I-67 A dual mechanism of 4-hydroxy-5-methyl-3[2H]-furanone inhibiting melanogenesis

Hyo Jung Kim1, Sang Mi An1 and Yong Chool Boo1,2
1Dept. of Molecular Medicine and 2Cell and Matrix Research Institute, Kyungpook National University School of Medicine, 101 Donggung-dong, Jung-gu, Daegu, 700-422, Korea.

Dermal accumulation of undesired melanin has a significant cosmetic relevance demanding effective and safe depigmenting agents. In our preliminary studies, 4-hydroxy-5-methyl-3[2H]-furanone (HMF) has been isolated as an antioxidant principle from pine needles and shown to decrease cell pigmentation, suggesting its potential use as a depigmenting agent. The present study investigated its action mechanism in murine melanoma B16 cells stimulated by theophylline, an activator of the cAMP/protein kinase A signaling. When the cells were stimulated with theophylline, there was a dose-dependent increase in cellular tyrosinase protein content and melanin formation as expected. HMF inhibited the theophylline-stimulated melanin formation as effectively as arbutin, one of the most widely used depigmenting agents in cosmetics. HMF appeared to down-regulate tyrosinase mRNA, protein content and activity in the cells stimulated by theophylline. HMF also effectively inhibited the tyrosinase-catalyzed melanin formation from L-tyrosine in melanocytes, suggesting its possible use in the treatment of melanosis.

I-68 A diterpene compound CG-ABTX2 binds to 17-beta hydroxysteroid dehydrogenase type IV and induces insulin-like growth factor binding protein 1

Hee Shim Choi1, Joong Sup Shim1, Chang-Hyuk Yoo2, Jeong Ho Yoon2, and Ho Jeong Kwon*1
1Chemical Genomics Laboratory, Department of Biotechnology, College of Engineering, Yonsei University, Seoul 120-749, Korea. 2Digital Genomics, Seoul 153-782, Korea.

Insulin-like growth factors (IGFs) including IGF-1 and IGF-2 are widely studied for stimulation of DNA synthesis and cellular proliferation. These growth factors are regulated by insulin-like growth factor binding proteins (IGFBPs). Among various type of IGFBPs (IGFBP-1, -2), mRNA level of IGFBP1 induced by treatment of CG-ABTX2 after 6 hours. However, the mechanism underlying IGFBP1 induction by the compound is unsolved. To identify the cellular target of CG-ABTX2, we performed phage display biopanning. Synthetic affinity probe of CG-ABTX2 directly binds to SC2P domain of 17-β-HSD4. Subcellular localization of CG-ABTX2 was detected in HT1080 cells by immunocytochemistry with synthetic molecular probe of CG-ABTX2. The compound was mainly localized in peroxisomes and its localization was inhibited by excessive treatment of free CG-ABTX2. whereas HBC, a curcumin derivative targeting C2a/C2α, did not compete the binding. This in vivo binding of CG-ABTX2 to 17-β-HSD 4 was validated in vitro with surface plasmon resonance analysis resulting in an apparent KD value of between CG-ABTX2 and SC2P was 1×10^-7M. In conclusion, CG-ABTX2 binds to SC2P of 17- β-HSD 4 both in vivo and in vitro and its biological relevancy in respect to IGFBP1 induction is under investigation.

I-69 A barbituric acid derivative inhibitor of the Hepatitis C virus NS5B polymerase

Jong-Ho Lee, Sangyoon Lee, Mi Young Park, Min Soo Kim and Heejoon Myung
Department of Biotechnology, Hanyang University, 167-2 Sangdong, Ansan, Kyunggi-do, 426-791, Korea.

NS5B, the RNA-dependent RNA polymerase of HCV, is a key viral protein involved in the replication of HCV genome, thus represents an attractive target for the development of specific anti-HCV therapeutics. From the screening of a chemical compound library from KRICT (Korea Research Institute of Chemical Technology), we could isolate a series of compounds that inhibited the RNA polymerase activity of HCV NS5B. They shared a conserved frame of barbituric acid derivative. The ability of these compounds to inhibit NS5B-directed viral RNA replication was determined using purified recombinant NS5B from Huh7 cell line harboring HCV subgenomic replicon. Estimated IC50 was 3 mM and ED50 was 10 mM. Kinetic analysis revealed that the mechanism of inhibition of the NS5B activity was non-competitive with the UTP substrate. This investigation is useful for the utility of such compounds for the development of an anti-HCV therapy.

I-70 3'-Deoxyadenosine plays an inhibitory role in differentiation and triacylglycerol synthesis in 3T3-L1 cells

Sung-Won Kim, So-Chan Lee, Il-Woong Kim, Si-Kwan Kim
Dept. of Life Science, College of Biological and Health Science, Konkuk University, Chungju, Chungbuk 380-701, Republic of Korea

This study has been carried out to develop an anti-obesity compound from natural resources. 3T3-L1 cells, preadipocytes differentiating into adipocytes in the presence of insulin, subcutis 1-methylcarnitine and dexamethasone, were employed for the screening of anti-obesity compounds. In the course of our screening program, methanol extract of Cordyceps militaris demonstrated a potent anti-differentiation effect on the cells. Isolation and characterization of the active compound led us to identify the active agent as 3'-deoxyadenosine, referred also to as cordycepin. Cordycepin potently inhibited differentiation of 3T3-L1 cells to adipocytes and synthesis of triacylglycerol (TAG) in the cells at the concentration of 32 μM without cytotoxicity. Inhibitory action of cordycepin against differentiation and TAG synthesis in the cells was suppressed by the supplementation of adenosine. Western blot analysis reveals that cordycepin down-regulated the proteins levels of C/EBPα, PPARγ and anti-leptin. Cordycepin-induced decrease in C/EBPα, PPARγ and anti-leptin levels were recovered by the supplementation of adenosine. From these results, it can be suggested that cordycepin can be used as an anti-obesity agent.