

トピックス

**In vitro変形性関節症モデルを用いたIL-4の軟骨保護効果の検討**

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原 著

**培養ヒト骨肉腫細胞の増殖およびリポ蛋白リパーゼと血管内皮細胞増殖因子の発現に及ぼすステロイドの影響**

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Summary

The effects of cortisol on cell proliferation and the expression of lipoprotein lipase (LPL) and vascular endothelial growth factor (VEGF) were examined in OST cells, a human osteosarcoma cell line. When OST cells were treated for 48 h with  $10^{-5}$  M cortisol, the DNA content of the cultures was lower than that of the untreated cultures. The amount of <sup>3</sup>H-thymidine incorporated into DNA in the cortisol-treated cultures was 45% of that in the untreated cultures. Western blot analysis for proliferating cell nuclear antigen (PCNA), which appears in the nuclei of proliferating cells, revealed that cortisol inhibited the expression of PCNA. RU 486, a glucocorticoid receptor (GR) antagonist, reversed the cortisol-induced decreases in the DNA content, <sup>3</sup>H-thymidine incorporation and expression of PCNA. First results indicate that cortisol inhibited proliferation of OST cells via the GR.

Next, the activity and mass of LPL were measured in the extract of acetone/ether powder of cells. The activity and mass of LPL in the cortisol-treated cultures were 50% and 58%, respectively, of those in the untreated cultures. No difference in the specific activity of LPL was observed between the untreated cultures and cortisol-treated cultures. RU 486 reversed the cortisol-induced decrease in the LPL activity. A study with [<sup>35</sup>S] methionine showed that cortisol inhibited LPL synthesis. Second results indicate that cortisol inhibited LPL synthesis via the GR, resulting in decreased LPL activity.

Immunohistochemistry for VEGF showed that the majority of cells in the cortisol-treated cultures were intensely immunostained but the intensity of VEGF expression in cells of the untreated cultures was weak. The VEGF-labeling score in the cortisol-treated cultures was 74% of that in the untreated cultures. Western blot for VEGF also showed that the level of VEGF was lower in the cortisol-treated cultures than in the untreated cultures. Third results indicate that cortisol inhibited the expression of VEGF. Thus, cortisol had the ability to inhibit the expression of LPL, a key enzyme involved in the energy metabolism in tumor cells, and the expression of VEGF, a potent angiogenic factor in the tumor.

Key Words : a human osteosarcoma cell line (OST cells), cortisol, lipoprotein lipase (LPL), vascular endothelial growth factor (VEGF)

**ラット嗅球の発生におけるプロサボシンmRNAの発現**

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#### Summary

Prosaposin is the precursor protein of saposin A, B, C and D that activate sphingolipid hydrolases in lysosomes. In addition, prosaposin itself is believed to be connected to several neurotrophic functions in the central and peripheral nervous systems. We examined the expression pattern of prosaposin mRNA in the postnatal developing rat olfactory bulb by in situ hybridization since the olfactory bulb is an excellent model to use for research on neurogenesis. The expression of prosaposin mRNA was observed throughout the examined periods (from postnatal day 0 to 60), and intense hybridization signals were observed in the following areas : in the mitral cells and tufted cells in the main olfactory bulb and in the mitral/tufted cells in the accessory olfactory bulb. Other kinds of neurons in the olfactory bulb also showed hybridization signals, but their signal intensity was weak. It was previously reported that in the developing nervous system, the expression of prosaposin became intense in the differentiated neurons ; the cortical neurons in the rat cerebrum began to express prosaposin intensely on the 10th day after birth. Therefore, our results suggest that the maturation of the mitral cells, tufted cells and mitral/tufted cells occurs relatively early in the developing central nervous system.

Key Words : prosaposin, development, olfactory bulb

#### 地域における軽度認知障害 (Mild Cognitive Impairment ; MCI) 群から痴呆への移行についての経時的研究

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#### Summary

Objective : This study aimed to estimate the rate at which subjects with Mild Cognitive Impairment (MCI) shift to dementia in a population-based cohort.

Methods : MCI subjects living in an elderly community-based dwelling were followed longitudinally. Subjects were selected among the participants in the 1st Nakayama study. MCI was defined as memory deficit with objective memory assessment, without dementia, impairment of general cognitive function, and disability in daily activities. The conversion rate was calculated using the person-year method.

Results : At base line, the sample consisted of 104 subjects (59 female ; 45 male) selected from 1,162 community dwellers over 65 year. After a five-year follow-up, 14 subjects were dead, 13 moved to other communities, and 6 refused to participate in our study. Eleven subjects (10.6%) were diagnosed with Alzheimer's disease (AD), 5 (4.8%) were diagnosed with vascular dementia (VaD), and 6 (5.8%) were diagnosed with dementia of other etiology. The annual conversion rate at which MCI shifted to AD is calculated on 8.5% per 100 person-year ; the annual conversion rate at which MCI shifted to dementia is 16.1% per 100 person-year.

