

RAJI LUKMON and A. R. M. RUHUL AMIN, Department of Pharmaceutical Sciences, Marshall University School of Pharmacy, Huntington, WV 25755. FLLL12, a curcumin analog, activates the oxidative stress response pathway in head and neck cancer: implication for chemoprevention.

Carcinogenesis is initiated with irreversible genetic mutation due to endogenously derived or carcinogen-induced oxidative stress. Activation of the antioxidant pathways ameliorates oxidative stress, protects cells from carcinogenic insults, and plays a pivotal role in chemoprevention. We have previously reported that FLLL12 is a potent curcumin analog, possesses *in vitro* and *in vivo* anticancer activity, and has better pharmacokinetic profiles than curcumin. The current study aims to identify novel pathways activated by FLLL12. MDA686, a head and neck cancer cell line, was treated with FLLL12 for 24h. Total RNA was used for RNA-Seq analysis. 2-fold differentially expressed genes were used for Ingenuity Pathway Analysis to identify the most significantly affected pathways. Real-time qPCR and western blotting were used to confirm the expression of the genes and their protein products, respectively, in normal, premalignant, and malignant cell lines. RNASeq identified 641 genes. Ingenuity Pathway Analysis identified the ferroptosis, the tumor microenvironment, and the oxidative response pathway as the top three most significantly affected pathways. We confirmed the activation of HMOX-1, NQO1, SLC7A11, and GCLC mRNA and proteins in normal, premalignant, and malignant cells. Although these genes are common for ferroptosis and the oxidative response pathway, treatment of cells with ferroptosis inhibitors, ferrostatin-1, and deferoxamine, did not affect FLLL12-induced cell death, suggesting that these genes are associated with the oxidative stress response pathway. Our results indicate that FLLL12 activates the oxidative stress response pathway in normal, premalignant, and malignant head and neck cancer cell lines and has strong promise for chemoprevention.