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Antibody-proteases as a generation of novel biomarkers and highly informative molecular tools to predict and to prevent demyelination

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The methodological bricks of subclinical diagnostic protocols should include basic algorithms to differ essentially from those employed in traditional clinical practice, i.e., (i) to confirm a diagnosis of subclinical stage of the disease course and (ii) to select a mode for preventive treatment to quench the autoimmune inflammation. In this sense, among the best-validated proteome-related biomarkers, antibodies (Abs) are the best known ones to represent one of the principal immune effectors and thus key mediators of inflammatory responses to generate the events. Most of 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. The property mentioned is appearing to sound as a functional property of the Ab molecule. The first example of Ab-proteases was an IgG found in bronchial asthma (BA) and was shown to hydrolyze vasointestinal peptide (VIP) which played a major role in the respiratory dysfunction. Similar examples would cover: (i) hemophilia where Ab-mediated hydrolysis of factor VIII as a pathogenically valuable bioregulator would prevail; (ii) autoimmune myocarditis (AIM) whilst demonstrating anticardiomyosine (anti-CM) autoAbs to attack and thus destroy the targeted CM, and (iii) anti-thyroid autoAbs to specifically proteolyze thyroid antigenic substrates. Cardiac- and thyroid-related Ab-proteases occur at different stages of the subclinical and clinical courses and evidently correlate with the severity and course of the disease. The major step is a primary myelin damage which is mediated by autoAbs to trigger the release of separate and pathogenically valuable myelin-associated epitopes into the bloodstream. Those epitopes act as sensitizing factors to generate via the immune system autoAbs which, in turn, would drive the disease progressionWe have demonstrated that anti-MBP autoAbs from MS patients and mice with EAE (SJL and C57BL/6 mice as an animal model of MS) exhibited specific proteolytic cleavage of the MBP molecule The activity of the MBP-targeted 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 latter means that when we saw a stable growth of the activity, we could predict transformation in the clinical course, i.e., changing of a remitting type (moderate one) into the secondary progradient type (aggressive one) prior to changing in a pattern of the clinical manifestations. Ab-mediated proteolysis of MBP results in generating a set of peptides with MW ranged in various but fixed boundaries to suit common principles of the molecular architectonics of MBP. The sequence-specificity of Ab-proteases demonstrates five sites of preferential proteolysis to be located within the immunodominant regions of MBP confirmed by the structural databanks. Cleavage at those sites occurred at a similar rate as determined by 32P-MBP degradation assay. 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 in SJL mice and to be attacked by the MBP-targeted Ab-proteases very often in MS patients with the most severe (progradient) clinical courses Meanwhile, sites localized within the frame of 43-68 and 146-170 peptide 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. To test the Ab-proteses specificity toward distinct MBP fragments, recombinant fusion proteins of Trx with the C-terminally fused MBP peptides were designed, and in all cases, recombinant substrates were cleaved only at preferential sites inside the MBP fragment, leaving the Trx part undegraded. These data further confirmed the substrate specificity of the Ab and its profound difference from trypsin, a common protease that cleaves at basic residues. Finally, in moderate (remission-type) courses, Ab-proteases focuse its proteolytic effect on low-immunogenic and low-encephalitogenic 43-68 и 146-170 sites but in aggressive cases (progradient courses), the Ab-mediated proteolysis was prevailed on highly-immunogenic and highly-encephalitogenic 81-103 and 82-98 sites. The fact established and confirmed is of great value for interpreting epitope spreading in terms of the evolution of demyelination to through a light on risks of transformations of moderate types into aggressive ones and risks of long-term chronization as well. In this sense, 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 (probands) were seropositive for low-active Ab-proteases from

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