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EDITORIAL

Hypoxia in the Gut

A continuous supply of molecular oxygen is essential for the maintenance of oxidative metabolism and thereby the function and survival of most cells of the human body. Over the course of evolution, we have developed the capacity, at the cellular level, to counteract the threat of developing hypoxia by eliciting an early warning adaptive response that is driven primarily by a transcription factor termed the *hypoxia-inducible factor* (HIF). In hypoxia, HIF becomes activated and drives the expression of a cohort of genes that promote adaptation to hypoxia including primary regulators of erythropoiesis (eg, erythropoietin), angiogenesis (eg, vascular endothelial growth factor), and metabolism (eg, glycolytic enzymes). More recent studies have shown a primary role for HIF in the control of innate and adaptive immune responses. HIF is a dimer composed of an oxygen-sensitive HIFα subunit and a constitutively expressed HIFβ subunit. The oxygen sensors responsible for conferring hypoxic-sensitivity on the HIF pathway are termed *HIF hydroxylases* and are a family of enzymes that, when sufficient oxygen is available, target HIFα subunits for ubiquitin-dependent proteasomal degradation and hence maintain HIF in a repressed state. In hypoxia, these hydroxylases become inactive, resulting in HIF accumulation, which in turn leads to the activation of the transcriptional adaptive response outlined earlier. There are 2 isoforms of HIF, termed *HIF-1* and *HIF-2* (depending on which of the HIFα subunits are present) that regulate distinct but overlapping gene cohorts.

Because of its juxtaposition with the oxygen-depleted lumen of the gut, the intestinal mucosa experiences relative hypoxia even in the normal healthy state. This feature of physiologic hypoxia represents an important stimulus that is vital for the maintenance of normal gut homeostasis. This occurs primarily through the expression of HIF-1α–dependent genes, which contribute to the maintenance of intestinal epithelial barrier function and innate immune activity in mucosal immune cells. Therefore, HIF-1α plays an important role in the maintenance of gastrointestinal homeostasis. Notably, the degree of hypoxia found in the intestinal mucosa is exacerbated significantly in inflammatory bowel disease, leading to a more extensive and severe hypoxia termed *inflammatory hypoxia*, which can contribute to disease development through the regulation of mucosal immune cell function. The role of HIF in intestinal inflammation has been the subject of a number of studies in recent years.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Toullec et al[1] show that removal of endothelial (but not epithelial) HIF-1α results in reduced radiation-induced toxicity in murine models implicating a negative role for HIF-1 in radiation-induced intestinal toxicity. This contrasts with a number of studies that have shown a protective role for epithelial HIF-1 in other models of intestinal inflammation. The opposite has been reported for the HIF-2 isoform, which is reported to be protective in radiation-induced intestinal injury but promotes intestinal inflammation. Therefore, it would appear that both isoform and context are important in determining the role of HIF in intestinal disease. Therefore, a number of studies have shown that hypoxia and the HIF pathway is important in the control of intestinal inflammation, albeit in a complex way.

Despite the differential roles for HIF-1 and HIF-2 in models of intestinal inflammation that have been reported, a consistent finding that now has been shown in multiple preclinical studies, is that mimicking hypoxia through the application of pharmacologic hydroxylase inhibitors (which activate the HIF pathway) is protective in multiple models of intestinal inflammation including radiation-induced intestinal toxicity.[2] This has given rise to the exciting possibility that hydroxylase inhibitors may be a useful class of drugs for the clinical treatment of intestinal diseases such as inflammatory bowel disease. Importantly, hydroxylase inhibitors now have been used in clinical trails for the treatment of anemia and, to date, have been found to be generally well tolerated and clinically effective. Therefore, the possibility of re-purposing hydroxylase inhibitors for the clinical treatment of intestinal inflammation is a tangible short- to medium-term possibility.

To further our understanding of the role of hypoxia and the HIF pathway in gut homeostasis and identify the characteristics of the most promising hydroxylase inhibitors for the treatment of intestinal inflammation, we need to develop our understanding of how pharmacologic hydroxylase inhibitors mediate their protective effects at the level of the intestinal mucosa including identification of the key target cells of both the epithelium and the mucosal immune system, the target hydroxylase isoforms involved and the relative role of HIF-1 and HIF-2 isoforms. The study by Toullec et al makes an important contribution to this knowledge.

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Conflicts of interest
The author is on the scientific advisory board of Akebia Therapeutics.

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