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[6]-Gingerol inhibits UVB-induced COX-2 expression and activation of NF-κB in mouse skin

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It has been demonstrated that chronically irradiated murine skin and UV light-induced squamous cell carcinomas overexpress the inducible isoform of cyclooxygenase (COX-2), and COX-2 inhibition reduces the risk of photocarcinogenesis in mice. UV radiation-induced inflammatory cytokines mediated by NF-κB reportedly play important roles in photoaging and cancer. NF-κB is activated upon UV irradiation and induces the various genes including COX-2. Using adult hairless mice (HRS/J hr+/+), we investigated the effects of [6]-Gingerol, a major polyphenolic constituent in ginger (Zingiber officinale Roscoe, Zingiberaceae), on UV-induced activation of transcription factor NF-κB and COX-2 expression. Imunohistochemical, Western blot, and RT-PCR indicated that both nuclear p65 and COX-2 gene expression were significantly induced by UVB (5 KJ/m²). NF-κB nuclear translocation and COX-2 expression induced by UVB were dramatically inhibited by treatment of [6]-gingerol (30 μM). In addition, [6]-Gingerol significantly suppressed UVB-induced erythema in mice. Our data suggest that [6]-gingerol can be applicable in preventing the UV-induced harmful effects.

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[6]-Gingerol suppress UVB-induced Apoptosis and COX-2 expression in HaCaT cells

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Ultraviolet B (UVB) irradiation induces intracellular production of ROS and acute skin inflammation such as sunburn, erythema and photoaging, and subsequently leads to apoptosis. ROS are known to play an important role in UVB-induced expression of COX-2. COX-2 may be a molecular target for the regulation of UVB-induced skin disorders such as photoinflammation and photocarcinogenesis. [6]-Gingerol, a naturally occurring plant phenol, is one of the major components of fresh ginger (Zingiber officinale Roscoe, Zingiberaceae) and has the diverse pharmacologic effects. Here, we describe its novel anti-oxidant, anti-apoptotic, and anti-inflammatory activity in vitro. UVB-induced intracellular ROS levels were significantly reduced by pre-treatment of [6]-Gingerol, and [6]-Gingerol down-regulated the activation of caspase-3, -8, -9 and Fas expression by UVB irradiation. It also down-regulated UVBinduced expression and transcriptional activity of COX-2, and translocation of NF-κB from cytosol to nuclear was inhibited by [6]-Gingerol through suppressing phosphorylation of IκBα (ser-32) in human keratinocyte cell line, HaCaT cells. These results suggest that [6]-Gingerol could be applicable as an effective therapeutic agent for protection against UVB-induced skin damage.

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Down-regulation of RECK by hypoxia stimulates the proliferation of epithelial cells through p38 MAP kinase and c-Jun N-terminal kinase pathways

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The reversion-inducing cysteine-rich protein with Kazal motifs (*RECK*) gene was initially isolated as a transformation suppressor gene. *RECK* down-regulation is reported in *ras*-transformed cells and it contributes to tumor cell metastasis. Here, we investigated the down-regulation of *RECK*by hypoxia and the possible role of *RECK* in early tumorigenesis. The exposure of immortalized human embryonic kidney epithelial cells, HEK293 cells, to hypoxia resulted in the down-regulation of RECK expression and increased cell proliferation. The inhibition of RECK by siRNA also promoted the proliferation of HEK293 cells under normoxic conditions. When we restored the hypoxia-induced down-regulation of RECK expression with a full length plasmid, hypoxia-induced proliferation was diminished as compared to the mock-transfected cells. The addition of SP600125 (a JNK inhibitor) or SB203580 (a p38MAP kinase inhibitor) under hypoxic conditions restored the RECK expression and the overexpression of the dominant-negative mutant of p38 MAP kinase or c-Jun N-terminal kinase (JNK) also recovered RECK expression under hypoxia. Furthermore, hypoxia-induced cell proliferation was abolished by either of these two dominant negative mutants. H-ras-MCF10A cells transfected with RECK siRNA formed colonise which were much larger than those of the control by colony-forming assay. From these results, we suggest that the hypoxia-induced proliferation of epithelial cells may be induced by *RECK* down-regulation, through the p38 MAP kinase and JNK signaling pathways. These results may be related to the early tumorigenic conversion by hypoxic stress.

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NO induced activation of Hypoxia-inducible factor-1

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Recently, nitric oxide emerged as a messenger with the ability to stabilize Hypoxia-inducible factor-1 (HIF-1) and to transactivate HIF-1 under normoxia. Here, we showed that NO donors such as SNAP and Spermine NONOate increased both the stabilization and the transactivation ability of HIF-1 even in normoxic HeLa cells in cGMP independent pathway. The findings that treatment these NO donors to partially purified or recombinant PHD2 does not changes either the activity of HIF-1 specific proline hydroxylase 2 (PHD2) or the interaction between HIF-1 and VHL suggest that NO donors activated HIF-1 by HIF-1-hydroxylation/VHL interaction-independent pathway. SNAP but not Spermine-NONOate increased transactivation by increasing the interaction with between HIF-1 and CREB binding protein (CBP). [This study was supported by the Molecular and Cellular BioDiscovery Research Program grant (2004-01967) from the Ministry of Science and Technology.]