Macrophage Skewing by Phd2 Haploinsufficiency Prevents Ischaemia by Inducing Arteriogenesis

Takeda et al

Prolyl hydroxylase domain (PHD) molecules sense oxygen availability in mammalian cells and can serve as drug targets. Recent work from Takeda et al suggest a previously unappreciated role for PHD2—the main HIF prolyl hydroxylase—in arteriogenesis via macrophage skewing. Deletion of PHD2 in macrophages associated with activation of the canonical NF-κB pathway and arteriogenesis.

Work done by many investigators over the last decade has shed light onto the mechanisms of oxygen sensing in cells and in organisms.1 The prolyl hydroxylase domain (PHD; also called Egln) proteins belong to a family of Fe(II) and 2-oxoglutarate–dependent dioxygenases, whose activity depends on oxygen bioavailability.2 One well-described substrate of PHDs is the master transcription factor hypoxia-inducible factor (HIF). HIF hydroxylation by PHDs targets HIF for degradation; hence, PHDs inhibit HIF activity. Whereas mammalian cells contain 3 PHD isoforms, PHD2 appears to be the primary HIF prolyl hydroxylase, although other PHD family members (PHD1 and PHD3) can contribute to HIF regulation in certain conditions.2 Multiple lines of evidence suggest that PHD molecules (particularly PHD2) act as “oxygen sensors” in mammalian cells. For example, genetic knockdown of PHD2 in mice recapitulates many of the hallmarks of hypoxia in vivo.1

In a recent paper in *Nature*, Mazzone and colleagues4 describe a novel, and previously unappreciated, role for PHD2 in the modulation of macrophage functions leading to increased arteriogenesis and tissue protection in the setting of hindlimb ischemia. The authors first show that PHD2 haplo-

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genic phenotype depends on the NF-κB pathway, a key orchestrator of inflammatory gene expression. Either pharmacological or genetic inactivation of the NF-κB pathway abolished arteriogenesis in the Phd2 haplosufficient state.

Interestingly, activation of NF-κB in the setting of Phd2 haplosufficiency depended on the hydroxylation activity of PHD2. It remains to be seen, however, how mechanistically PHD2 hydroxylation attenuates the NF-κB pathway. In addition, complete inactivation of PHD2 did not induce NF-κB activation, presumably due to compensatory effects by another PHD isoform, PHD3. Because PHD3 is a direct transcription target of HIF and HIF activity is necessary for this feedback activity of PHD3,7 it would be interesting to examine the crosstalk between the HIF and NF-κB pathways in this context.

The authors’ findings are intriguing when juxtaposed with previously published work from this group and other groups. For example, Aragones et al showed that Phd1−/− mice exhibit protection against hindlimb ischemia as a result of skeletal muscle metabolic reprogramming, with no differences in arteriogenesis noted between the Phd1−/− mice and Phd1+/− mice.8 On the other hand, Taubman and colleagues have shown that PHD3 regulates skeletal muscle differentiation via protein stability of myogenin.9 These findings would suggest that the different PHD isoforms play unique and nonredundant roles in the cellular response to hypoxia in the skeletal muscle (see Figure). Interestingly, however, Aragones et al did not observe a protection by PHD2 haploinsufficiency against hindlimb ischemia following femoral artery ligation, although this may result from different skeletal muscle groups being examined.8 In addition, separate work by Mazzone and colleagues suggests that heterozygous deficiency of PHD2 restores tumor oxygenation and inhibits metastasis via normalization of endothelial cells in a HIF-dependent manner.10

PHD molecules can serve as drug targets, highlighting the clinical relevance of this work. Indeed, clinical trials are currently evaluating several nonselective PHD inhibitors for the treatment of anemia.11 Future PHD inhibitors, targeted to one PHD isoform, may offer more specific treatment strategies with fewer adverse effects. The data from Mazzone et al, for example, suggest that PHD2 inhibitors may have particular use in disorders that involve chronic hypoxia, such as peripheral artery disease. A recent trial of gene therapy of HIF-1α in patients with claudication was negative.12 PHD2 inhibitors, on the other hand, may recapitulate more closely the normal response of the skeletal muscle to hypoxia and activate other pathways important in cellular response to hypoxia (such as NF-κB). The more we learn about the molecular pathways involved in cardiovascular disease, the more we encounter intersections with inflammation. The current evidence linking responses to hypoxia as modulators of the macrophages involved in innate immunity serves as another example of the confluence of important host defense pathways.

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You Can't Run From Inflammation: Lower Extremity Ischemia, Hypoxia Signaling, and Macrophage Subtypes
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