wolves, where aggression from breeding animals to subordinates is similarly rare, gene expression signatures of dominance are also undetectable (Charruau et al., 2016).

In females, our preliminary analyses indicate that the dominance status signature in meerkats more closely resembles that observed in male baboons than in other mammalian females (Figure 5). This observation argues that previously reported differences between male and female primates are not a consequence of sex per se, but instead arise due to other facets of social status that can vary by sex-species combination. We speculate that one important correlate may be related to sex biases in reproductive skew, which is higher in male baboons and rhesus macaques than in females, but higher for female meerkats than male meerkats (Figure 5a; Alberts et al., 2006; Hodge et al., 2008; Lukas & Clutton-Brock, 2014; Spong et al., 2008; Widdig et al., 2004; Widdig et al., 2016). However, despite convergence at the gene expression level, the explanation for high skew in female meerkats differs from that in male baboons: whereas in female meerkats, skew is achieved through a combination of long tenure for dominants and a high rate of pup production (Hodge et al., 2008), male-biased skew in baboons is achieved through monopolizing mating opportunities with multiple females, typically over a shorter period of time (Alberts et al., 2003). Testing the hypothesis that sex differences in reproductive skew predict sex differences in the gene expression signatures of dominance status—a comparison that will require systematic exploration in an expanded set of species—will therefore also help disentangle the effects of physical competition during rank attainment and maintenance from energetic investment in reproduction itself.

The present study leaves the proximate drivers and consequences of social status-associated gene expression differences unclear. Our analyses suggest that these consequences cannot be easily explained by differences in body mass, age, pregnancy status, or cell-type composition (although compositional effects could occur at more granular levels of cell classifications than we were able to achieve here). A candidate behavioural mechanism is the rate of aggressive behaviour, which mediates status-related variation in glucocorticoid levels in male chimpanzees (Muller et al., 2021) and social gradients in gene expression in captive rhesus macaques (Simons et al. (2022); but see Lea et al. (2018) in male baboons). Denser behavioural data or targeted sampling during subordinate evictions will be needed to test whether a similar phenomenon applies in female meerkats. At a physiological level, steroid hormones may also play an important role, as both glucocorticoid and testosterone levels are higher in breeding female meerkats than in subordinate females in this population (Barrette et al., 2012; Davies et al., 2016; Drea & Davies, 2022). Upon activation by hormone binding, glucocorticoid receptor and androgen receptor translocate into cell nuclei to remodel gene expression. Notably, experimental manipulations of both androgen levels and glucocorticoid levels have been successfully conducted in wild meerkats, with consequences for cooperative and dominance-related behaviours (Dantzer, Goncalves, et al., 2017; Drea & Davies, 2022). The meerkat system thus has the potential to reveal how social status, endocrine function and immune gene regulation are causally linked in a natural social mammal population, as a model for the social determinants of health and fitness more broadly.

Finally, the specific signature of dominance we observe in female meerkats points to elevated activity of inflammation-related pathways, a pattern that has been identified as a conserved hallmark of aging (López-Otín et al., 2013). On the face of it, our results contradict the observation that dominant female meerkats in the Kalahari population live longer than subordinate female helpers (Clutton-Brock et al., 2001). However, the greater longevity of dominant females, compared to subordinate females, is likely explained by increased extrinsic mortality risk to subordinates, who can be evicted and forced to spend more time separated from their social group in unfamiliar areas (Cram et al., 2018). Indeed, longitudinal blood sampling reveals that dominant female meerkats exhibit *faster* rates of telomere attrition, a biomarker of cellular senescence, than subordinates, despite their longer lifespans (Cram et al., 2017; Maag et al., 2022). Combined with our findings here, the emerging picture suggests that dominant meerkat females do experience physiological costs as a result of their repeated investment in reproduction, despite their longer mean lifespans (Thorley et al., 2020). Taken together, our results thus show that while studies of life history and demography alone have revealed examples of these trade-offs at an organismal level (e.g., Bauch et al., 2013; Fairlie et al., 2016; Lemaitre et al., 2014; Nussey et al., 2008; Sharp & Clutton-Brock, 2011), physiological and molecular analyses can contribute to a more complete picture.

AUTHOR CONTRIBUTIONS

CRC, LB, TCB and JT conceived and designed the study. KW, MS, LB, TCB, MM and JT collected data. CRC processed data and performed analyses. TCB, MM, LB and JT provided data and resources, provided supervision and oversight and acquired funding. CRC and JT wrote the manuscript with edits and revisions from all authors.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts.

DATA AVAILABILITY STATEMENT

The raw reads generated in this study and a matrix of gene counts are available in the NCBI Gene Expression Omnibus (GEO) repository, GSE247525. Other data sets used in this study are contained within the article supplementary data files and analysis code is available at https://github.com/cryancampbell/meerkatPaper.

ETHICS STATEMENT

Ethical and sample collection clearance for this project was granted by the Northern Cape Province Department of Environment and Nature Conservation of South Africa (FAUNA 0930/2022 and FAUNA 1020/2016) and the Animal Ethics Committee of the University of Pretoria (EC047-16 and NAS003/2022). All research followed the standards outlined in the ASAB/ABS (2012) Guidelines for the Treatment of Animals in Behavioural Research and Teaching.

BENEFIT-SHARING STATEMENT

Benefits from this research accrue from the sharing of our data and results on public database repositories.

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SUPPORTING INFORMATION

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