Living on the Edge
Hypoxia-Induced Tissue Damage
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How a seemingly simple signal (ie, hypoxia) becomes transduced into biochemical and molecular responses that mediate maladaptive tissue damage is the defining enigma in various events that lead to oxygen deprivation, such as myocardial infarction, stroke, and venous thromboembolism. It is well established that acute hypoxia leads to numerous cellular events, such as formation of reactive oxygen species and induction of hypoxia-inducible factor-1.1 Furthermore, the immediate early gene, early growth response (Egr)-1, appears as an integral component of the biological response to hypoxia,2 because its upregulation induces the expression of fundamental inflammatory and prothrombotic stress genes.3 Nevertheless, the exact role of the above molecules and the link between hypoxia and Egr-1 upregulation/inflammation remains elusive. It is certainly desirable to better characterize the molecular basis of hypoxic cellular injury to develop pathway-specific therapeutic strategies to limit hypoxia-induced tissue damage in various organs such as the heart, brain, and vasculature.

Formation of advanced glycation end products (AGEs) are implicated in the pathogenesis of diabetic micro- and macrovascular complications, resulting in diabetic heart disease, accelerated atherosclerosis, end-stage renal failure, a variety of neuropathies, and acquired blindness.4 For several years, it has been known that high blood glucose concentrations promote AGE formation inside and outside cells.5 In addition, there is increasing evidence that AGE formation also occurs independent of plasma glucose levels. For example, oxidants generated by the NADPH oxidase of neutrophils, monocytes, and macrophages may also play a role in AGE formation in vivo by a glucose-independent pathway.6

The interaction of glucose-modified and inflammation-promoting ligands with the receptor for advanced glycation end products (RAGE) is emerging as a central mechanism contributing to the diverse complications of diabetes.7 RAGE is found on many cell types, particularly those affected in diabetes.8 It belongs to the immunoglobulin superfamily of cell surface molecules with potential similarities to members of the family of Toll-like receptors.9 RAGE, in its nontruncated form, consists of one “V”-type and two “C”-type immunoglobulin domains for ligand recognition, a short transmembrane domain, and a cytoplasmic tail, which is essential for intracellular signaling.10 A broad repertoire of ligands besides AGEs, all sharing the propensity to accumulate in tissues during aging, chronic degenerative diseases, inflammation, and the host response, are bound to this receptor.11 RAGE expression is dynamically induced by proinflammatory molecules such as tumor-necrosis-factor-α12 and C-reactive protein.13 In addition, RAGE expression is also augmented by hypoxia in a hypoxia-inducible factor-1–dependent manner.14 Conversely, activation of antiinflammatory molecules like peroxisome proliferator-activated receptor-γ leads to depression of RAGE expression.15

Ligand engagement of RAGE with AGEs or other nonglycated peptide ligands leads (through a positive-feedback loop that further increases RAGE expression) to perpetuation of inflammatory signaling pathways, resulting in expression of proinflammatory mediators such as monocyte chemoattractant protein-1, vascular cell adhesion molecule-1, and activation of the transcription factor nuclear factor-kB, which all play key roles in acute and chronic disease states.16 Thus, it has been recognized and established for a long time that deletion of RAGE and pharmacological interventions targeting interruption of RAGE-ligand interaction suppress inflammation and dampen tissue damage in experimental models of inflammatory disorders.17

Although the importance of chronic RAGE activation by its ligands for diabetic and nondiabetic inflammatory states, including atherosclerosis, has been appreciated for more than a decade now, no reports have been published investigating the involvement of RAGE in the immediate inflammatory response caused by hypoxia.

In this issue of Circulation Research, Chang et al18 provide evidence for a molecular link among hypoxia, RAGE, and the expression of the immediate early gene Egr-1, which is known to play a key master regulatory role in multiple cardiovascular pathological processes.19 In their report, the authors convincingly demonstrate that upregulation of Egr-1 by hypoxia requires RAGE signaling. This is shown in a fairly elegant series of experiments, involving RAGE-deficient mice, small interfering RNA–targeted RAGE gene silencing, as well as functional RAGE antagonism using an AGE inhibitor, soluble RAGE, and neutralizing/blocking antibodies against AGE and RAGE. Furthermore, it is shown that hypoxia-induced Egr-1 transcription is mediated via a rapid production and cellular release of AGES with subsequent activation of an axis involving RAGE-dependent membrane translocation of the protein kinase C βII isoform (PKC)βII and consequent activation of c-Jun N-terminal kinase in endothelial cells.19 It is noteworthy that the authors
excluded alternative events that may impinge on their results, such as activation of RAGE by non-AGE proinflammatory RAGE ligands including S100/calgranulins or high-mobility group box 1 proteins under hypoxic conditions and the involvement of other PKC isoforms than PKCβI.

The release of specific RAGE ligands by endothelial cells under hypoxic conditions and the importance of RAGE signaling for Egr-1 expression and hypoxia-induced tissue damage is a novel finding that substantially improves our understanding of the molecular consequences of oxygen deprivation. This concept is further supported by other recent studies demonstrating that RAGE expression is induced by hypoxia in neuronal cells, as well as in the myocardial tissue, indicating that RAGE has a functional role in the heart and the brain. However, whereas genetic deficiency of RAGE protects the myocardium against ischemia/reperfusion injury, suggesting a detrimental role for RAGE in the heart, expression of RAGE in neuronal cells appears to be neuroprotective because genetic deletion of RAGE leads to increased infarct size in the mouse brain after experimental stroke and systemic hypoxia. Thus, the functional consequences of RAGE-induced signals during oxygen deprivation appear to differ depending on the particular organ system.

In any case, the findings by Chang et al in this issue of Circulation Research certainly provide the basis for the development of novel therapeutic strategies to modulate hypoxic tissue damage. Hopefully, further studies will dissect the specific role of hypoxic RAGE signaling in various organ systems and will also elucidate the mechanism by which hypoxia leads to induction of AGE release by endothelial cells.

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References


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