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Antibodies with functionality as a new generation of translational tools to monitor, to predict and to prevent demyelination

Abs against myelin basic protein/MBP endowing with proteolytic activity (Ab-proteases) is 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 exhibited specific proteolytic cleavage of MBP. The activity of the MBP-targeted Ab-proteases markedly differs between: MS patients and healthy controls; different clinical MS courses and; EDSS scales of demyelination to correlate with the disability of MS patients to predict the 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 immuno-dominant regions of MBP confirmed by the structural databanks. Two of them were falling inside the sequence covering 81-103 peptides and its 82-98 sub-segments with the highest encephalitogenic properties both to act as a specific inducer of EAE and to be attacked by the MBP-targeted Ab-proteases in MS patients with the most severe (pro-gradient) clinical courses. Sites localized within the frame of 43-68 and 146-170 peptide sub-segments while being less immunogenic happened to be EAE inducers very rare but were shown to be attacked by Ab-proteases in MS patients with moderate (remission-type) clinical courses. The activity of Ab-proteases was first registered at the subclinical stages one to two years prior to the clinical illness. About 24% of the direct MS-related relatives were seropositive for low-active Ab-proteases from which 38% of the seropositive relatives established were being monitored for two years while demonstrating a stable growth of the Ab-associated proteolytic activity. 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 (translational) value of the tools as applicable for personalized monitoring protocols. And close association between the proteolytic sensitivity of MBP and post-translational modifications of the latter may represent one of the key regulatory mechanisms in the epitope generation. Ab-proteases can be programmed and re-programmed to suit the needs of the body metabolism or could be designed for the development of principally new catalysts with no natural counterparts. By changing sequence specificity of the Ab-mediated proteolysis one may reach reduction of a density of points of the negative proteolytic effects within the myelin sheath and minimizing scales of demyelination. Auto-Ab-mediated proteolysis could thus be applied to isolate from Ig molecules the efficient catalytic domains directed against particular autoimmune epitopes pathogenically and clinically relevant (encephalitogenic epitopes).

Biography

Sergey Suchkov is a Professor of Immunology and Medicine and Chair of Department for Personalized and Translational Medicine at I.M. Sechenov First Moscow State Medical University, Russia. He completed his MD at Astrakhan State Medical University, Russia in 1980; PhD at I. M. Sechenov First Moscow State Medical University in 1985; Doctor Degree at National Institute of Immunology, Russia in 2001. He is a Post-doctorate Research Associate at Institute of Medical Enzymology and; Head of the Lab of Immunology, Helmholtz Eye Research Institute in Moscow.

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