Conclusions : The rate at which subjects with MCI whose conditions shifted to dementia was the same as the rate that subjects with MCI shifted to dementia in previous reports. This suggests that MCI could be a good predictor of AD or dementia. It would be useful to identify groups of high-risk individuals for dementia by simple diagnostic methods.

Key Words : Mild Cognitive Impairment (MCI), MMSE, conversion rate

## ラット神経系内のプロサポシンの分布

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### Summary

Prosaposin, the precursor of the sphingolipid activator proteins called saposins A, B, C, and D, is abundant in the nervous system and muscle tissue. Besides its role as a precursor of saposins in lysosomes, it is a neurotrophic factor that initiates neural differentiation and prevents neuronal cell death in vivo and in vitro. In this experiment, we examined the distribution of prosaposin in the central and peripheral nervous systems and its intracellular distribution. Using specific anti-saposin A, B, C, and D antibodies, we demonstrated that prosaposin is abundant in almost all neurons in both the central and peripheral nervous systems. Even when immunostaining with anti-saposin D antibody, which showed the most intense immunoreactivity, we could not find immunoreactive synaptic terminals or nerve fibers in any nerve areas. Immuno-electron microscopy using double staining with anti-saposin D and anti-cathepsin D antibodies showed that prosaposin immunoreactivity (IR) is restricted to the lysosomal granules. Our results suggest that prosaposin is synthesized ubiquitously in neurons and that it plays an important protective role in the nervous system.

Key Words : prosaposin, central nervous system, peripheral nervous system

## びまん性大細胞型B細胞リンパ腫におけるCD21抗原のフローサイトメトリー解析とその臨床的意義

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### Summary

Recent immunological and molecular technologies have prompted proposals for changing tumor classification and its treatment strategies. Cell surface antigens are easy to access, and tumor origin and clinical characteristics are identified readily. However, in diffuse large B-cell lymphoma (DLBCL), one of the heterogeneous forms of hematologic malignancy, the clinical significance of the tumor surface antigens has not been well documented. In the current study, tumor surface antigens of fifty tumors from newly diagnosed DLBCL patients were analyzed by flow cytometry according to their clinical characteristics and a follow-up study was carried out (median follow-up : 3.7 years). After the statistical analysis, we found that CD21 expression was associated significantly with survival in DLBCLs (CD21 negative versus positive ; Relative Risk : 2.36,  $P < .05$ ). After these clinical observations, we generated CD21-overexpressed (CD 21+) lymphoma cell lines after gene transfection and analyzed cell growth in vivo using immunocompromised mice. Mice were challenged with vector-only transfectants, and parental cells that served as controls died within 50 days. In contrast, mice injected with CD21+ transfectants exhibited significantly reduced tumor growth, and 83% experienced long-term survival (versus control groups,  $P < .05$ ). Interestingly, all established CD21+ transfectants (six clones from different bulks) showed homotypic aggregation during in vitro cell culturing, suggesting that other adhesion molecules may be involved in the tumor survival and homotypic aggregation. After the screening of several integrins, CD21+ transfectants highly expressed LFA-1 (CD11a/CD18) on their cell surfaces compared to vector-only transfectants and parental cells. CD21+ transfectants displayed tight adhesion when in contact with recombinant ICAM-1, and cell aggregation of CD21+ transfectants was blocked by an anti-LFA-1 monoclonal antibody. Northern analysis revealed that the mRNA

levels of CD11a and CD18 were the same for the CD21+ transfectants and controls. We conclude that the expression of CD21 is associated strongly with the survival of DLBCLs, and the explanation of this association may be due to the expression and interaction between LFA-1 and ICAM-1 on the cell surface of CD21+ DLBCLs.  
Key Words : Diffuse large B-cell lymphoma, CD21, homotypic aggregation

