Cancer Chemother Pharmacol. 2013 Jan 6. [Epub ahead of print]

(-)-Epigallocatechin-3-gallate inhibits human papillomavirus (HPV)-16 oncoprotein-induced angiogenesis in non-small cell lung cancer cells by targeting HIF-1α

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Abstract

PURPOSE: To investigate the effects of (-)-epigallocatechin-3-gallate (EGCG) on human papillomavirus (HPV)-16 oncoprotein-induced angiogenesis in non-small cell lung **cancer** (NSCLC) cells and the underlying mechanisms.

METHODS: NSCLC cells (A549 and NCI-H460) transfected with EGFP plasmids containing HPV-16 E6 or E7 oncogene were treated with different concentrations of EGCG for 16 h. The effects of EGCG on angiogenesis in vitro and in vivo were observed. The expression of HIF-1α, p-Akt, and p-ERK1/2 proteins in NSCLC cells was analyzed by Western blot. The levels of HIF-1α mRNA in NSCLC cells were detected by real-time RT-PCR. The concentration of VEGF and **IL-8** in the conditioned media was determined by ELISA. HIF-1α, VEGF, and CD31 expression in A549 xenografted tumors of nude mice was analyzed by immunohistochemistry.

RESULTS: HPV-16 E6 and E7 oncoproteins HIF-1α-dependently promoted angiogenesis in vitro and in vivo, which was inhibited by EGCG. Mechanistically, EGCG inhibited HPV-16 oncoprotein-induced HIF-1α protein expression but had no effect on HIF-1α mRNA expression in NSCLC cells. Additionally, 50 and 100 μmol/L of EGCG significantly reduced the secretion of VEGF and **IL-8** proteins induced by HPV-16 E7 oncoprotein in NSCLC A549 cells. Meanwhile, HPV-16 E6 and E7 oncoproteins HIF-1α-dependently enhanced Akt activation in A549 cells, which was suppressed by EGCG. Furthermore, EGCG inhibited HPV-16 oncoprotein-induced HIF-1α and HIF-1α-dependent VEGF and CD31 expression in A549 xenografted tumors.

CONCLUSIONS: EGCG inhibited HPV-16 oncoprotein-induced angiogenesis conferred by NSCLC through the **inhibition** of HIF-1α protein expression and HIF-1α-dependent expression of VEGF, **IL-8**, and CD31 as well as activation of Akt, suggesting that HIF-1α may be a potential target of EGCG against HPV-related NSCLC angiogenesis.

PMID: 23292117 [PubMed - as supplied by publisher]

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