order to thrive. Interestingly, we revealed a dramatic increase of immature granulocytes only in bone marrow of EBV-infected mice. In addition, GM-CSF, a cytokine that is essential for differentiation of the myeloid lineage, was significantly increased in EBV-infected mice. These results were also reproduced in patients with EBV-related disorders.

This research revealed that abnormal hematopoiesis was occured in mice following EBV infection. Considering the above results, the hematopoietic alteration might be involved in a cause of lymphoproliferative disorders in human by reduction of tumor immunity.

**2-3.**

**Expression of intracellular cytokines in twins with intractable epilepsy associated with lissencephaly**

（社会人大学院博士課程 2 年小児科・思春期科学分野）
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Purpose : Involvement of immunological processes in the pathogenesis of epilepsy has been suggested on the basis of accumulating evidence. This study aimed to determine whether twins presenting with intractable epilepsy exhibited immune system dysfunctions. Despite sharing a common diagnosis of lissencephaly and the same genetic mutation, the twins had different developmental prognoses : twin A had a severe developmental delay, while twin B had a moderate developmental delay.

Methods : Through flow cytometry, we examined the intracellular cytokine profiles of peripheral blood mononuclear cells collected from the twins and their plasma cytokine levels in reference to two age-matched controls.

Results : The twins had a higher percentage of interleukin-1 beta（IL-1β）-positive CD14+ monocytes than the controls. Twin A had higher percentages of IL-1 receptor antagonist（IL-1RA）-positive and tumor necrosis factor-alpha（TNF-α）-positive CD14+ monocytes than twin B and the controls. The plasma cytokine levels of IL-1β, IL-1RA, and TNF-α were lower in twin A than in twin B and the controls.

Conclusions : While a slight difference in the proportions of cytokine-producing cells between the twins was observed, it is unclear how this difference is involved in their respective pathophysiology. Further studies with more patients should assess whether minor differences in the number of cytokine-producing cells can influence the pathogenesis of intractable epilepsy.

**3-I-1.**

**DNA-damaging drugs in combination with a macrolide antibiotic enhance cytotoxicity for non-small cell lung cancer cells**

（大学院博士課程 3 年呼吸器内科学分野）
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For the treatment of lung cancer, new drugs such as tyrosine kinase inhibitors（TKIs）and immune checkpoint inhibitors are being developed one after another, but patients who show interstitial pneumonia or do not carry gene mutations of targets for each TKIs are not applicable for them. Therefore, conventional DNA-damaging drugs are still useful for such patients. In recent years, it has been revealed that cancer cells utilize autophagy for their own growth and that autophagy acts cytoprotectively when cancer cells are exposed to anticancer drugs. Because hydroxychloroquine（HCQ）is the only clinically available autophagy inhibitor but causes severe retinopathy and cardiomyopathy, the development of other autophagy inhibitors is desired. Our group has been reported that macrolide antibiotics have an autophagy inhibitory effect and that their combined use with TKIs or proteasome inhibitors

enhanced cytotoxicity in various cancer cells. In this study, we evaluated the effect of combination therapy with DNA-damaging drugs and a macrolide antibiotic.

We found that DNA-damaging drugs in combination with azithromycin (AZM), one of the macrolide antibiotics, enhanced cell death including apoptosis in a non-small cell lung cancer cell line, A549. This enhanced cytotoxicity by the drug combinations was significantly decreased in a p53-mutated lung cancer cell line and a p53 KO A549 cells. We also found that the combined use of a DNA-damaging drug and AZM significantly changed the morphology with an increased number of the enlarged LAMP2-positive organelles which were considered as autolysosomes and/or lysosomes. These data suggested that DNA-damaging drugs in combination with AZM strongly induced cell death in A549 cells by activating apoptosis which might be caused by the damaged lysosomes and dependent on the p53 signaling pathway.

**3-I-2.**

**Increased APOBEC3C-H Gene Expression is Associated with Improved Outcome in Breast Cancer**

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Background : APOBEC3 are strong mutagenic enzymes. The association between APOBEC3B (A3B) expression and DNA mutation has been well studied. However, it is still unclear on other A3s (A3A, C-H). We investigated the clinical relevance of A3s on their mutagenic and cancer immunity angles.
Methods : 1) A3s gene expression level was examined on 55 breast cancer cell lines.

2) The association of A3s with the clinical outcome and other molecular features were investigated from TCGA-BRCA data. Patients were divided into 3 groups by the A3s gene expression level ; high, intermediate and low. The clinical outcome were compared between high and low groups. Molecular features were quantified with bioinformatics workflow and examined the association with A3s expression level.
Results : 1) A3B & 3C represented 91% of A3s expression in cell lines. 2) A3C-H expression was significantly associated with improved clinical outcome (HR, 0.45-0.66). A3A and A3B expression levels were correlated with both tumor mutation burden and neoantigen load (Spearman r = 0.28-0.34), while not for A3C-H. Expression of genes related to immune function like interferon response and complement activation was enriched in high A3C-H expressors, which significance was observed in CD4 and CD8 T cells, TCR diversity and tumor immune cytolytic activity (2.3-4.0x, 2.1-5.4x, 1.3-2.1x & 3.1-7.9x, resp.).
Conclusion : Unlike A3B, A3C-H were expressed in stromal cells, not in breast cancer cells. A3C-H expression may activate immune cells. A3C-H gene expression was associated with better outcome in breast cancer patients. It is speculated that up-regulating immune function by A3C-H may explain this clinical finding.