Roles for hypoxia-regulated genes during cervical carcinogenesis: somatic evolution during the hypoxia-glycolysis-acidosis sequence.

李文瑛

Lee WY;Huang SC;Hsu KF;Tzeng CC;Shen WL

摘要

Abstract

OBJECTIVES: Malignant phenotypic traits are caused by microenvironmental selection pressures during carcinogenesis. Hypoxia can drive a tumor toward a more aggressive malignant phenotype. The objective was to better understand the role of the hypoxia-regulated genes in cervical carcinogenesis. METHODS: We analyzed the expression of the hypoxia-regulated genes, including hypoxia-inducible factor-1alpha (HIF-1alpha), erythropoietin (Epo), vascular endothelial growth factor (VEGF), glucose transporter 1 (GLUT1), carbonic anhydrase IX (CAIX), and MET, in cervical cell lines and human tissue samples of cervical intraepithelial neoplasia (CIN I-III) and invasive squamous cell carcinoma (ISCC). RESULTS: CAIX and MET were expressed in cervical carcinoma cell lines, but not in normal or human papillomavirus-immortalized cervical cells. In clinical tissue samples, Epo, VEGF, GLUT1, and CAIX were not detected in normal squamous epithelia. GLUT1 was expressed in nearly all cases of CIN and ISCC, however, CAIX was expressed only in CIN III and ISCC. HIF-1alpha and MET expression was confined to the basal cells in normal squamous epithelia and was detected in the dysplastic cells of CIN and ISCC. CONCLUSIONS: The role of HIF-1alpha and MET changes from response to proliferation to tumor progression during cervical carcinogenesis. GLUT1 expression, a glycolytic phenotype adaptive to glycolysis, occurs early during cervical carcinogenesis and is a specific marker for dysplasia or carcinoma. MET and CAIX may contribute tumor progression in later stage. CAIX expression, an acid-resistant phenotype, may be a powerful adaptive advantage during carcinogenesis. Successful adaptation to the hypoxia-glycolysis-acidosis sequence in a microenvironment is crucial during carcinogenesis