The Heat Is On: An Expanding Role for Hypoxia-Inducible Factors in Kidney Transplantation

Masaomi Nangaku
Division of Nephrology and Endocrinology, University of Tokyo School of Medicine, Tokyo, Japan


Advances in surgical techniques, immunosuppressive therapies, and posttransplant monitoring have led to impressive increases in patient and allograft survival in kidney transplantation, and this procedure now serves as the standard of care for patients with end-stage renal disease. One determinant of graft dysfunction is cold and warm ischemia time of the allograft, as well as acute cellular rejection, which involves T cell–mediated mechanisms of injury, which typically occurs in the first three months after transplantation. Although transplant kidneys are apparently hypoxic during the preservation period, the oxygenation status of the kidney and its potential effects in the posttransplant period remain unknown.

Cells are endowed with endogenous mechanisms to cope with hypoxia. A key discovery has revealed the heart of this system: a family of related proteins called hypoxia-inducible factors (HIF). HIF are transcription factors that respond to oxygen scarcity by massively upregulating adaptive responsive genes. This crucial role in a variety of physiologic and pathologic conditions has made HIF the focus of intense investigation in a wide range of fields (1,2). Among other effects, suboptimal activation of HIF may contribute to heart attack, stroke, and other diseases including chronic kidney disease (3–5). Conversely, many kinds of cancers carry elevated levels of HIF, which possibly contributes to the cancer’s ability to provide tumors with the new blood vessels that fuel its growth.

Despite the technical challenge of evaluating the oxygenation status of organs in vivo, sufficient evidence has now been obtained to support a pathogenic role of hypoxia in a number of diseases. Some light has been shed by blood oxygen level–dependent magnetic resonance imaging, a novel imaging technique that visualizes deoxyhemoglobin (6,7), but its use in nephrology is limited by technical problems, which include motion artifacts. HIF, which represent a defense mechanism against hypoxia, accumulate in accordance with local oxygen concentration, which renders them suitable markers of low oxygenation status in vivo. In practice this is notoriously difficult, however, because the short half-life of HIF seriously hampers their immunostaining. Although one study investigated HIF-1α expression in biopsies of living donor kidneys and cadaveric donor kidneys using real-time PCR analysis (8), evaluation of HIF-1α expression at mRNA levels may be misleading because the main regulation of this protein is at the degradation level and is induced by prolyl hydroxylation and subsequent recognition by von Hippel Lindau protein (9,10). Recent advances in molecular biology have enabled the establishment of oxygen-sensing transgenic animals that use a reporter gene controlled by the HIF system (11,12). These animals are highly useful in experimental conditions and have helped expand our knowledge in this field, but the methodology cannot be applied to humans.

Against this background, Rosenberger and colleagues developed a high-amplification HIF-1α immunohistochemical method that they used to evaluate HIF-1α expression in renal biopsies (13). In this issue of JASN, they continue these studies by using this method to investigate temporal changes in HIF-1α expression in kidney grafts (14). Although upregulation of HIF-1α was observed during the preservation period, as expected, most grafts showed persistent upregulation of HIF-1α at 2 wk after transplantation, a particularly surprising result given the short half-life of this factor. Although further study is required, upregulation of HIF-1α may act as a favorable counterbalance to the negative impact of renal ischemia.

Among other findings, expression of HIF-1α at 3 mo was observed in acute rejection. Strong staining of HIF-1α was noted in glomeruli, tubules, and interstitial cells, which possibly reflects the exacerbation of functional deterioration in rejected grafts by rejection-induced hypoxia. It is intriguing to speculate that some HIF-1α–positive cells may in fact be inflammatory cells. Inflammation is characterized by localized hypoxia caused by increased metabolic demand, and tubulitis is a cardinal feature of rejection. The classic cellular infiltrate of rejection is characterized by T cells with occasional neutrophils and plasma cells. HIF-1α is essential for the regulation of glycolytic capacity and energy production in myeloid cells, and selective deletion of HIF-1α in macrophages/monocytes and granulocytes leads to the impairment of inflammatory response (15). The hypoxic condition in the tissue microenvironment also protects peripheral T cells from activation-induced cell death concomitant with HIF-1α expression (16). Furthermore, leukocyte adhesion in inflammation is mediated by transcriptional mechanisms dependent on HIF-1 (17). All these findings sug-
gest a possible role of HIF-1 in the regulation of immune reactions, and may also be relevant in transplant settings.

Some recent studies suggest that, in addition to oxygen concentration per se, HIF might also be regulated by oxygen-independent factors such as cytokines and oxidative stress (18). Nevertheless, other studies using blood oxygen level–dependent magnetic resonance imaging (19) are consistent with the hypothesis of Rosenberger and colleagues that HIF-1α expression in rejected kidneys reflects hypoxia in the kidney.

These findings raise a number of questions with fascinating clinical implications. One is whether HIF expression in transplants predicts the long-term outcome of the graft or response to immunosuppressants. Whereas activation of the immune response in acute rejection is mainly the result of allore cognition, hypoxia, a nonalloreactive factor, seems to amplify the immune response by triggering inflammatory mechanisms that make the graft more prone to immunologic recognition and rejection (20,21). The possible link between early expression of HIF-1α and acute rejection could not be determined in the study by Rosenberger et al. because of the limited number of patients, but this possible link clearly needs to be addressed.

Furthermore, the findings suggest a potential role for HIF-modulating therapy in renal transplantation. Theoretically, stabilization of HIF in resident renal cells would make cells tolerant to hypoxia and improve graft function. Development of HIF stabilizers is a hot topic, and promising results have been reported in a model of ischemia reperfusion injury (22–24). Modulation of HIF in infiltrating inflammatory cells may also have therapeutic application in allograft rejection.

Another question concerns changes in HIF-2 expression in transplant kidneys. HIF-2 is predominantly expressed in the endothelium and interstitial cells of the kidney (25); because endothelial cells are the main target of ischemia reperfusion injury, the potential role of HIF-2 in kidney transplantation also warrants investigation.

Oxygen is indispensable to life, and the field of HIF research is progressing and expanding rapidly. Rosenberger and colleagues have provided tantalizing insight into an exciting new field of transplantation science. The challenge now is to use the understanding gained as a focus for future investigation of HIF-related processes in renal pathophysiology and therapeutics.

Disclosures

None.

References

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See the related article, “Immunohistochemical Detection of Hypoxia-Inducible Factor-1α in Human Renal Allograft Biopsies,” on pages 343–351.