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General Summary

We have 9 subspecialty research groups: (1) the Congenital Metabolic Diseases, Endocrinology, and Medical Genetics group, (2) the Allergy and Immunology group, (3) the Neurology group, (4) the Hematology and Oncology group, (5) the Cardiology group, (6) the Infectious Diseases group, (7) the Neonatology group, (8) the Nephrology group, and (9) the Pediatric Psychiatry group. The final aim of these subspecialty groups is supplying practical benefits to patients and their families through basic and clinical research. To accomplish this purpose, both cooperation and a high motivation for research are needed.

Research Activities

Congenital Metabolic Diseases, Endocrinology, and Medical Genetics

Accomplishments of our group this year are as follows.

1. We clarified the minimum required number of donor cells in bone marrow transplantation for lysosomal diseases.
2. We found that the autophagy build-up in lysosomal disease cells was reduced by a chemical chaperon.
3. We developed a novel gene therapy approach using a lentiviral vector.
4. We found that regulatory T cells are essential in inducing tolerance to enzymes in enzyme replacement therapy for lysosomal diseases.
5. We prepared rats with left ventricular heart failure and analyzed the expression patterns of urocortin 2, urocortin 3, and nesfatin 1 in their brains. Furthermore, we compared messenger RNAs of these genes before and after administration of human atrial natriuretic peptide to these rats.
6. We are developing methods for the molecular diagnosis of genetic diseases by means of competitive genomic hybridization arrays and multiple ligation-dependent probe amplification.

Neurology

1. We investigated sequelae of acute encephalopathy in 103 children. Mental retardation was found in 89.3%, higher cortical dysfunction in 77.7%, epilepsy in 68.9%, and motor disturbance in 27.2%. The severity of disabilities due to sequelae was greatest in acute encephalopathy caused by metabolic disorders. Attention deficit and visuospatial disturbance were the main symptoms of higher cortical dysfunction.

2. We reviewed the medical records of 21 patients with neonatal cerebral infarction to evaluate clinical characteristics. Eighteen patients were born at term. The onset of cerebral infarction was within 2 days in 90% of patients. Seizures were found in 52.4% of patients, and respiratory disorders were found in 33.3%. Infarctions occurred more frequently in the left hemisphere and in the territory of the middle cerebral artery (81.0%). Motor impairments were found as sequelae in 8 patients, mental retardation in 5, and epilepsy in 3.

Hematology and Oncology

We investigated the effects and the molecular mechanisms of histone deacetylase (HDAC) inhibitors valproic acid and depsipeptide on ionizing radiation (IR)-induced apoptosis in Y79 and WERI-Rb1 retinoblastoma cells. We found that valproic acid and depsipeptide synergistically enhanced IR-induced apoptosis, associated with activation of caspase-3 and cleavage of poly (ADP-ribose) polymerase in both cell types. Both valproic acid and depsipeptide enhanced IR-induced phosphorylation of histone H2AX on Ser139 preceding apoptosis. Exposure of cells to IR in the presence of valproic acid or depsipeptide induced the accumulation of p53 acetylated at Lys382 and phosphorylated at Ser46 through the reduction of binding affinity with MDM2 and MDMX. These results suggest that acetylation of p53 by HDAC inhibitors is a promising new therapeutic target in refractory retinoblastoma.

Infectious Diseases and Immunologic Disorders

We focus on identification of causative pathogen using polymerase chain reaction (PCR) techniques, genetic diagnosis, treatment of primary immunodeficiency syndrome, and analysis of immune response in pediatric rheumatic diseases.

Our research and development are as follows.

1. Rapid identification of causative pathogen on inflammatory diseases using multiplex PCR
2. Quantification of herpesviridae genome using real-time PCR
3. Molecular analysis of drug resistance genes of bacteria
4. Retrovirus gene therapy for X-linked chronic granulomatous disease
5. Disease activities and prognosis of juvenile idiopathic arthritis, systemic lupus erythematosus, and dermatomyositis
6. Efficacy and safety of biologic agents against refractory rheumatic diseases

Nephrology

We retrospectively analyzed the long-term outcomes of 82 children (10 with steroid-resis-

tant nephrotic syndrome [SRNS], 35 with steroid-dependent nephrotic syndrome [SDNS], and 37 with infrequently relapsing nephrotic syndrome [IRNS]) who were initially treated with the International Study of Kidney Disease in Children (ISKDC) regimen at Saitama Children's Medical Center. The ISKDC regimen consists of treatment with prednisolone, 60 mg/m²/day, for 4 weeks, followed by alternate day treatment with 40 mg/m² for another 4 weeks. The aims of our study were to identify factors at onset that could predict the pattern of relapse after the initial treatment with the ISKDC regimen and to assess the prognosis and renal histology after long-term ciclosporin A therapy in 31 children.

All 6 asymptomatic children, without edema and identified with proteinuria incidentally detected with a urinary screening program, had an extremely favorable clinical course.

An initial remission time of 9 days or more and the interval from the initial therapy to the first relapse were significant predictors of steroid dependency. These findings had a sensitivity and specificity of 100% and 90%, respectively, a positive predictive value of 95%, and negative predictive value of 100%.

In addition, after the introduction of ciclosporin A therapy, steroid therapy could be stopped in 56% of patients with SRNS and 64% of patients with SDNS. However, after ciclosporin A therapy was tapered or stopped, nephrotic syndrome relapsed in most patients (21 of 20; 95%). Of these patients, 80% (16 of 21) again had SDNS, which was treated with ciclosporin A. Ten of the 22 patients treated with ciclosporin A (mean duration, 31.3 months) had chronic nephrotoxicity.

In conclusion, the initial ISKDC regimen is useful for the early prediction of SDNS. When pediatric nephrologists introduce ciclosporin A therapy in children with SDNS, an alternative strategy should be considered after long-term use of the agent.

Cardiology

The Pediatric Cardiology group is interested in both basic and clinical cardiology research to improve treatment outcomes for children with congenital heart conditions. Our study results were presented at annual meetings of the Japan Pediatric Society and the Japan Pediatric Cardiology Society. Grants from 2 national foundations were distributed to our group to study right ventricle heart failure and copy number variant in congenital heart disease. Specific projects under way in our group include the following.

1. The effect of telmisartan in right heart failure
2. Cardiac apoptosis in right heart failure
3. Clinical outcome of cardiac morphology involved in congenital metabolic disorders
4. Gene transmutation in patient with noncompaction

We also are interested in specific clinical research projects, as follows.

1. Making appropriate management plans based on fetal diagnosis.
2. Long-term outcomes in patients with total cavopulmonary connection circulation.
3. Interventional catheterization (balloon angioplasty and valvuloplasty, coil embolization, transcatheter stenting, and catheter closure of congenital heart defects).

Publications

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