発性 3.1 倍、家族性 3.5 倍)。またアポトーシスを亢進するマーカーとして知られる BCL2 associated X（BAX）の遺伝子発現も加圧により亢進していたが（健常者 1.6 倍、特発性 1.3 倍、家族性 1.5 倍)、アポトソームの 1 つである apoptotic peptidase activating factor1（APAF1）の遺伝子発現は加圧により抑制されていた（健常者 0.9 倍、特発性 0.8 倍、家族性 0.6 倍)。

【考察】 肺動脈組織に加わる過剰な圧力は、肺動脈平滑筋細胞に酸化ストレスを与えて、UCP2 の発現亢進を促進し、それによりアポトーシスを抑制することで PAH 病態に関与することが示唆された。

5-②-5.

Molecular genetic analysis of severe hemophilia A patient without bleeding symptom

（社会人大学院博士課程 4 年臨床検査医学分野）
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Introduction
Hemophilia A is an X-linked bleeding disorder caused by a quantitative and qualitative abnormality in coagulation factor VIII（FVIII）. Based on the correlation between FVIII activity（FVIII : C）and clinical severity, FVIII : C<1% was classified as severe hemophilia.
Aim
A 20's man was diagnosed with severe hemophilia A at his childhood, FVIII : C was <1% characterized by one stage assay（OA）. However, he had no episodes of bleeding. The purpose of this study was to elucidate the cause of the significant discrepancy between the clinical phenotype and the type of disease classification.
Methods
FVIII : C was determined by OA and chromogenic assay（CA）. FVIII antigen was measured by ELISA. Global coagulation activities were evaluated by ROTEM® and CAT®. FVIII genes were analyzed by NGS. Recombinant mutant protein expression study was conducted.
Results
FVIII : C in patient was <1% using OA, 4.3% and <1% using CA, and FVIII antigen was 9.7%. Although parameters of ROTEM® and CAT® were inferior to normal control, it showed coagulability compared to positive control such as severe hemophiliac. Patient's causative mutation was identified p.His118Arg（Legacy : H99R）. In culture media of the expression studies, although FVIII : C of H99R using OA were 4.0% comparing to Wild-type, H99R antigen was equal to Wild-type.
Discussion
Both patient pathological analysis and expression study showed that this case was a molecular abnormality of cross-reacting material reduced（CRMR）. It was suggested that patient's clinical phenotype was appropriately evaluated by global coagulation tests. It was speculated that the H99R influences the evaluation of FVIII : C test.
Conclusion
The FVIII H99R was molecular abnormality hemophilia in which the clinical phenotype and the phenotype as a severity classification were discrepancy.

5-②-6.

Immune complexes-activated neutrophils contribute to atherosclerosis in systemic lupus erythematosus

（免疫学分野）
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Atherosclerosis leading to cardiovascular diseases is a common comorbidity associated with systemic lupus erythematosus（SLE）. The molecular mechanisms contributing to lupus-induced atherosclerosis are unknown and warrant further investigation. Macrophages augment the expression of scavenger receptors in response to increased presence of inflammatory mediators, thereby increasing the uptake of modified lipoproteins. This process transforms the macrophages into foam cells, triggering inflammatory responses, and promoting plaque formation in atherosclerosis. Recent studies have presented an evidence that neutrophil activation contributes to the initiation of atherosclerosis. Anti-β2 glycoprotein I antibodies associated with SLE have been observed in

human atherosclerotic plaques, suggesting that the formation of immune complexes（IC）with lupus-associated antibodies at vascular sites could potentiate atherosclerosis through Fcγ receptors（FcγR）on inflammatory cells. We hypothesize that FcγR-mediated activation of innate immune cells contributes to the progression of atherosclerosis in SLE patients. This hypothesis was tested using mouse bone marrow derived macrophages（Mϕ）exposed to IC. Mϕ treated with sera from lupus prone mice secreted inflammatory cytokines. Macrophages treated with sera from SLE patients also exhibited increased secretion of IL-1β. We investigated whether exposure to IC exacerbated macrophage foam cell formation. Our findings revealed that IC caused enhanced macrophage inflammatory responses and foam cell formation. Moreover, we found that IC-priming of neutrophils augmented foam cell formation, and that sera from SLE patients enhanced neutrophil extracellular traps formation. Collectively, our findings suggest that lupus-associated IC promote macrophage inflammatory responses and foam cell formation.