

TANAKA S: Tryptophan Degradation by Indoleamine 2,3-dioxygenase (IDO) and Tryptophan 2,3-dioxygenase (TDO) in Murine Concepti 1-9

Indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) are the tryptophan (Trp) degradation enzymes that catalyze the oxygenation of an essential amino acid, Trp, into N-formylkynurenine.

In 1998, David Munn et al reported that IDO initiated Trp degradation in the placenta and that it might play an important role in the prevention of allogeneic fetus rejection by maternal T cells.

However, the role of IDO has not been fully elucidated. The expression patterns of Trp degradation activity, IDO protein and IDO mRNA were examined in embryonic and extra-embryonic mouse tissue.

Although Trp degradation activity was very low at 5.5 days post-coitus (dpc), it dramatically increased to the peak level at 6.5 dpc, and then gradually decreased to the zero level by 18.5 dpc.

IDO protein, however, was detected between 8.5 and 12.5 dpc. IDO mRNA was also very low before 8.5 dpc, reaching its highest peak at 9.5 dpc. These results suggest that IDO does not contribute to the early phase of Trp degradation in gestation. IDO mRNA and protein were not expressed during such early gestation. On the other hand, TDO mRNA and protein were strongly expressed during the early gestation period. The Trp degradation activity of the early gestation period was not inhibited by a specific IDO inhibitor, 1-methyl-Trp, but that at 12.5 dpc was strongly inhibited. These findings suggest that the Trp degradation activity of the early period is not caused by IDO, but by TDO. TDO has been reported to be localized exclusively in the adult liver. This is the first report in which extra-hepatic expression of TDO has been clearly demonstrated. These results suggest that TDO, rather than IDO, functions in Trp deprivation in early concepti to maintain nidation, and that shortly induced IDO functions in local Trp deprivation to prevent allogeneic fetus rejection, while allowing supplement of Trp to the fetus in middle phase conception.

KUBOZOE T: Preventive Effects of An Angiotensin Converting Enzyme Inhibitor and A Calcium Antagonist on The Development of Spontaneous Pancreatitis in Salt-loaded Dahl Salt-sensitive and Salt-resistant Rats 11-21

Pancreatic lesions were examined histopathologically in Dahl salt-sensitive rats (DS-S) and Dahl salt-resistant rats (DS-R) fed a high-salt (8% NaCl) diet from the age of 5 weeks to 11 weeks. The DS-S rats were divided into three groups; group 1 received drinking water throughout the experimental period, group 2 received 0.001% trandolapril (antihypertensive), and group 3 received 0.2% verapamil (antihypertensive). The DS-R rats were also divided into three groups; group 4 received drinking water throughout the experimental period, group 5 received 0.001% trandolapril, and group 6 received 0.2% verapamil. Systolic blood pressure in group 1 was significantly higher than that in groups 2 and 3 throughout the experiment. The pancreatic blood flow of the 11-week-old DS-S in group 2 was significantly greater than that in groups 1 and 3. Acinar degeneration with inflammatory changes and stromal fibrosis were observed in the pancreas of group 1 animals at 11 weeks of age, together with periarteritis nodosa. These pancreatic pathological findings were not observed in groups 2 and 3 at 11 weeks of age. TUNEL positive cells were not observed in the pancreas of 6-11 week DS-S in groups 1, 2 and 3. The process of apoptosis appears to have no effect on the pathology of pancreatic fibrosis in chronic ischemic pancreatitis. The body weight, systolic blood pressure and pancreatic blood flow of the 11-week-old DS-R did not significantly differ among the three groups. Pancreatic pathological findings were not observed in groups 4, 5 and 6 throughout the experiment, nor were TUNEL positive cells noted in the pancreas of 6-11 week DS-R in these groups. In conclusion, the pancreatic ischemia caused by stenosis of the arteries was an important factor in the pathogenesis of the pancreatitis in DS-S.

FUJII T: Effects of Hypoxia on Human Seminoma Cell Lines

23-31

Hypoxia is considered to play an important role in tumor progression through vascular endothelial growth factors (VEGF). In this study, the effects of hypoxia on human testicular seminoma cells were analyzed. A human testicular seminoma line (JKT-1) and its highly metastatic subline (JKT-HM), established at Kawasaki Medical School, were used to analyze the effects of hypoxia on these cells with regard to growth, morphological changes, production of VEGF-A, and various gene expressions including angiogenic factors, induction of apoptosis, and cell cycle perturbation. Hypoxia suppressed cell growth, caused morphological changes that transformed the cells into large and spindle-shaped cells, and enhanced VEGF-A production in both lines. In JKT-1 cells, the gene expressions of VEGF-A, -B, and -D were enhanced until day 2 in hypoxia, and then reduced. However, VEGF-C expression was enhanced continuously. There was no change in HIF-1 (hypoxia inducible factor-1) gene expression. In addition, upregulation of stress proteins (HSP70 and HSP90), cyclin-dependent kinase-inhibitors (CDK-Is) (p21, p27, and p15), and adhesion molecules (CD44 and Vimentin) was observed in JKT-1 cells cultured in hypoxia. Although both lines showed G₁ cell cycle block in hypoxia, no appearance of apoptotic fractions was noted. These results indicate that the upregulation of angiogenic factors caused by hypoxia was observed in seminoma cells in similar manner to that in other solid tumors. Specifically, the constitutive upregulation of VEGF-C, which has been identified as one of the most important factors in lymphatic metastasis of cancer cells as well as VEGF-D, lead us to clarify the role of this factor in clinical lymphatic metastasis found in seminoma patient in the future.

