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Tissue-specific autoimmune disorders: Antibody-proteases as a generation of highly informative and unique biomarkers to monitor subclinical and clinical stages of demyelination in multiple sclerosis (MS)

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Most autoimmune disorders including multiple sclerosis (MS) are preceded by a symptom-free subclinical stage in which the patients can be identified by specific auto-Abs. Proteolytic Abs are multivalent immunoglobulins (Igs) endowed with a capacity to proteolyze the antigenic substrate. Abs against myelin basic protein/MBP endowed with proteolytic activity (Ab-proteases) are of great value to monitor demyelination to illustrate the evolution of multiple sclerosis (MS). Anti-MBP auto-Abs from MS patients and mice with EAE (SJL and C57BL/6 mice as an animal model of MS) exhibited specific proteolytic cleavage of MBP. The activity of the Ab-proteases markedly differs between: (i) MS patients and healthy controls; (ii) different clinical MS courses; (iii) EDSS scales of demyelination to correlate with the disability of MS patients to predict transformation prior to changes of the clinical course. The sequence-specificity of Ab-proteases demonstrates five sites of preferential proteolysis to be located within the immunodominant regions of MBP. Those sites are located within the immunodominant regions of MBP; and two of them falling inside the sequence covering a 81-103 peptide segment and its 82-98 subsegment as well, with the highest encephalitogenic properties both to act as a specific inducer of EAE and to be attacked by the MBP-targeted Ab-proteases very often in MS patients with the most severe (pro-gradient) clinical courses. Meanwhile, sites localized within the frame of 43-68 and 146-170 subsegments whilst being less immunogenic happened to be EAE inducers very rare but were shown to be attacked by Ab-proteases very often in MS patients with moderate (remission-type) clinical courses. In moderate courses, Ab-proteases focus their proteolytic effect on low-immunogenic 43-68 и 146-170 sites but in aggressive cases (progradient courses), the proteolysis prevailed on highly-immunogenic 81-103 and 82-98 sites. The activity of Ab-proteases was first registered at the subclinical stages 1-2 years prior to the clinical illness. About 24% of the direct MS-related relatives (proband) were seropositive for low-active Ab-proteases from which 38% of the seropositive relatives established were being monitored for 2 years whilst demonstrating a stable growth of the Ab-associated proteolytic activity. Moreover, we see also low-active Ab-proteases (to target 43-68 and 146-170 sites) in persons at MS-related risks (at subclinical stages of MS) and primary clinical and MRT manifestations observed were coincided with the activity to have its mid-level reached. And registration in the evolution of highly immunogenic Ab-proteases to attack 81-103 and 82-98 sites predominantly would illustrate either risks of transformation of subclinical stages into clinical ones, or risks of exacerbations to develop. The activity of Ab-proteases in combination with the sequence-specificity would confirm a high subclinical and predictive value of the tools as applicable for personalized monitoring protocols. Moreover, Ab-proteases can be programmed and re-programmed to suit the needs of the body metabolism. Of tremendous value are Ab-proteases directly affecting the physiologic remodeling of tissues with multilevel architectonics (for instance, myelin). By changing sequence specificity of the Ab-mediated proteolysis one may reach minimizing scales of demyelination. Further studies on targeted Ab-mediated proteolysis may provide a supplementary tool for predicting demyelination and thus the disability of the MS patients.

Biography

Sergey Suchkov graduated from Astrakhan State Medical University and was awarded with MD. In 1985, he obtained his PhD from the I.M. Sechenov Moscow Medical Academy and Institute of Medical Enzymology, USSR Academy of Medical Sciences, Russia. In 2001, he finished the Post-doc Research Fellowship Program and maintained his Doctor degree at the National Institute of Immunology, Russia. From 1987 through 1989, he was a senior Researcher, Lab of Developmental Immunology, Koltzov Institute of Developmental Biology, USSR Academy of Sciences to deal to developmental immunology. From 1989 through 1995, he was Head of the Lab of Clinical Immunology and Immunobiotechnology, Helmholtz Eye Research Institute in Moscow. From 1995 through 2004, he was the Chairman of the Department for Clinical Immunology, Moscow Clinical Research Institute (MONIKI) and the Immunologist-in-Chief of the Moscow Regional Ministry of Health. At present, he is Professor in Immunology, Department of Pathology, School for Pharmacy, I.M. Sechenov First Moscow State Medical University, Dean of the Department (Faculty) of The PPPM Development, and the First Vice-President of the University of World Business, Politics and Law and Secretary General, United Cultural Convention (UCC), UK.

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