氏　　名	世良田（せらだ）　聡（さとし）
博士の専攻分野の名称	博　士（理　学）
学 位 記 番 号	第　２１３３６　号
学位授与年月日	平成 19 年 3 月 23 日
学位授与の要件	学位規則第４条第１項該当 生命機能研究科生命機能専攻
学 位 論 文 名	Proteomic analysis of autoantigens associated with systemic lupus erythematosus. （プロテオミクス手法による全身性エリテマトーデス自己抗原の解析）
論文審査委員	（主査） 教　授　木下　修一 （副査） 教　授　長田　重一　　教　授　内山　安男 医学系研究科招へい教授　仲　　哲治

論 文 内 容 の 要 旨

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease, which includes dysregulation of immune systems and various autoimmune disorders resulting in multi-organ injury. Lupus nephritis is a typical symptom and one of the most severe organ disorders associated with SLE. It is found in about 50% of patients and has a major impact on prognosis, however, there are few reliable marker for lupus nephritis other than urinalysis. Another typical feature of SLE is production of autoantibodies such as anti-double-stranded DNA antibody. Deposition of autoantibodies and immune complex causes renal injury. In clinical practice, autoantibodies are useful for the diagnosis of autoimmune diseases as well as for prognosis and evaluation of disease activities. In SLE, analysis of autoantigens was not performed by proteome scale. Therefore, we screened for novel autoantibodies associated with SLE, particularly lupus nephritis by proteomic approaches described below.

We used human umbilical vein endothelial cell protein extracts as the object of autoantigen screening, because vasculitis is one of the clinical symptoms in SLE patients. Extracted proteins were separated by two dimensional-polyacrylamide gel electrophoresis. To detect autoantigens, western blotting was performed using sera from SLE patients and healthy controls. By western blotting, positive spots only detected in SLE patients' sera were considered possible autoantigens, and these proteins were identified by LC-MS/MS analysis.

In this study, we detected several autoantigens by proteomic approach. One of the identified novel autoantigen was aldolase A, which is known as a glycolytic enzyme. To investigate the anti-aldolase A antibodies, we performed ELISA analysis. Anti-aldolase A antibodies were detected in SLE (29.3%), rheumatoid arthritis (RA) (8.2%) and absent in healthy control. In SLE patients suffering nephritis, 43.4% were positive for anti-aldolase A autoantibodies, which was significantly higher than the prevalence for those without nephritis (11.1%). Although anti-aldolase A antibodies were detected in RA patients' sera as previously reported, we found that the epitope regions were different from SLE by western blotting using various deletion

mutants. Therefore, these results indicate that autoantibodies against aldolase A may serve as an alternative clinical biomarker of SLE associated with nephritis, and epitope regions were useful to distinguish SLE and RA.

論文審査の結果の要旨

全身性エリテマトーデス（SLE）において様々な自己抗体が見られるが、臨床上、抗 Sm 抗体等が診断に用いられている。しかし、抗 Sm 抗体は感度が低いため、より感度の高い自己抗体や臨床症状に相関したマーカーとなる自己抗体の同定が望まれている。学位申請者は、２次元電気泳動法と SLE 患者血清を用いた Western Blot 法を組み合わせたプロテオミクス手法により、新規自己抗原のスクリーニングを行い、aldolase A を同定した。そして、ELISA 法により抗 aldolase A 抗体が腎炎を伴う SLE に高く検出されること、及び、抗 aldolase A 抗体の epitope 領域が関節リウマチと異なることを明らかにした。本研究は SLE におけるプロテオームレベルでの自己抗原解析の初報告であり、腎炎を伴う SLE のマーカーとしての有用性を明らかにした。よって、本論文の審査ならびに最終試験の結果を併せて、申請者に対し、学位の授与に値すると考えられる。