Helicobacter pylori Induced Phosphatidylinositol-3-OH Kinase/mTOR Activation Increases Hypoxia Inducible Factor-1α to Promote Loss of Cyclin D1 and G0/G1 Cell Cycle Arrest in Human Gastric Cells

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H. pylori is a human gastric pathogen that has been linked to the development of several gastric pathologies, such as gastritis, peptic ulcer, and gastric cancer. In the gastric epithelium, the bacterium modifies many signaling pathways, resulting in contradictory responses that favor both proliferation and apoptosis. Consistent with such observations, H. pylori activates routes associated with cell cycle progression and cell cycle arrest. H. pylori infection also induces the hypoxia-induced factor HIF-1α, a transcription factor known to promote expression of genes that permit metabolic adaptation to the hypoxic environment in tumors and angiogenesis. Recently, however, also roles for HIF-1α in the repair of damaged DNA and inhibition of gene expression were described. Here, we investigated signaling pathways induced by H. pylori in gastric cells that favor HIF-1α expression and the consequences thereof in infected cells. Our results revealed that H. pylori promoted PI3K/mTOR-dependent HIF-1α induction, HIF-1α translocation to the nucleus, and activity as a transcription factor as evidenced using a reporter assay. Surprisingly, however, transcription of known HIF-1α effector genes evaluated by qPCR analysis, revealed either no change (LDHA and GAPDH), statistically insignificant increases SLC2A1 (GLUT-1) or greatly enhance transcription (VEGFA), but in an HIF-1α-independent manner, as quantified by PCR analysis in cells with shRNA-mediated silencing of HIF-1α. Instead, HIF-1α knockdown facilitated G1/S progression and increased Cyclin D1 protein...