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Areca nut components stimulate COX-2 expression and PGE2 production of gingival keratinocytes: role of TGF-β-activated kinase-1

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Introduction: Betel quid (BQ) chewing is popular in India, Sri Lanka, Taiwan and many other countries. There are about 600 million BQ chewers in the world. BQ usually comprises of areca nut (AN), tobacco, lime with/without betel leaf. This oral habit increases the incidence of oral cancer and oral submucous fibrosis (OSF), possibly due to the induction of toxicity and inflammatory mediators' release of oral mucosal cells. AN components have been shown to stimulate cyclooxygenase-2 (COX-2) expression and PGE2 production of gingival keratinocytes (GKs). However, the role of TGF-β1-activated kinase-1(TAK1) in mediating these events is not clear.

Materials and methods: In this study, human GKs were incubated with AN extract (ANE) with/without pretreatment and co-incubation with 5z-7oxozeaenol (a TAK1 inhibitor). Cytotoxicity was estimated by 3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay. The level of COX-2 mRNA and protein expression was studied by reverse transcriptase-polymerase chain reaction (RT-PCR) and western blotting. PGE_2 production was quantified by enzyme-linked immunosorbent assays.

Results: ANE stimulated COX-2 expression and PGE2 production of GK. ANE-induced COX-2 mRNA and protein expression can be attenuated by 5z-7oxozeaenol. Similarly, ANE-induced PGE2 production of GK was also prevented by 5z-7oxozeaenol. However, pretreatment and co-incubation by 5z-7oxozeaenol was not able to suppress the ANE-induced intracellular vacuoles formation as well as cytotoxicity to GKs as analyzed by MTT assay. 5z-7oxozeaenol further prevented the ANE-induced hemeoxygenase-1 and phosphor-cytosolic phospholipase A2 (p-cPLA2) expression of GKs.

Conclusions: These results indicate that TAK1 signaling pathway plays an important role in the ANE-induced pathogenesis of inflammatory response in oral cancer and OSF. Inhibition of TAK1 may be potentially used for targeting therapy for prevention and treatment of ANE-induced oral cancer and other related diseases. (This study is supported by grants from Ministry of Science and Technology, Taiwan and Chang Gung University of Science and Technology, as well as Chang Gung Memorial Hospital, Taiwan).

Biography

Dr. Me-Chi Chang received her master and Ph.D degree in Department of Pharmacology, National Taiwan University Medical College (1995). Currently she is a professor, researcher and teaching staff in the Chang Gung University of Science and Technology. She has published many papers in scientific journals including Blood, Thrombosis & Haemostasis, BBA, Biomaterials, Acta Biomaterialia, J Endod, Int Endod J, Carcinogenesis etc. She also served as a reviewer and editorial board member of many journals such as Toxicology, J Dent Res, Carcinogenesis, Int Endod J, Austin Dent J.

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