

2-1.

The efficacy of phage therapy in a murine model of *Pseudomonas aeruginosa* pneumonia

(大学院博士課程4年微生物学)

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The emergence of multi-drug resistant *Pseudomonas aeruginosa* necessitates the search for treatment options other than antibiotic use. The use of bacteriophages is currently being considered as an alternative to antibiotics for the treatment of bacterial infections; however, this method has not yet been evaluated on pneumonia caused by *P. aeruginosa*. We used the potent bacteriophage KPP10 against *P. aeruginosa* strain D4-induced pneumonia mouse models and observed their outcomes. We found that the nasal inhalation of bacteriophage KPP10 (MOI = 80) significantly improved survival rate in pneumonia models ($P < 0.01$). The number of viable bacteria in the lungs decreased to undetectable levels in phage-treated mice but not in control mice ($P < 0.01$). Pathological examination showed that the phage-treated group had significantly reduced bleeding, inflammatory cell infiltration, and mucus secretion in the lung interstitium. We also measured inflammatory cytokine levels in the serum and lung homogenates of mice. In phage-treated models, serum TNF- α , IL-1 β and IFN- γ levels were significantly lower ($P < 0.05$, $P < 0.01$ and $P < 0.05$, respectively) and in the lung homogenate, the mean IL-1 β level in phage-treated models was significantly lower ($P < 0.05$) than that of the control group. There was no significant difference in High mobility group box 1 (HMGB1) levels in both groups. Thus, our results suggest that phage therapy can potentially be used in treating lung infections caused by *P. aeruginosa* after it is evaluated more thoroughly.

2-2.

Increased Granulopoiesis in the Bone Marrow following Epstein-Barr Virus Infection

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Epstein-Barr virus (EBV) is associated with several disorders. EBV is known to modulate the proliferation and survival of hematopoietic cells such as B cells and T cells in human. However, the effects of EBV on hematopoiesis itself have not been investigated.

To study EBV infection in murine models, their hematopoiesis must be humanized, since EBV infection is limited only in some primates. To engraft the human hematopoiesis, NOD/Shi-scid-IL2 γ null (NOG) mice were used. Usually, the hematopoiesis humanized mice reconstitute only lymphoid cells, but myeloid cells are not. However, we revealed human macrophages (hM ϕ) and their precursor monocytes were increased in peripheral tissues of EBV-infected mice. Furthermore, our previous report indicated M ϕ accumulation in spleen was essential for development of EBV-positive tumors, suggesting that EBV modulates human hematopoiesis in

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 occurred 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-1 β)-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-1 β , 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