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Targeting the hypoxia-adenosine link for controlling excessive inflammation

Agnieszka Czopik[1], **Xiaoyi Yuan**[1], **Scott Evans**[2], **Holger K. Eltzschig**[1]

[1]Department of Anesthesiology, McGovern Medical School at UTHealth, Houston, Texas, USA

[2]Department of Pulmonary Medicine, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA.

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In the present edition of Anesthesiology, Ngamsri et al. provide compelling experimental evidence that a molecular pathway involving stabilization of hypoxia-inducible transcription factors and subsequent enhancement of extracellular adenosine signaling can be targeted to treat excessive inflammation and collateral tissue damage in two animal models of peritonitis.[1] Experimental models of peritonitis are frequently used in laboratory studies to gain mechanistic inside on the pathogenesis of sepsis or systemic inflammatory response syndrome. Consistent with previous studies,[2] their findings suggest that excessive inflammation and uncontrolled collateral tissue damage is part of the pathogenesis of sepsis or systemic inflammatory response syndrome. Their findings have translational implications for patients where pharmacologic strategies to enhance hypoxia-inducible transcription factors or adenosine receptor signaling could be used to prevent or treat harmful and excessive inflammation.

In their studies, the authors demonstrate that treatment with sevoflurane promotes the stabilization of hypoxia-inducible transcription factors. Hypoxia-inducible transcription factors have been discovered as molecular enhancers of hypoxia-responsive target genes in the early 1990ies by the physician-scientist Gregg Semenza who was subsequently honored for his discovery by receiving the Nobel Prize in 2019.[3] Initially, hypoxia-inducible factors were discovered as a transcriptional enhancer of erythropoietin during conditions of limited oxygen availability. They undergo a post-translational regulation, where during normoxic conditions, the hypoxia-inducible transcription factor protein is rapidly targeted for proteasomal degradation. This molecular pathway controlling concentrations of hypoxia-inducible factors is inactivated during hypoxia, leading to the stabilization and subsequent activation of hypoxia-inducible factors during limited oxygen availability. For example,

Corresponding Author: Holger K. Eltzschig, M.D., Ph.D., Chairman and Professor, John P. and Kathrine G. McGovern Distinguished University Chair, Associate Vice President for Translational Medicine, Director, Center for Perioperative Medicine, Department of Anesthesiology, McGovern Medical School, The University of Texas Health Science Center at Houston, 6431 Fannin St, MSB 5.020, Houston, TX 77030, Phone: 713-500-6222 or 713-500-6114, Fax: 713-500-6208, holger.eltzschig@uth.tmc.edu.

during high-altitude exposure, hypoxia-inducible transcription factors are stabilized, bind to the promoter region of erythropoietin, and increase its transcription. Subsequently, elevated plasma concentrations of erythropoietin will lead to increased erythropoiesis to adapt to limited oxygen. In surgical patients who lose blood during surgery, activation of this pathway will lead to restored concentrations of hemoglobin in patients who experience anemia. As such, oxygen-sensing mechanisms that control the stabilization of hypoxia-inducible transcription factors are critical for allowing surgical patients to regain normal blood hemoglobin concentrations.

As pointed out in the studies by Ngamsri,[1] the effects of hypoxia-inducible transcription factors are not limited to erythropoietin or restoration of hemoglobin concentrations. It is estimated that over 1000 genes are under the control of hypoxia-inducible transcription factors, including genes critical for adaptation to conditions of limited oxygen availability, immune responses, angiogenesis, cancer, and extracellular adenosine signaling.[4] In their studies, Ngamsri et al. used two model systems to examine harmful inflammation. First, they used a sterile model of peritonitis, by injecting an irritant into the peritoneal cavity to cause excessive inflammation. For this purpose they treated mice with an intra-peritoneal injection of zymosan - a polysaccharide cell wall component derived from Saccharomyces cerevisiae – causing self-resolving acute inflammatory peritonitis. As a second model of peritonitis, they used cecal-ligation and puncture, where peritonitis is caused by live bacteria. In short, the cecum is ligated and punctured, causing fecal peritonitis. The fact that the authors found similar outcomes of their experimental interventions in both models highlights the rigor of their research and indicates that their findings are more broadly applicable. The authors show that hypoxia-inducible transcription factors are stabilized in the intestine, liver and particularly in the lungs following sevoflurane treatment. Additional functional studies indicate that sevoflurane treatment and concomitant stabilization of hypoxia-inducible transcription factors are associated with reduced inflammatory responses during peritonitis, including reduced accumulation of inflammatory cells (such as neutrophils), and attenuated neutrophil adhesion molecules. Together, those findings indicate that stabilization of hypoxia-inducible transcription factors plays a functional role in attenuating experimentally-induced peritonitis to limit uncontrolled inflammation.