## 臨床経験録

### アンケート調査結果から見た愛媛県の末梢血管インターベンション治療の現況

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愛媛医学 24(1):46-49, 2005

#### Summary

The peripheral intervention has been accepted widely in the U. S. A. and vascular echo laboratory has been instituted for the peripheral vascular disease. However, vascular echo laboratory has never often found in Japanese hospitals. The purpose of this study was to examine retrospectively the state of peripheral intervention in Ehime Prefecture. We distributed a questionnaire that was concerned with the number of peripheral echocardiographies and peripheral interventions during the last two years at 41 hospitals in Ehime, and 66% (27/41) of the hospitals responded. The results show that : 1) carotid echocardiographies were performed on 7,300 patients : 5,412 echocardiographies were performed by cardiologists, 1,243 by radiologists and 645 by neurosurgeons ; 2) echocardiographies on the lower extremities were performed on 2,339 patients : 1,167 echocardiographies on the lower extremities were performed by cardiologists, 1,072 by vascular surgeons and 100 by radiologists ; 3) peripheral interventions were performed on 271 lesions : peripheral interventions performed on 177 lesions by vascular surgeons, 58 by cardiologists, 18 by radiologists and 18 by neurosurgeons within two years ; 4) target lesion of the peripheral intervention was the iliac artery in 217 patients, femoral artery in 26 patients, below-knee in 2 patients, carotid artery stenting in 14 patients, subclavian artery in 5 patients, vertebral artery in 2 patients and renal artery in 5 patients ; 5) the number of peripheral interventions in Ehime (excluding those on the iliac artery) were minimal compared to the national average of peripheral intervention procedures performed in Japan. In conclusion, the widespread of vascular echo laboratory has been necessary to investigate patients with peripheral vascular disease in Ehime.

Key Words : Vascular laboratory, Peripheral intervention, Ehime Pref

### アンケート調査結果から見た愛媛県の末梢血管検索状況と末梢血管インターベンション治療に関する意識

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#### Summary

The number of peripheral interventions performed in Japan is only 4—5% of these performed in the U. S. A. The purpose of this study was to examine the knowledge of peripheral intervention in Ehime Prefecture, where the knowledge of peripheral intervention may be different at the each hospital. The questionnaire inquired about various aspects of peripheral intervention, such as peripheral echocardiography, an investigational tool for peripheral arterial disease, appropriate doctors for each peripheral arterial disease, and trouble and lawsuits related to peripheral intervention. The collection rate was 66% (27/41). The study yielded many results : 1) At

present, there is no Vascular Echo Lab. in Ehime and the majority of doctors do not think that one is necessary to investigate peripheral arterial disease. 2) Many doctors used MRI and CT scans to investigate peripheral arterial disease rather than peripheral echocardiography and ABI. 3) Cardiologists and vascular surgeons agreed regarding the trouble and legal issues related to peripheral intervention, but neurosurgeons disagreed with cardiologists about the potential for trouble and lawsuits following carotid artery stenting. 4) Neurosurgeons alone felt that performing carotid artery stenting and subclavian artery and vertebral artery interventions were preferable. 5) Cardiologists do not generally perform peripheral angiograph when doing coronary angiograph in Ehime. 6) Doctors did not build enough close connections with each other in Ehime. In conclusion, the knowledge of peripheral intervention is not advanced in Ehime and doctors should endeavor to build closer connections with skilled technicians when performing peripheral interventions.

Key Words : Knowledge of peripheral intervention, Questionnaire, Ehime

### **病児保育カンガルーハウスの現状と今後の課題**

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愛媛医学 24(1):55-58, 2005

#### Summary

The sick-child day care program has been instituted in our hospital as part of a regional effort to provide support for child rearing. A comparison between our patient statistics and the national averages all reveal our achievements and problems. Here we examine patient distribution in the 2003 fiscal year based on age and type of illness.

The total number of patient-days per year has averaged nearly 800 children since the 2001 fiscal year. The total number of patient-days to capacity ratio was 77.3%, significantly more than the mean of Japan overall. There were many cases of acute conjunctivitis, acute otitis media, and impetigo contagiosa, as well as the expected enteritis and upper and lower respiratory tract infections.

The number of sick-child day care centers has been increasing, but it has not yet reached 500-center target planned in Angel-Plan. Two major reasons for this are unproductiveness and negative attitudes on the part of government agencies, as well as poor understanding in the general populace of sick-child day care in their lives.

Sick-child day care reduces the inconvenience of childrearing to working mothers. We suggest that this sort of support is critical in encouraging young women to become mothers, and thus prevent declining fertility.

Key Words : sick-child day care, infant, child rearing

### **症例報告**

#### **小腸gastrointestinal stromal tumor(GIST)の2例**

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愛媛医学 24(1):59-63, 2005

#### Summary

We report two cases of GIST of the small bowel. Patient 1 was a 84-year-old woman who complained of abdominal pain and abdominal fullness and was admitted with a diagnosis of ileus. Computed tomography showed a low density tumor in the right lower abdomen. Laparotomy revealed an adhesion of the small intestine

to the abdominal wall and obstruction at the site of the adhesion. A submucosal tumor was identified approximately 5 cm from the adhesion and a partial resection of the small intestine was performed. Patient 2 was a 66-year-old man who complained of melena. Computed tomography revealed a low density tumor in the lower abdomen. Superior mesenteric arteriography showed a well stained tumor. He was diagnosed with a tumor originating in the small intestine and a partial resection of the small intestine was performed.

