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Low ascorbate levels are associated with increased hypoxia-inducible factor-1 activity and an aggressive tumor phenotype in endometrial cancer.

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Abstract

Activation of the transcription factor hypoxia-inducible factor (HIF)-1 allows solid tumors to thrive under conditions of metabolic stress. Because HIF-1 is switched off by hydroxylation reactions that require ascorbate, inadequate intracellular ascorbate levels could contribute to HIF-1 overactivation. In this study, we investigated whether the ascorbate content of human endometrial tumors [known to be driven by HIF-1 and vascular endothelial growth factor (VEGF)] influenced HIF-1 activity and tumor pathology. We measured protein levels of HIF-1alpha and three downstream gene products [glucose transporter 1 (GLUT-1), Bcl-2/adenovirus E1B 19 kDa interacting protein 3 (BNIP3), and VEGF], as well as the ascorbate content of tumor and patient-matched normal endometrial tissue samples. HIF-1alpha and its downstream gene products were upregulated in tumor tissue, with the highest levels being present in high-grade tumors. High-grade tumors also had reduced capacity to accumulate ascorbate compared with normal tissue; however, all grades contained tumors with low ascorbate content. Tumors with the highest HIF-1alpha protein content were ascorbate deficient. Low ascorbate levels were also associated with elevated VEGF, GLUT-1, and BNIP3 protein levels and with increased tumor size, and there was a significant association between low tissue ascorbate levels and increased activation of the HIF-1 pathway ($P = 0.007$). In contrast, tumors with high ascorbate levels had lesser levels of HIF-1 activation. This study shows for the first time a likely in vivo relationship between ascorbate and HIF-1, with low tumor tissue ascorbate levels being associated with high HIF-1 activation and tumor growth.

PMID: 20570889 [PubMed - indexed for MEDLINE]

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