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トピックス

癌組織におけるリンパ管新生

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原　著

顔面神経高度麻痺モデルにおける表情筋での遺伝子発現

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Summary

This study investigated and identified differentially expressed facial muscle genes in rats with facial nerve damage. Two types of adult Wistar rats : 1)the main trunk of the facial nerve was transected(Group A)and 2)the main trunk was compressed for ten minutes(Group B)were used for the analysis. Global gene expressions of facial muscles were analyzed using a micro-array system. A total of 26,835 RNA molecules were examined. Up-regulated genes in Group A were more than in Group B at 7, 14 and 28 days after the procedures. Three differential genes which fluctuated widely at 7 days were detected based on this micro-array analysis and quantified using two step RT-PCR. Myogenin mRNA expression increased to the highest level at 7 days after denervation, thereafter it gradually decreased in Group A. Vesicle-associated membrane protein 2 and insulin-like growth factor binding protein 6 expression increased at 7 and 14 days in Group A.

The gene expression was different depending on the degree of the facial nerve damage. Therefore, we concluded that analysis of the facial muscle profile gene expression could be a possible diagnostic tool for use in as the prognosis after facial nerve injury.
Key Words : facial nerve damage, facial muscle, gene expression

VLDL受容体とNPC1の二重欠損マウスは小脳形成異常を引き起こす

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Summary

To investigate the roles of lipoprotein receptors in lipoprotein metabolism of central nervous system （CNS)and the accumulating mechanism of unesterified cholesterol in Niemann-Pick type C(NPC)disease, we generated the double knockout(DKO)mice lacking VLDLR and NPC1. DKO mice exhibited severe abnormality in the layer structure in cerebellum development in NPC1 dose-dependent manner. Histological analysis showed cerebellar dysplasia and impairment of neuronal migration and lamination in cerebellum of the DKO mice but not in hippocampus and cerebral cortex. These phenotypes were not observed in other DKO mice such as ApoE／NPC1 and LDLR／NPC1 mice, suggesting that the impairment of neuronal migration and lamination is not due to abnormal lipoprotein metabolism, but rather due to the dysfunction of molecules involved in reelin signaling.

However, there is no difference between VLDLR／NPC 1 mice and age-matched single knockout mice in expression levels of ApoER2, integrin α 3 β 1 and reelin, and also in the phosphorylation level of Dab1. These results suggest that there may be a novel pathway of reelin signaling to play an important role in cerebellar development.

Key Words : VLDLR／NPC1 DKO mice, reelin, cerebellum

2種類の自殺遺伝子を組み込んだ腫瘍選択増殖型アデノウイルスによる乳癌の遺伝子化学療法

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Summary

Background : The treatment of breast cancer has improved remarkably over the past ten years. However, the therapeutic results for advanced or recurrent breast carcinomas are not satisfactory because this disease is still the most frequent cause of death in middle-aged Japanese women. We investigated the feasibility of an oncolytic adenovector with two suicide genes for the treatment of breast cancer.

Materials and Methods : We developed a new conditionally replicating adenovirus（AxE1CAUT）with the uracil phosphoribosiltransferase（UPRT）gene and the herpes simplex virus thymidine kinase（HSV-tk）gene, and compared its anti-tumor effects with a replication defective adenovector（AxCAUT）that had both the UPRT and HSV-tk genes. We evaluated the effects of these adenoviruses with 5-fluorouracil（5-FU）and／or ganciclovir（GCV）tests on human breast cancer cells（SK-BR-3, with mutant p53）in vitro and in vivo. In a subcutaneous tumor model of nude mice, 14-days of continuous drug administration using an ALZET Osmotic Pump was started 3 days or 10 days after the AxE1CAUT injection, in order to estimate the effectiveness of the vector's intra-tumor replication.

Results : AxE1CAUT and AxCAUT induced a 1 : 1 expression of UPRT and HSV-tk at each MOI. The drug sensitivity of SK-BR-3 cells to 5-FU and／or GCV increased with an increase in the multiplicity of infection（MOI）. The IC50（ μM）decreased when 5-FU and GCV were given at the same time, but a synergetic effect from the combination of 5-FU and GCV was not observed in the subcutaneous tumor model of nude mice directly injected with AxCAUT or AxE1CAUT. The relative expressions of UPRT or HSV -tk genes 10 days after the vector injection were higher than 3 days after the vector injection. The tumors with 5-FU alone, started 10 days after the AxE1CAUT injection, showed the best response among the 5- FU and／or GCV groups.

Conclusion : The delayed administration of 5-FU with the conditionally replicating AxE1CAUT adenovirus was effective on human breast cancer cells with a p53 mutation.

