P-3354 **Target transcriptional factor of SK-1009, a novel IL-6 suppressor, in colon cancer cells.**

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SK-1009における IL-6産生阻害作用メカニズムの検討

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Obesity and chronic inflammation are risk factors for colon cancer. In these situations,adipocytokines and inflammatory cytokines, such as interleukine-6 (IL-6), are suggested to play an important role in development of colon cancer. A novel compound, SK-1009, has been shown to inhibit IL-6 production in LPS-stimulated human macrophages. However, a detailed mechanism by SK-1009 has not been clarified yet. In this study, we examined whether nuclear factor-kappa B (NF-κB) is involved in the regulation of IL-6 production in SK-1009-treated colon cancer cells or not. SK-1009 suppressed several inflammatory cytokine mRNA levels,such as IL-1b and IL-8, in HCT-116 cells under TNFα stimulation. SK-1009 inhibited IκBα degradation and p50 nuclear transport induced by TNFα stimulation.Furthermore, SK-1009 inhibited NF-κB transcripitional activity with the same potential as shown in another IL-6 inhibitor, 5HPP-33. These results suggested that SK-1009 suppressed TNFα-induced IL-6 expression in colon cancer cells by NF-κB signaling inactivation, in part. The potential of SK-1009 as a cancer chemopreventive agent is now under investigation in our laboratory.

Keywords: IL-6, NF-kB

P-3355 **Synergistic Growth Inhibition by Acyclic Retinoid Plus GW4064 in Human Hepatocellular Carcinoma Cells**

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非環式レチノイドと GW4064(FXRリガンド) 併用による肝癌抑制効果

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Abnormalities in the expression and function of nuclear receptors, including retinoid X receptor (RXR) and farnesoid X receptor (FXR), are associated with the development of hepatocellular carcinoma (HCC). The combined effects of acyclic retinoid (ACR), a synthetic retinoid targeting RXRα, plus GW4064, a ligand for FXR, on the growth of human HCC cells were examined. ACR and GW4064 preferentially inhibited the growth of human HCC cells in comparison with normal hepatocytes by inducing apoptosis. This combination cooperatively induced cell cycle arrest in the G0/G1 phase and inhibited the phosphorylation of RXRα by inhibiting ERK and Stat3 phosphorylation in HLE human HCC cells. This combination increased the expression levels of p21 and SHP mRNA, while decreasing the levels of c-myc and cyclin D1 mRNA in HLE cells. The FXRE promoter activity was also significantly increased by this combination. These results suggest that ACR and GW4064 inhibit RXRα phosphorylation, modulate the expression of FXR-regulated genes, thus resulting in the induction of apoptosis and the inhibition of growth in HCC cells. This combination might be effective for the chemoprevention and chemotherapy of HCC.

Keywords: Acyclic retinoid, FXR

Room R-P4 Sep. 21 (Fri) 16:40 - 17:30

P23-3 Cancer prevention (1)
がんの予防 (1)

Chairperson: Hirokazu Takahashi (Yokohama City Univ. Hosp.)
座長：高橋 宏和 (横浜市立大学附属病院)

P-3356 **Inhibitory effect of synthetic cannabinoids on tumor promotion in two-stage carcinogenesis in mouse skin**

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合成カンナビノイド類におけるマウス皮膚二段階発癌実験の腫瘍抑制効果

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[Objective] Synthetic cannabinoids were reported so far, but their biological activity excepting cannabimimetic effects has not been fully investigated. We tested the structure-activity relationships influencing the anti-inflammatory activity of structurally different cannabinoid analogues and the inhibitory activity of them against tumour promotion *in vivo*. [Methods] Effects of 23 analogues on the induction of edema were examined in the ear of mice applied 12-*O*-tetradecanoylphorbol-13-acetate (TPA). Furthermore, effects of JWH-018(1), 122(2) and 210(3) on the tumor promotion were studied using the mouse carcinogenesis model with the topical application of 7,12-dimethylbenz[a]anthracene (DMBA) and promoted by TPA. [Results] Among tested compounds, the structure-activity relationships were observed for their inhibitory effects against the TPA-induced ear edema formation. Especially, 1-3 showed the most potent activity, with ID50 values of 168, 346 and 541 nM for 1, 2 and 3 respectively, which were lower than that of indometacin (908 nM). Furthermore the above 3 compounds markedly suppressed the tumour-promotiong activity of TPA following the initiation by DMBA in the mouse skin.

Keywords: Synthetic cannabinoids, anti-tumor-promoting effect

P-3357 **Mechanistic study of growth-inhibitory and apoptosis-inducing activities of curcumin in Src/Ras-activated human cells**

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クルクミンの SrcおよびRas活性化ヒト癌細胞に対する抗増殖作用およびアポトーシス誘導作用の解析

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Curcumin, a phytochemical in turmeric, has been studied as a potential anticancer drug targeting multiple signaling molecules. We found recently that activation of either Src or Ras, major oncogene products implicated in the pathogenesis of many human cancers, did not confer resistance to curcumin. We investigated therefore the molecular mechanism of anti-proliferative and apoptotic activities of curcumin in human cells transfected with activated Src or Ras. Effects of curcumin on proliferation, apoptosis, cell cycle perturbation, and activation of signal proteins (Erk, Akt, mTOR, 4EBP1, and S6K1) as well as apoptosis-associated proteins were evaluated by WST-1 assay, FACS analyses and Western blotting. Curcumin down regulated the activity of Akt and mTOR, resulting in an inactivation of 4EBP1 and S6K1, but enhanced Erk activity irrespective of the presence of either activated Src or Ras. These data suggest that curcumin might inhibit the PI-3K-Akt-mTOR pathway but enhance the Ras-MAP kinase pathway, and that activation of Src or Ras did not influence the cytotoxic activity of curcumin. The effects of curcumin on apoptosis-associated proteins are underway.

Keyword: Curcumin

P-3358 **Demethoxycurcumin induces apoptotic and autophagic responses in photodynamic therapy**

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Curcumin (CUR), demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC) are major forms of curcuminoids found in the rhizomes of turmeric. Photodynamic therapy (PDT) has been developed as an anticancer treatment which could trigger various signal transduction cascades and induce cell death. Here we show that curcuminoids-treated breast cancer cell lines with illumination can significantly inhibit cell viability; especially DMC has shown high potential anti-proliferative effect in human breast cancer cell lines. The present study suggested that both autophagy and apoptosis were induced following DMC-PDT. PDT can trigger the generation of ROS by exciting the photosensitizer, and high level ROS concentration can activate the Mitogen-activated protein kinase (MAPK) pathway. Our data showed JNK and p38 but not ERK played a crucial role in mediating DMC-PDT induced autophagy and apoptosis. Moreover, the inhibition of AMPK by compound C or transfection with shRNA enhanced apoptosis via the suppression of mTOR-mediated autophagy. Taken together, DMC-PDT induced cell death by different mechanisms.

Keywords: Demethoxycurcumin, Apoptosis

P-3359 **Suppressive Effect of Pine Cone Lignin Glycosides on Cyclooxygenase-2 Expression in Colon Cancer Cells**

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松かさリグニン配糖体の大腸がん細胞における COX-2発現の抑制効果

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A considerable body of evidence suggests that chronic inflammation is closely related to colon carcinogenesis. Cyclooxygenase-2 (COX-2), catalyze synthesis