Most studies of hypoxia-inducible transcription factors will attempt to reveal a specific target gene that is transcriptionally enhanced in the context of a specific disease. Here, the authors identified adenosine receptors as a transcriptional target of hypoxia-inducible transcription factors during experimentally induced peritonitis.[5] Adenosine is known famously for its role as molecular building block of the genetic code (as part of the DNA) or as a part of the universal energy currency adenosine triphosphate. However, in the extracellular compartment, adenosine can function as a signaling molecule via activation of adenosine receptors. As of today, four distinct adenosine receptors have been described. Many anesthesiologists are familiar with the A1 adenosine receptor since this receptor mediates the heart-rate slowing effects of intravenous adenosine when used in the treatment of supraventricular tachycardia.[6] In addition to its effects on slowing the heart rate, extracellular adenosine signaling has been shown to limit deleterious inflammation by activating the A2A or A2B adenosine receptor.[7] Importantly, the promoter of the A2B adenosine receptor contains a hypoxia-response element which allows binding of hypoxia-

inducible transcription factors and the A2B receptor has previously been shown to be induced directly by hypoxia-inducible transcription factors, for example during conditions of hypoxia or inflammation.[4] A2B adenosine receptors are widely expressed with functional studies indicating signaling effects for A2B adenosine receptors expressed for example on alveolar epithelial cells of the lungs,[8] innate or adaptive immune cells,[9] vascular endothelia, or cardiac tissues.[4,10] Consistently, Ngamsri et al. demonstrated that the A2B adenosine receptor transcript and protein expression were increased with sevoflurane treatment. Moreover, the protection provided by sevoflurane was abolished in mice with genetic deletion of the A2B adenosine receptor. Based on these findings, the authors conclude that sevoflurane-mediated stabilization of hypoxia-inducible transcription factors results in the transcriptional induction of the A2B adenosine receptor as a mechanism to provide protective effects during experimental peritonitis.

In their studies, Ngamsri et al propose the use of sevoflurane to activate the protective effects of this hypoxia-adenosine pathway. However, the use of sevoflurane for treating excessive inflammation has several limitations. Similar to most volatile anesthetics, sevoflurane causes vasodilation and concomitant decreases in blood pressure, which could limit its use in patients who are experiencing severe hypotension as a consequence of severe inflammation, such as during sepsis or septic shock. Moreover, the therapeutic use of sevoflurane for treatment of excessive inflammation requires intubation and mechanical ventilation. However, many patients who experience excessive inflammation are not intubated, particularly at an earlier stage of the disease, thereby limiting the usefulness of sevoflurane. Based on these concerns, pharmacologic approaches that are specifically designed to directly stabilize hypoxia-inducible transcription factors may potentially be more effective than sevoflurane. Pharmacologic activators of hypoxia-inducible transcription factors (e.g. roxadustat or vadadustat) have recently become available as oral medication, and have a good safety record in randomized clinical phase 3 trials.[7,11] Alternatively, direct agonists of the A2B adenosine receptor could be used for the treatment of inflammatory conditions such as peritonitis, sepsis, or acute respiratory distress syndrome. For example, experimental studies suggest that the A2B agonist BAY 60-6583 is effective in attenuating myocardial inflammation during reperfusion injury[10] or in the treatment of lung injury induced by mechanical ventilation or LPS inhalation.[4] However, attempts to bring agonists of the A2B adenosine receptor from bench to bedside have yet to be undertaken.

Taken together, Ngamsri et al.[1] provide compelling evidence that treatment of inflammatory peritonitis with sevoflurane is associated with attenuated inflammatory responses via stabilization of hypoxia-inducible transcription factors and concomitant increases in extracellular adenosine signaling through the A2B adenosine receptor. To take these findings from bench to bedside, additional studies for example examining inflammatory responses in patients who are receiving sevoflurane anesthesia could provide additional evidence to consider sevoflurane treatment in prospective and randomized trials for treatment of excessive inflammation. Alternatively, recently established hypoxia-inducible transcription factors activators that have already undergone randomized phase-3 clinical trials in patients with renal anemia may represent an alternative for activation of the hypoxia-adenosine pathway for the treatment of detrimental inflammation.

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