Key Words : gastrointestinal stromal tumor, small intestine

### **著明な白質病変を呈した単純ヘルペス脳炎の1例**

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愛媛医学 24(1):64-66, 2005

#### Summary

A 72-year-old man was admitted to our hospital on December 6, 2002, due to impairment of mental function. The patient developed acute progression of gait disturbance and disorientation with high fever beginning December 1, 2002. On admission, he was somnolent with signs of meningeal irritation. Lumbar puncture revealed pleocytosis and elevated protein in the CSF. Based on a tentative diagnosis of herpes simplex encephalitis (HSE), aciclovir was administered, followed by corticosteroid. Despite the treatment, his mental function did not improve, resulting in persistent apallic syndrome. Anti-HS virus titre was high in the CSF, which significantly decreased a month later. MRI showed scattered lesions in the periventricular white matter, internal capsule, cerebral peduncle, and middle cerebellar peduncle a month after admission, mimicking acute disseminated encephalomyelitis (ADEM). Widespread white matter lesions have rarely been reported in HSE. Because in this patient, along with previous cases, the white matter was involved in the chronic stage of HSE, allergic process is the most likely mechanism underlying the white matter lesions. This case suggests that ADEM-like white matter lesions can follow HSE.

Key Words : herpes simplex encephalitis, acute disseminated encephalomyelitis, magnetic resonance imaging

### **扁桃腺摘出術により夜尿症の改善を認めた小児閉塞型睡眠時無呼吸低呼吸症候群の1症例**

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愛媛医学 24(1):67-69, 2005

#### Summary

An 11-year-old boy was referred to the university hospital because he was experiencing nocturnal enuresis almost every night. The patient's physical examination revealed the presence of adenotonsillar hypertrophy, and his mother witnessed his snoring. Polysomnographic data revealed frequent episodes of obstructive sleep apnea /hypopnea associated with desaturation and EEG arousal. The apnea/hypopnea index was 21.9/hour, and the patient was diagnosed as obstructive sleep apnea hypopnea syndrome (OSAHS).

Adenotonsillectomy was conducted, and one month after the surgery, the patient's enuresis frequency reduced to only two or three times per month.

Although OSAHS is not a rare disorder even among children, it still is often underdiagnosed. OSAHS is known to disturb the mental and physical growth, and therefore, early detection and treatment of OSAHS helps children

resume their normal growth.

OSAHS due to adenotonsillar hypertrophy should be considered as one of the causal factors of enuresis in children.

Key Words : obstructive sleep apnea hypopnea syndrome (OSAHS), enuresis, adenotonsillectomy

#### **Incidentalomaで発見された副腎褐色細胞腫の1例**

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愛媛医学 24(1): 70-74, 2005

#### **Summary**

Incidentally discovered adrenal masses, or adrenal incidentalomas, have become a commonly recognized clinical problem owing to the progression of clinical radiological imaging techniques. The etiology of adrenal masses includes benign or malignant and hormonally active or inactive adrenal cortical tumors, adrenal medullary tumors, and other lesions. We report a case of pheochromocytoma initially diagnosed as adrenal incidentaloma. A 69-year old woman consulted our hospital for anal pain and anal bleeding. Abdominal CT examination suggested an oval tumor 3.0 cm in size on the right adrenal gland. She was admitted to the hospital for further examination and treatment. Abdominal MRI suggested the same tumor on right adrenal gland which showed hypo intense mass on T1-weighted image but hyper intense on T2- weighted image. Both plasma and urinary concentrations of noradrenalin were markedly elevated. Adrenal medullary scintigraphy by 131I-MIBG showed focal increased uptake in right adrenal tumor. She was diagnosed with pheochromocytoma and underwent total right adrenalectomy. Postoperative histopathological studies were consistent with pheochromocytoma. She has remained well in the 18th months since surgery and no recurrence of tumor was revealed by any clinical examinations.

In making the diagnosis of adrenal incidentalomas, pheochromocytoma must be kept in mind as a possible diagnosis.

Key Words : adrenal incidentaloma, pheochromocytoma

#### **研究会抄録**

##### **第85回愛媛脳神経外科懇話会**

愛媛医学 24(1): 75-78, 2005

##### **第4回愛媛県摂食嚥下研究会**

愛媛医学 24(1): 79-80, 2005

##### **第12回愛媛形成外科研修会**

愛媛医学 24(1): 81-82, 2005

##### **第57回愛媛外科集談会総会**

愛媛医学 24(1): 83-92, 2005

##### **第98回愛媛整形外科集談会**

愛媛医学 24(1): 93-95, 2005