IMMUNITY

The naked mole rat's unique innate immunity

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While the natural lifespan of the average mouse, *Mus musculus*, lasts only a few short years, that of its similarly sized relative, the naked mole rat, *Heterocephalus glaber*, can stretch upwards of three decades. Whereas most long-lived animals—humans included—will experience various age-related declines in health and increased mortality as they get older, naked mole rats seem to thrive 'til the very end. The blind, hairless, subterranean-dwelling animals found in eastern Africa are also notably resistant to cancer.

How naked mole rats live so long and with so few ill effects as they enter their golden years is of interest to researchers who want to better understand the aging process. A new paper published in *PLoS Biology* by researchers at Calico Life Sciences, a San Francisco-based biotech firm focused on aging, explores the animals' immune system and finds an alternative means by which naked mole rats achieve innate immunity, compared to what's typical of other mammals.

Relative to the other rodents that are mainstays of the basic and preclinical world, research with such 'non-model' organisms as naked mole rats can be hindered by a lack of species-specific reagents that are commonly needed to investigate the different components of the animals' immune system. Such resources aren't widely available and often need to be made from scratch. Instead, the Calico researchers created a molecular profile of the naked mole rat immune system with single-cell RNA sequencing.

The team sampled spleens—an organ typically replete with cells important to an organism's immune system—from naked mole rats and from C57BL/6 mice and compared the genes expressed in each species. Differences in cellular composition were apparent in the single-cell sequencing results, and in follow-up comparative histomorphological and *in situ* hybridization analyses.

Whereas mouse spleens were dominated by lymphoid cells, these lineages, which include B cells, T cells, and Natural Killer cells, made up less than half of the splenic immune cell population in the naked mole rat; rather, myeloid cells were more prominent. Lymphoid-derived Natural Killer cells were lacking entirely, despite the team's best efforts to find them. To check that the absence wasn't a technical artifact of the team's single-cell

Looking in on the immune secrets of the naked mole rat, *Heterocephalus glaber*. Credit: dpa picture alliance / Alamy Stock Photo

sequencing workflow, they performed RNA sequencing on whole naked mole rat spleens, as well as additional single cell sequencing of blood samples to confirm the result wasn't a spleen-specific quirk. No evidence of Natural Killer cells was to be found.

Looking for an evolutionary explanation, the team compared 45 additional mammalian genomes, including several other rodent suborders. This comparison revealed that the naked mole rats lack genes that normally control the production of Natural Killer cells in other mammals.

Natural Killer cells are a component of the innate immune system and a first line of defense in fighting off infections—particularly viral challenges, to which naked mole rats are in fact particularly susceptible. Living underground though, they likely encounter more bacteria than viruses. How then does the naked mole rat achieve the immune surveillance necessary to stay healthy? Upon lipopolysaccharide (LPS) administration—a means to mimic acute bacterial infection—the immune system of the Natural Killer-less naked mole rats instead increased the transcription of neutrophils, relative to saline controls and mice that

received the LPS challenge. Neutrophils are white blood cells with a role in both innate and adaptive immunity that are derived from myeloid cells—a lineage found in abundance in the naked mole rat transcriptome.

These results suggest that naked mole rats, lacking the means to make canonical Natural Killer cells, have evolved an alternative approach to stay healthy in the face of immune challenges. The authors posit that this could be the result of their environment, suggesting that because the animals live underground with limited exposure to airborne viral challenges their immune system may have instead evolved in response to stronger bacterial pressures and subsequent reliance on myeloid-based innate immunity.

These results don't yet explain the naked mole rat's remarkable life- and health-span, but they do add to the growing list of unique features found in these animals that warrant additional investigation.

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