In 1925, Dr Carlos Monge presented to the National Academy of Medicine in Lima, Peru, his observations of a new disease. His patient had bluish skin, dizziness, and confusion when working at high altitudes, but symptoms were ameliorated once the patient returned to the coast. In a storied and impactful career, Monge went on to study the physiological differences between sufferers of Monge’s disease, those who were able to acclimatize to the altitude, and finally those who thrived in the low oxygen conditions. Today, we now know this condition as chronic mountain sickness (CMS). Caused by exposure to low oxygen conditions, CMS affects a significant proportion of high-altitude populations and can lead to pulmonary hypertension, cardiac hypertrophy, and eventual heart failure.

See Article by Zarndt and Walls et al

Today, CMS still afflicts a large number of individuals, including a striking one sixth of residents of Cerro de Pasco in Peru, designating CMS as a significant medical challenge in many high-altitude populations. Understanding the mechanisms by which hypertension and cardiac hypertrophy occur as a result of hypoxia is important not only for those living at high altitudes but also for the much larger population of people experiencing chronic pulmonary diseases which cause local hypoxia and that also result in cardiac hypertrophy and similar symptoms.

In this issue, the collaborative groups of Zarndt et al investigate the cardiac specific molecular and genetic processes responsible for the 3 different physiological responses that Monge investigated, using the genetically amenable Drosophila system. In their study, 2 treatments were used: chronic hypoxia–treated flies, which were raised for 3 weeks at 4% O₂, or hypoxia-selected flies, which were selected for survival in 4% O₂ over >250 generations. The authors found differential cardiac performance for both treatments, such as an increased heart period compared with controls, and a differential gene expression profile depending on genotype and treatment. In addition, overall heart size was reduced in the hypoxia-selected flies, although in other instances hypoxia did not affect heart size. Although these studies underlined how different genetic backgrounds can significantly impact cardiac performance and growth, 2 genes that showed similarly reduced expression profiles in the 2 hypoxic treatments were very familiar: the Calcineurin A genes CanA14F and Pp2B.

We are rapidly approaching the 20-year anniversary of the seminal discoveries that a calcium/calmodulin-dependent mechanism of murine cardiac hypertrophy occurs through Calcineurin signaling and that blocking Calcineurin activity can attenuate pathological hypertrophy. Numerous subsequent studies have investigated this process and importantly demonstrated a further requirement for Calcineurin activity in postnatal cardiac growth. The unbiased approach offered by the Drosophila model system suggested a common role for Calcineurin signaling in cardiac growth and prompted the authors to focus on these 2 genes.

Back with the fly model, because CanA14F and Pp2B were both downregulated in chronic hypoxia and hypoxia-selected flies, and given the role of Calcineurin signaling in promoting cardiac growth, the investigators hypothesized that heart-specific knockdown of one or both of these Calcineurin A subunit genes would cause a reduction in heart size under normal and hypoxic conditions. Indeed, heart size was reduced in both knockdowns. Further, knockdown of Pp2B under hypoxic conditions resulted in lethality, indicating that combination of these treatments can sufficiently abrogate heart function to prevent survival. The authors also attempted to use chronic hypoxia to attenuate cardiac growth when overexpressing Calcineurin. Whereas overexpression of Calcineurin can result in cardiac hypertrophy under normal conditions in flies, when combined with chronic hypoxia the flies died. This finding suggests that a careful balance of pro- and anti-growth signaling is necessary for correct cardiac development or function.

Overall, Zarndt et al have developed a powerful model for investigating the molecular effects of hypoxia on heart structure and function and importantly demonstrated that Calcineurin signaling has a conserved role in regulating heart size. The combination of heart-specific changes in gene expression with potentially lethal phenotypes also raises the feasibility of carrying out genetic screens to investigate further the molecular events occurring during hypoxia. As with any valuable study, the research also leads to many questions. First, how does the genetic background cause differential responses to hypoxia? Understanding why some genotypes but not others show changes in heart size after hypoxia can lead to the identification of genes associated with resistance to hypoxia, as observed with some human populations.
Second, although a reduced heart size resulting from reduction in Calcineurin expression matches precisely the role of Calcineurin signaling in mammalian heart growth, why does the Drosophila heart not show hypertrophy under hypoxic conditions? This is presumably because of differences in the physiology of the organisms, where CMS arises from increased resistance to blood flow, but such a change in circulation probably does not occur in flies.

