TRANSLATIONAL PERSPECTIVES

Sickle cell vasculopathy: vascular phenotype on fire!

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Clinicians, scientists and lay people alike grasp the concept that sickle-shaped cells flow poorly in the circulation. Red cell stiffness is the basis of sickle cell vaso-occlusion, but growing evidence shows that the blood vessel wall assumes classical features of vasculopathy in a subgroup of patients. Large arteries in sickle cell patients with ischaemic stroke or pulmonary arterial hypertension show intimal and medial hyperplasia, irregular endothelium with *in situ* thrombosis and luminal obliteration, functionally characterized by vasomotor dysfunction. Solid evidence for pulmonary hypertension turns up in approximately 10% of sickle cell anaemia patients, with milder findings in another 25% or so. Pulmonary arterial hypertension occurs in about 6%, which is about 2000-fold greater prevalence in adults with sickle cell anaemia than in the general population.

Sickle cell anaemia is a risk factor for the development of these vasculopathic complications. This smouldering risk is fanned into flames by additional risk factors, including haemolytic intensity, ageing, chronic liver or kidney disease, and iron overload (Kato *et al.* 2017). This multifactorial risk for pulmonary vasculopathy is reminiscent of the additive effect of vascular risk factors for atherosclerosis in the general population. In fact, many typical risk factors for atherosclerosis are also associated with pulmonary vasculopathy in sickle cell anaemia, such as systemic hypertension, low apolipoprotein A-I expression, hypertriglyceridaemia and impaired bioavailability of nitric oxide.

Thanks to an article in this issue of *The Journal of Physiology* by Ferguson and colleagues, we can now add environmental hypoxia to the list of stressors that fan the flames of pulmonary hypertension in sickle cell mice (Ferguson *et al.* 2019). These investigators show that sickle cell mice develop more severe characteristics of pulmonary hypertension during ageing under conditions mimicking the altitude of Denver, CO (5280 ft or 1609 m) or Addis Ababa, Ethiopia (nearly 8000 ft or 2400 m). Presumably driven by erythropoietin response, the mice developed higher haematocrit, but they also showed markers of accelerated haemolysis, including higher serum bilirubin and plasma cell-free haemoglobin. Observed markers of worsening pulmonary hypertension include right ventricular systolic pressure, right ventricular weight, Fulton index, exercise intolerance, perivascular inflammation and pulmonary vessel remodelling. Lung expression of endothelial nitric oxide synthase (eNOS) declined, associated with altered phosphorylation patterns of eNOS. By comparison, hypoxia induced minimal changes in wild-type mice under the same environmental conditions. Clearly, sickle cell mice are far more sensitive to chronic hypoxia induction of pulmonary hypertension.

Perhaps we should not be surprised that chronic hypoxia can trigger pulmonary hypertension in a susceptible host. Hypoxia combined with Sugen-5416 treatment of mice yields one of the most familiar animal models of pulmonary hypertension (Ryan *et al.* 2013). Ascent to high altitude can promote pulmonary hypertension acutely and chronically in some humans. Pseudohypoxia caused by inherited disorders of oxygen sensing such as Chuvash polycythaemia is associated with high pulmonary artery systolic pressure. All of these pathways feature strong activation of hypoxia-inducible factor-1 (HIF-1). Conversely, HIF-1$\alpha^{+/-}$ mice are protected against hypoxia-induced pulmonary hypertension.

What makes sickle cell mice susceptible to hypoxia-induced pulmonary hypertension? Mice and people with sickle cell disease have diminished vasodilatory reserve. Severe anaemia promotes a compensatory increase in cardiac output, but respect for Ohm's law yields vasodilatation with a very low peripheral and pulmonary vascular resistance. In this setting, a decline in nitric oxide bioavailability impairs this critically needed vasodilatation. In the face of high flow, impaired vasodilatation results in high pressures. In the work of Ferguson and colleagues, hypoxia-induced pulmonary vasoconstriction is compensated in wild-type mice by other undetermined mechanisms, but not so in the sickle cell mice with their diminished vasodilatory reserve. In the sickle cell mice, hypoxia intensifies the haemolysis and cell-free haemoglobin that scavenges nitric oxide. Pulmonary hypertension ensues.

Additional mechanisms might be involved. First, Ferguson *et al.* find that hypoxia increases the haematocrit in the sickle cell mice, almost certainly augmenting the already high viscosity of sickle cell blood, which might promote higher pulmonary artery pressure (Vanderpool & Naeije, 2018). Second, the researchers also found evidence of eNOS dysfunction, for which there is other published evidence in sickle cell mouse and patients. Finally, a peptide angiogenic factor called placenta growth factor is secreted into plasma at high levels in sickle cell disease, and published evidence suggests this enhances normoxic HIF-1 activation of the promoter of the gene encoding endothelin-1, a potent endogenous vasoconstrictor abundant in many cases of pulmonary hypertension, including sickle cell disease (Patel *et al.* 2008). Could hypoxia further activate the HIF-1 activity on the endothelin promoter? It's an appealing hypothesis, although Ferguson *et al.* did not find evidence for this. Many known genes in the hypoxia response pathway are highly expressed in blood cells from patients with sickle cell disease, very closely overlapping with the pattern seen in Chuvash polycythaemia (Zhang *et al.* 2014).

This is a time of widespread pharmaceutical investigation in sickle cell disease (Kato *et al.* 2018). Several approved drugs treat pulmonary hypertension by blocking endothelin-1 from binding to its receptor, with some past experience and current clinical trial activity in patients with sickle cell disease, including bosentan and macitentan. Riociguat, a vasodilator that activates the major receptor for nitric oxide, soluble guanylyl cyclase, is already approved for pulmonary arterial hypertension and is in currently in clinical trial in sickle cell disease.

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The most obvious clinical extrapolation from the present animal model study by Ferguson and colleagues is that patients with sickle cell anaemia residing in Denver, Addis Ababa and other high altitude cities face a higher risk of developing pulmonary hypertension. High altitude hypoxia may fan the flames of the vascular phenotype on fire in sickle cell disease.

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Additional information

Competing interests

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Sole author.

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