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High Heart: A Role for Calcineurin Signaling in Hypoxia-Influenced Cardiac Growth

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In 1925, Dr. Carlos Monge presented to the National Academy of Medicine in Lima, Peru, his observations of a new disease. His patient suffered from blueish skin, dizziness and confusion when working at high altitudes, but symptoms were ameliorated once the patient returned to the coast[1]. In a storied and impactful career, Monge went on to study the physiological differences between sufferers of Monge's Disease, those that were able to acclimatize to the altitude, and finally those that thrived in the low oxygen conditions[2]. 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[3].

Today, CMS still afflicts a large number of individuals, including a striking one-sixth of residents of Cerro de Pasco in Peru[4], 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 suffering from chronic pulmonary diseases which cause local hypoxia and that also result in cardiac hypertrophy and similar symptoms.

In this issue, the collaborative groups of Dr. Rolf Bodmer and Dr. Karen Ocorr investigate the cardiac specific molecular and genetic processes responsible for the three different physiological responses that Monge investigated, using the genetically amenable Drosophila system[5]. In their study, two treatments were utilized: chronic hypoxia (CH) treated flies,

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which were raised for 3 weeks at 4% O_2; or hypoxia–selected (HS) flies, which were selected for survival in 4% O_2 over more than 250 generations. The authors found differential cardiac performance for both treatments, such as an increased heart period compared to controls, and a differential gene expression profile depending upon genotype and treatment. In addition, overall heart size was reduced in the HS flies, although in other instances hypoxia did not affect heart size. While these studies underlined how different genetic backgrounds can significantly impact cardiac performance and growth, two genes that showed similarly reduced expression profiles in the two 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[6], and that blocking Calcineurin activity can attenuate pathological hypertrophy[7]. Numerous subsequent studies have investigated this process, and importantly demonstrated a further requirement for Calcineurin activity in postnatal cardiac growth[8,9]. 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 upon these two genes.

Back with the fly model, since *CanA14F* and *Pp2B* were both down-regulated in CH and HS 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 CH to attenuate cardiac growth when overexpressing Calcineurin. Whereas over-expression of Calcineurin treatment can result in cardiac hypertrophy under normal conditions in flies[10], when combined with CH 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.[5], 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 a number of questions. First, how does the genetic background cause differential responses to hypoxia? Understanding why some genotypes but not others show changes in heart size following hypoxia can lead to the identification of genes associated with resistance to hypoxia, as observed with some human populations[11,12].

Second, while 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

due to 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 following hypoxia, perhaps this same mechanism can be exploited to understand the etiology and treatment of CMS.

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