Key Words : adenovector, E1B-deletion, breast cancer

ヒトデ幼生食道輪状筋線維数に対する鉱物性汚染物質曝露の影響

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Summary

Recently, mineral contaminants and sea pollution are thought to affect the health of many animals including humans. This is an especially serious problem in developing countries. It has been reported that the axis and

germ layer formation of sea urchin embryos are affected by mineral contaminants. In contrast, there are few reports in asteroids. In this study, we investigated the effects of mineral contaminants on the circular muscle fibers of larval esophagi in sea bats, one kind of asteroids. The circular muscle fibers were examined using TRITC-phalloidin. The intact and contaminants-exposed larvae at 72 hours after 1-MeAde treatment. Zinc-exposed larvae showed a decrease in esophageal circular muscle fibers to 30%（at 0.005mM）, 53%（at 0.0025 mM）and 77%（at 0.00125 mM）. Nickel-exposed larvae showed a decrease in esophageal circular muscle fibers to 32%（at 0.05 mM）, 49%（at 0.025 mM）and 77%（at 0.0125 mM）. Cadmium-exposed larvae showed a decrease in esophageal circular muscle fibers to 37%（at 0.1 mM）, 59 %（at 0.05 mM）and 78%（at 0.025 mM）. Our results suggest that measuring the mineral contamination found in the circular muscle fibers of asteroid larval esophagi has advantages for monitoring sea pollution.

Key Words : asteroid larva, circular muscle fiber, mineral contaminants

口腔扁平上皮癌センチネルリンパ節生検におけるOSNA法の有用性

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Summary

Nodal status of the cervical lymph nodes in oral squamous cell carcinoma（OSCC）remains an important prognostic factor. Management of the N0 neck is an important issue for oral surgeons. We have performed sentinel lymph node biopsies for clinical N0 cases routinely and reported the usefulness. The sentinel lymph node biopsy was followed by a histopathological examination using semiserial sectioning and a molecular diagnosis via real-time quantitative RT-PCR. However, these methods took about two hours to get diagnosis. The aim of this study was to develop a more accurate and quick molecular detection system. We examined an intraoperative diagnosis using One Step Nucleic acid Amplification（OSNA method）, and measuring cytokeratin 19（CK 19）mRNA. Two-hundred forty seven lymph nodes resected during sentinel lymph node biopsy and neck dissection were diagnosed by histopathological examination using semiserial sectioning. Alternative halves of these lymph nodes were diagnosed by calculating CK 19 mRNA copy numbers using the OSNA method. The sensitivity, specificity and accuracy of OSNA were 95.1%, 97.1% and 96.8%, respectively. In addition, OSNA analysis could be completed within 30 min. The high accurate OSNA method can be used in intraoperative molecular diagnoses as a tool for detecting metastasis in the sentinel lymph nodes of OSCC.

Key Words : Oral squamous cell carcinoma, OSNA, Sentinel lymph node biopsy

統合失調症における向精神薬の多剤併用からperospironeによる単剤化への経験

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Summary

Objective : To investigate the effects of switching from psychotropic polypharmacy to antipsychotic monotherapy using the atypical antipsychotic perospirone in eleven patients with schizophrenia.

Materials and Methods : Subjects were eleven individuals who had been diagnosed as schizophrenia based on

ICD－10 classification. We applied the plateau cross-titration method when switching antipsychotics. After the switch, concomitant administration such as anticholinergic drugs, anxiolytics and hypnotics etc were gradually discontinued, as much as possible. We assessed the clinical psychiatric symptoms, extra-pyramidal symptoms, fasting blood sugar（FBS）, prolactin（PRL）, body weight（BW）and quality of life（QOL）by the assessment scales. These items were assessed at the start and end of the switch, 4, 8 and 12 weeks later.

Results : It was impossible to switch from psychotropic polypharmacy to antipsychotic monotherapy using perospirone. But negative symptoms and QOL improved, PRL and BW were also decreased. All anticholinergic drugs were decreased or stopped.

Discussion : Five patients dropped out of this protocol due to hallucination and delusion. It was also impossible for the continuing six patients to complete antipsychotic monotherapy using perospirone. But those patients who continued saw their negative symptoms improve after switching to perospirone. We concluded that perospirone was a useful drug when switching from psychotropic polypharmacy to antipsychotic monotherapy.

Key Words : schizophrenia, perospirone, switching

腎足細胞由来新規KRAB-zinc finger型転写制御因子ZIPOの遺伝子クローニングとその特徴化

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Summary

Podocytes are terminal differentiated cells that form glomerular slit diaphragms. Podocyte injury causes irreversible renal dysfunction and protein urine. The molecular mechanism that causes podocyte differentiation remains unknown. Understanding this mechanism is essential to developing a strategy for regenerating podocytes and applying it in a clinical setting. In order to obtain some clues to understand the molecular mechanism of podocyte differentiation, we performed DNA chip analysis between pre and post podocyte differentiation using conditionally-immortalized mouse podocyte cell line MPC cells. This resulted in the identification of novel three upregulated genes present in post differentiation encoded KRABC2H2 zinc finger proteins. We termed these zinc-finger protein in podocyte I, II and III（ZIPO I, II and III）. cDNA cloning and alignment on the chromosome revealed that ZIPO I, II and III were closely related and repeated in tandem on mouse chromosome 2. ZIPO mRNAs are expressed in various tissues of adult mouse and whole mice embryos. We further identified Zfp 709 as a mouse ZIPO paralogue, and ZFP 709 alone as a human ZIPO orthologue. Their functions are still unknown. Interestingly, human ZNF 709 has no other paralogues and was expressed mainly in fetal brains and kidneys. We suggest that ZNF 709 will be a key player in human podocyte differentiation.

Key Words : KRAB-C2H2 zinc finger, ZNF 709, podocyte differentiation

研究会抄録

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愛媛医学 28(2):108-109, 2009

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愛媛医学 28(2):116-118, 2009

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