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Radicicol, microbial transformation suppressor, reduces the hypoxia-induced gene expression and angiogenesis.

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Under low oxygen tension, cells increase the transcription of specific genes involved in angiogenesis, erythropoiesis and glycolysis. Hypoxia-induced gene expression depends primarily on stabilization of the α subunit of Hypoxia-Inducible Factor-1 (HIF-1α), which acts as a heterodimeric transactivator with the nuclear protein, Aryl hydrocarbon receptor nuclear translocator (Arnt). The resulting heterodimer (HIF-1α/Arnt) interacts specifically with the hypoxia-responsive element (HRE), thereby increasing transcription of the genes under HRE control. Our results indicate that radicicol reduces the hypoxia-induced expression of both endogenous vascular endothelial growth factor (VEGF) and HRE-driven reporter plasmids. Radicicol treatment (0.5 μg/ml) does not significantly change the stability of the HIF-1α protein and does not inhibit the nuclear localization of HIF-1α. However, this dose of radicicol significantly reduces HRE binding by the HIF-1α/Arnt heterodimer. Our results, the first to show that radicicol specifically inhibits the interaction between the HIF-1α/Arnt heterodimer and HRE, suggest that Hsp90 modulates the conformation of the HIF-1α/Arnt heterodimer, making it suitable for interaction with HRE. Furthermore, we demonstrate that radicicol reduces hypoxia-induced VEGF expression to decrease hypoxia-induced angiogenesis.
[This study was supported by a grant from the 1999 Korean National Cancer Control Program, Ministry of Health & Welfare (to H. Park)].