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RATIONALE:

Hypoxia regulates the inflammatory-antiinflammatory balance by the receptor for advanced glycation end products (RAGE), a versatile sensor of damage-associated molecular patterns. The multiligand nature of RAGE places this receptor in the midst of chronic inflammatory diseases.

OBJECTIVES:

To characterize the impact of the hypoxia-RAGE pathway on pathogenic airway inflammation preventing effective pathogen clearance in cystic fibrosis (CF) and elucidate the potential role of this danger signal in pathogenesis and therapy of lung inflammation.

METHODS:

We used in vivo and in vitro models to study the impact of hypoxia on RAGE expression and activity in human and murine CF, the nature of the RAGE ligand, and the impact of RAGE on lung inflammation and antimicrobial resistance in fungal and bacterial pneumonia.

MEASUREMENTS AND MAIN RESULTS:

Sustained expression of RAGE and its ligand S100B was observed in murine lung and human epithelial cells and exerted a proximal role in promoting inflammation in murine and human CF, as revealed by functional studies and analysis of the genetic variability of AGER in patients with CF. Both hypoxia and infections contributed to the sustained activation of the S100B-RAGE pathway, being RAGE up-regulated by hypoxia and S100B by infection by Toll-like receptors. Inhibiting the RAGE pathway in vivo with soluble (s) RAGE reduced pathogen load and inflammation in experimental CF, whereas sRAGE production was defective in patients with CF.

CONCLUSIONS:

A causal link between hyperactivation of RAGE and inflammation in CF has been observed, such that targeting pathogenic inflammation alleviated inflammation in CF and measurement of sRAGE levels could be a useful biomarker for RAGE-dependent inflammation in patients with CF.