

[*Jpn. J. Cancer Res.*, **91**, 148-155 (2000)]

[Lab. of Biochemistry]

### **Suppression of N-Nitrosomethylbenzylamine-induced Rat Esophageal Tumorigenesis by Dietary Feeding of 1'-Acetoxychavicol Acetate.**

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At the termination of the study (20 weeks), 75% of rats treated with N-nitrosomethylbenzylamine (NMBA) alone had esophageal neoplasms. However, the groups given a dose of 500 ppm 1'-acetoxychavicol acetate (ACA) during the initiation phase developed a significantly reduced incidence of tumors (29%). Exposure to ACA (500 ppm) during the post-initiation phase also decreased the frequency of the tumors (38%). A reduction of the incidence of preneoplastic lesions was obtained when ACA was administered in the initiation phase. Cell proliferation in the esophageal epithelium, determined by assay of proliferating cell nuclear antigen, was lowered by ACA. Blood polyamine contents in rats given NMBA and the test compound were also smaller than those of rats given the carcinogen. These findings suggest that dietary ACA is effective in inhibiting the development of esophageal tumors by NMBA when given during the initiation or post-initiation phase, and such inhibition is related to suppression of cell proliferation in the esophageal epithelium.

[*Xenobio. Metabol. and Dispos.*, **15**, 338-348 (2000)]

[Lab. of Biochemistry]

### **Studies on the Metabolic Fate of TA-510, a Hepatic Anti-inflammatory Agent (III): Identification of TA-510 Reductase in Human Liver**

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To identify TA-510 reductase and obtain information on the stereochemical aspects, the reductase activity has been studied in subcellular fractions from 15 human livers, and finally purified using TA-510 enantiomers as substrates. 1. This activity was present in the cytosolic fraction and exhibited strong product stereoselectivity, i.e. both enantiomers as were reduced exclusively to *trans*-alcohol (M1), but not *cis*-alcohol. Human microsomes showed practically no ketone reductase activity. 2. There was also a remarkable variation between the subjects in the substrate stereoselectivity, suggesting that racemic TA-510 was metabolized by at least two reductive enzymes with different stereochemical requirements. 3. The enzyme responsible for the reduction of (+)-TA-510 enantiomer was co-eluted with carbonyl reductase during purification steps, and separated from another enzyme with preference to (-)-TA-510 enantiomer as a substrate. Identity of (+)-TA-510 reductase and carbonyl reductase was also suggested by comparing the kinetic analysis and susceptibility to inhibitors of human liver cytosols and the purified enzyme. 4. (-)-TA-510 reductase was purified to a homogeneous protein and was shown as a monomeric protein with a molecular weight of 36 kDa. Amino acid sequences of five peptides obtained by proteolytic digestion of the purified enzyme were completely identical to the corresponding regions of previously reported 3 $\alpha$ -hydroxysteroid/dihydrodiol dehydrogenase.

[*Br. J. Pharmacol.*, **129**, 299-306 (2000)]

[Lab. of Pharmacology]

### **Different Role of IL-4 in the Onset of Hapten-induced Contact Hypersensitivity in BALB/c and C57BL/6 Mice.**

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The effect of IL-4 gene-depletion and anti-IL-4 monoclonal antibody treatment on dinitrofluorobenzene (DNFB)-induced contact hypersensitivity were examined in BALB/c and C57BL/6 mice. The reaction in BALB/c mice was greater than that in C57BL/6 mice and was suppressed by gene-depletion and antibody treatment. In contrast, the dermatitis in C57BL/6 mice was slightly affected by the treatment. Present findings indicate that IL-4 plays an important role in the onset of the contact hypersensitivity in BALB/c mice, but not in C57BL/6 mice.

[*Planta Med.*, **66**, 25-29 (2000)]

[Lab. of Pharmacology]

### **Effects of Luteolin and Other Flavonoids on IgE-mediated Allergic Reactions.**

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The effects of luteolin on the rodent allergic reactions were examined and compared to those of baicalein, quercetin, and prednisolone. Although luteolin as well as baicalein, quercetin and prednisolone inhibited the IgE antibody-mediated biphasic cutaneous reaction in mice, they did not affect the histamine-, serotonin-, and platelet activating factor-induced cutaneous reactions in rats. Luteolin, baicalein and quercetin inhibited IgE-mediated histamine, TNF- $\alpha$  and IL-6 release from mouse and rat mast cells. Luteolin, therefore, inhibited the IgE-mediated biphasic cutaneous reaction mainly by the inhibition of histamine and cytokine release from mast cells.