Finally, what are the molecular mechanisms by which Calcineurin subunit expression is reduced during hypoxia? If we can understand why Calcineurin expression levels go down in flies after hypoxia, perhaps this same mechanism can be exploited to understand the cause and treatment of CMS.

Sources of Funding

Dr Lovato is supported by a Pilot Project Program award from the Department of Biology’s Center for Evolutionary and Theoretical and Immunology, supported by National Institutes of Health (NIH) grant P20 GM103452 from the Institute Development Award Program of the National Institute of General Medical Sciences (NIGMS). Dr Cripps is supported by R01 GM061738 from the NIH/NIGMS.

Disclosures
None.

References

1. West JB. High Life: A History of High-Altitude Physiology and Medicine. New York, NY: Springer; 1998.
2. Monge C. Life in the Andes and chronic mountain sickness. Science. 1942;95:79–84. doi: 10.1126/science.95.2456.79.
3. León-Velarde F, Villafuerte FC, Richelet JP. Chronic mountain sickness and the heart. Prog Cardiovasc Dis. 2010;52:540–549. doi: 10.1016/j.pcd.2010.02.012.
4. Sahota IS, Punwar NS. Prevalence of chronic mountain sickness in high altitude districts of Himachal Pradesh. Indian J Occup Environ Med. 2013;17:94–100. doi: 10.4103/0019-5278.130839.
5. Zarndt R, Walls SM, Ocor K, Bodmer R. Reduced cardiac Calcineurin expression mimics long-term hypoxia-induced heart defects in Drosophila. Circ Cardiovasc Genet. 2017;10:e001706. doi: 10.1161/CCIRCGENETICS.117.001706.
6. Molkentin JD, Lu JR, Antos CL, Markham B, Richardson J, Robbins J, et al. A Calcineurin-dependent transcriptional pathway for cardiac hypertrophy. Cell. 1998;93:215–228.
7. Sussman MA, Lim HW, Gude N, Taigen T, Olson EN, Robbins J, et al. Prevention of cardiac hypertrophy in mice by Calcineurin inhibition. Science. 1998;281:1690–1693.
8. Bueno OF, Wilkins BJ, Tymitz KM, Glascok BJ, Kimball TF, Lorenz JN, et al. Impaired cardiac hypertrophic response in Calcineurin Abeta-deficient mice. Proc Natl Acad Sci USA. 2002;99:4586–4591. doi: 10.1073/pnas.072647999.
9. Schaeffer PJ, Desantiago J, Yang J, Flagg TP, Kovacs A, Weinheimer CJ, et al. Impaired contractile function and calcium handling in hearts of cardiac-specific Calcineurin b1-deficient mice. Am J Physiol Heart Circ Physiol. 2009;297:H1263–H1273. doi: 10.1152/ajpheart.00152.2009.
10. Lee TE, Yu L, Wolf MJ, Rockman HA. Galactokinase is a novel modifier of Calcineurin-induced cardiomyopathy in Drosophila. Genetics. 2014;198:591–603. doi: 10.1534/genetics.114.166777.
11. Lorenzo FR, Huff C, Myllymäki M, Olenchock B, Swierczek S, Tashi T, et al. A genetic mechanism for Tibetan high-altitude adaptation. Nat Genet. 2014;46:951–956. doi: 10.1038/ng.3067.
12. Udpa N, Ronen R, Zhou D, Liang J, Stobdan T, Appenzeller O, et al. Whole genome sequencing of Ethiopian highlanders reveals conserved hypoxia tolerance genes. Genome Biol. 2014;15:R36. doi: 10.1186/gb-2014-15-2-r36.

Key Words: Editorials ◼ Calcineurin ◼ Drosophila ◼ heart failure ◼ hypoxia ◼ oxygen