INSIDE JEB

Alpha haemoglobin helps high-altitude deer mice breathe more deeply

A juvenile deer mouse (*Peromyscus maniculatus*). Photo credit: Catherine Ivy.

No self-respecting crime drama would be the same without a liberal sprinkling of blood. Yet, the haemoglobin that gives blood its distinctive shade has a perfectly mundane role, transporting oxygen around the body and returning CO_2 to the lungs. The haemoglobin of animals, such as deer mice (*Peromyscus maniculatus*), that live at high altitude is also specially adapted to pick up oxygen when the air is much thinner than that experienced by species nearer to sea level. But Catherine Ivy from McMaster University, Canada, explains that simply breathing more deeply can also increase the amount of oxygen getting into an animal's body when the air pressure falls: high-altitude deer mice breathe more slowly and deeply than lowland mice. There were also hints that members of the haemoglobin family of proteins that occur in other parts of the body, such as the nervous system, might be able to control how an animal breathes. Could the specialised haemoglobin that allows high-altitude deer mice to carry sufficient oxygen also help the animals breathe more deeply?

Ivy and Graham Scott (McMaster University) decided to find out, so they enlisted the help of Zachary Cheviron (University of Montana, USA) and Jay Storz (University of Nebraska, USA) to breed mice that carried specific combinations of the high- and low-altitude haemoglobins, to check how the proteins affected the animals' breathing. The team, including colleagues from Canada and the USA, collected deer mice from Mount Evans, CO, USA, living at 4350 m, and from Nine Mile Prairie, NB, USA, living at 430 m, before transporting the animals to Cheviron's lab at 978 m in Montana. There, Rena Schweizer, Jonathan Velotta and Shane Campbell-Staton allowed a high-altitude male to have a family with a low-altitude female and those offspring to interbreed before Natalie Gutierrez-Pinto and Chandrasekhar Natarajan (both from University of Nebraska) checked the youngsters' DNA to be certain which combinations of the high- and low-altitude haemoglobins they carried.

Once the mice were a year old, they joined Ivy at McMaster University, where they remained at an altitude of 50 m for 8 weeks before she recorded their breathing as she lowered the air pressure, to simulate the animals climbing in altitude. Then, she transferred the mice to a pressure chamber where she could simulate life at 4300 m and rechecked their breathing after 8 weeks.

Sure enough, as the air grew thinner, all of the mice breathed more to compensate for the effective lack of oxygen. However, when Ivy compared the haemoglobin combinations that the mice had inherited with their breathing patterns, it was clear that the animals that had inherited two high-altitude forms of the alpha chain component of haemoglobin were taking particularly slow and deep breaths. In contrast, the mice that only inherited low-altitude versions of the alpha haemoglobin chain breathed more shallowly. And when Ivy compared the breathing patterns of the specially bred mice with the patterns of mice that had arrived directly from the mountains, they were essentially indistinguishable. Having high-altitude versions of the haemoglobin α chain seems to be key to regulating how deer mice breathe.

'Our findings are against the dogma that globins don't affect breathing', says Ivy, and she is keen to find out whether the red blood cells, or some other tissue, are the source of the haemoglobin α chain that seems to be crucial to the mountain deer mouse's laid-back breathing style.

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Ivy, C. M., Wearing, O. H., Natarajan, C., Schweizer, R. M., Gutiérrez-Pinto, N., Velotta, J. P., Campbell-Staton, S. C., Petersen, E. E., Fago, A., Cheviron, Z. A., Storz, J. F. and Scott, G. R. (2022). Genetic variation in haemoglobin is associated with evolved changes in breathing in high-altitude deer mice. *J. Exp. Biol.* **225**, jeb243595. doi:10.1242/jeb.243595.

Kathryn Knight
kathryn.knight@biologists.com