Programmed cell death (PCD) is an important process for eliminating unnecessary tissues during embryonic development for proper morphogenesis at genetically determined stages. In this study, we analyzed transcriptional changes of 1176 genes in mouse limb programmed cell death (PCD) using DNA microarray technique. Many genes were up- or down-regulated during PCD. Homeobox genes *Msx2*, insulin-like growth factor binding protein 2 (*IGFBP2*) or apolipoprotein E (*apoE*) genes were up-regulated in interdigital PCD, revealed by DNA Expression Array using total RNA extracted from day 11.5 or 13.5 limb buds. Topological transcriptional patterns of selected genes were examined by *in situ* hybridization. PCD was revealed by Nile blue, HE staining or TUNEL method. *In situ* hybridization of *apoE* showed similar pattern as the Nile blue staining, and its expression was detected not in dying cells, but in macrophage-like cells. This observation suggested that *apoE* would be involved in engulfment of apoptotic cells. We found that its expression was also significantly reduced in BrdU-treated limbs, suggesting that *apoE* expression had been induced by unknown signals from dying cells.

The effects of long-term (72 hours) exposure to a low concentration (0.1 μ M) of nicotine on various types of voltage-dependent Ca^{2+} channels (VDCCs) and neuronal nicotinic acetylcholine receptors (nnAChRs) were examined using primary cultures of mouse cerebral cortical neurons. Thirty millimolar KCl stimulated [$^{45}\text{Ca}^{2+}$] influx into the neurons increased with increase in the duration of nicotine exposure and its concentrations. The maximal increase of KCl-stimulated [$^{45}\text{Ca}^{2+}$] influx was observed 24 hours after the initiation of exposure and thereafter was maintained up to 72 hours, at which time it was completely suppressed by mecamylamine, an inhibitor for nnAChRs. The KCl-induced [$^{45}\text{Ca}^{2+}$] influx observed after long-term exposure to nicotine, which was sensitive to nifedipine, an inhibitor of L-type VDCCs, was facilitated while the [$^{45}\text{Ca}^{2+}$] influx through P/Q- and N-type VDCCs showed no changes. Moreover, enhanced immunoreactivity against antibodies for $\alpha 1\text{C}$, $\alpha 1\text{D}$ and $\alpha 2/\delta 1$, subunits of L-type VDCCs was recognized, whereas no changes in immunoreactivity against antibodies for $\alpha 1\text{A}$ and $\alpha 1\text{B}$ subunits of other types of VDCCs were noted. In addition, the expression of mRNA for L-type VDCC subunit, $\alpha 1\text{F}$, was also enhanced, although $\beta 4$ mRNA expression did not change. Up-regulation of $\alpha 4$ and $\beta 2$ subunits, but not $\alpha 3$ subunit of nnAChRs, was also noted after the nicotine exposure. Taken together, these results indicate that long-term exposure of the neurons to a low concentration of nicotine induces both increased [$^{45}\text{Ca}^{2+}$] influx through up-regulated L-type VDCCs and nnAChR up-regulation.

GOTO T, GYOUTEN M, IMAI S, YAMASHITA T, HIGASHI H,
KAJIHARA Y : Percutaneous Arterial Embolization for Renal Rupture in a Long
Term Dialysis Patient 59-62

Transcatheter arterial embolization (TAE) was performed on a long term dialysis patient to treat a retroperitoneal hemorrhage that concurrently developed with acquired cystic disease of the kidney (ACDK) and good results were obtained. Generally, in many patients undergoing TAE for renal hemorrhage, only the hemorrhagic site is selectively embolized to preserve renal function. However, the present patient had been receiving dialysis, and marked atrophy of the kidney and renal hypofunction were observed.

Therefore simple TAE was performed through the renal arterial trunk.

Simple TAE for hemorrhage of a kidney being treated by dialysis can be noninvasively performed for a short duration and may be an effective treatment.

MITSUI Y, KUNIEDA T, MIMURA N, IGUCHI Y, SHIMABARA M,
KUBOKI M, OHMOTO K, YAMAMOTO S, SADAHIRA Y,
SUEMORI S, WADA H, SUGIHARA T: A Case of Primary Hepatic
Lymphoma Complicated by Chronic Hepatitis C 63-68

Abstract : The patient was a 49-year-old male, who in a follow-up on chronic hepatitis C, was found ultrasonographically to have multiple hypoechoic tumors in both liver lobes. These tumors exhibited low density areas by plain CT, and were not enhanced by early enhancement CT. These tumors appeared as low intensity mass lesions on T1-weighted image and as high intensity mass lesions on T2-weighted image by MRI. The laboratory data showed AFP, PIVKA II, CEA and CA 19-9 levels to be within normal range. By a sonographically-guided tumor needle biopsy, tumors were histologically diagnosed as diffuse large B cell lymphoma. Neither a Ga scintigram nor a bone scintigram detected space-occupying lesions in other organs or lymph nodes. Therefore, this case was diagnosed as primary hepatic lymphoma complicated by chronic hepatitis C.

Recently, it has been suggested that hepatitis C virus plays a role in the development of lymphoid proliferative disease as well as in the development of hepatocellular carcinoma.

We discussed the clinical and diagnostic image findings, and reviewed the literature regarding primary hepatic lymphomas.