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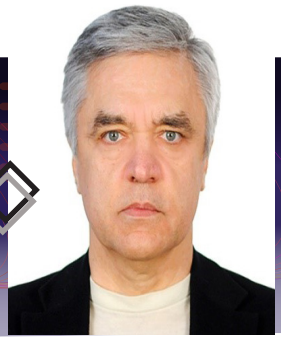

Precision pathology as part of personalized and precision neurology (ppn): antibody-proteases as the unique translational tools of the next-step generation in monitoring subclinical and clinical stages of The neurodegeneration development

Abstract:

Neurological diseases such as Alzheimer's disease, multiple sclerosis (MS) and related conditions can be difficult to diagnose and treat, because the same disease may cause different symptoms in individual patients. But they have high degrees of genetic and pathophysiological heterogeneity, irrespective of clinical manifestations. Advances in disease modeling and methodological design have paved the way for the development of Personalized & Precision Medicine (PPM), and PPM-driven Neurology as well.

For many neurodegenerative diseases, such as multiple sclerosis (MS) and related conditions, conventional drug development strategies have barely scratched the surface in curing the disease in patients. Meanwhile, patient and persons-at-risk phenotyping is considered today as the collection of information that best captures the presentation of their medical conditions. And in this context, the biomarkers of the next step generation enable pre-early diagnosis, guide targeted therapy and monitor the active ty and therapeutic responses across the diseases. Moreover, novel biomarkers for neurodegenerative diseases may surpass these issues, especially for early identification of disease risk. Biomarkers are critical for the targeted identification of specific molecules, cells, tissues, or proteins that dramatically alter throughout the progression of neurodegenerative conditions.

In recent decades, biomarkers have been progressively incorporated in clinical routine and clinical trials in the field of neurology. The arsenal of biomarkers in neuropathology is likely to keep growing as our ability to measure accurately multiple biological variables and our knowledge about the pathophysiology of the neurodegenerative diseases increase.

A major advance in the field of neurology has been the development of blood-based biomarkers. Despite initial scepticism in peripheral markers due to the physical restrictions imposed by the blood brain barrier, recent technological advances have made possible to measure bioanalytes in different biofluids in very low concentrations. The new instruments are mostly based on immunochemical assays and mass-spectrometry, which provide an optimal analytical sensitivity. A key advance in the field is the possibility to measure protein biomolecules in blood as a measure of neuronal and/or myelin damage in a wide range of neurological conditions, such as neurodegenerative disorders and multiple sclerosis, in particular!

Among the best-validated predictive biomarkers are autoimmunity-related ones to predict and prognosticate risks of the chronification, complications and thus disabling. The latter is so much valuable and important since chronic autoimmune inflammation course is structured to consist from different stages including subclinical and clinical ones.

Multiple sclerosis (MS) is just one of the chronic tissue-specific autoimmune diseases resulting in a destruction of myelin by different tools, including autoAbs of very broad specificity. Along with canonical Abs, some of the families proven to occur are Abs possessing with catalytic activity (abzymes), and thus to belong to Abs with func-

tionality!
Abs against myelin basic protein/MBP endowing with proteolytic activity (Ab-proteases with functionality) are of great value to monitor demyelination to illustrate the evolution of MS. Anti-MBP autoAbs from MS patients and mice with EAE exhibited specific proteolytic cleavage of MBP which, in turn, markedly differed 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 the transformation prior to changes of the clinical course.
Ab-mediated proteolysis of MBP was shown to be sequence-specific whilst demonstrating five sites of preferential proteolysis to be located within the immunodominant regions of MBP and to fall inside into 5 sequences fixed. Some of the latter (with the highest encephalitogenic properties) were proved 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 (progradient) clinical courses. The other ones whilst 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) courses.
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 were seropositive for low-active Ab-proteases from which 22% of the seropositive relatives established were being monitored for 2 years whilst demonstrating a stable growth of the Ab-associated proteolytic activity. Moreover, some of the low-active Ab-proteases 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. Registration in the evolution of highly immunogenic Ab-proteases would illustrate either risks of transformation of subclinical stages into clinical ones, or risks of exacerbations to develop. And the "escalation" illustrating re-orientation of the sequence specificity to focus on the more important targeted sites for proteolysis might be an early prognostic and/or predictive sign to monitor demyelination progressing and thus the clinical illness to come. 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.
Sequence-specific Ab-proteases have proved to be greatly informative and thus valuable biomarkers to monitor MS at both subclinical and clinical stages! And the translational potential of this knowledge is in the rational design of new diagnostic tools and new therapeutics based on principles of artificial biocatalysts and Biodesign.
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. Therefore, the proposed predictive value of MBP-targeted Ab-proteases for the development of MS is being challenged! Of tremendous value in this sense are Ab-proteases directly affecting the physiologic remodelling of tissues
with multilevel architectonics (for instance, myelin)., whilst securing the requests and standards of regeneration and remyelination
So, further studies on Ab-mediated MBP degradation and other targeted Ab-mediated proteolysis may provide biomarkers of newer generations and thus a supplementary tool for assessing the dis-ease progression and predicting disability of the patients and persons-at-risks.
In years to come, we will see new additional exciting biomarkers that will allow detection of neuro-logical diseases at the pre-early (subclinical) disease stages and simultaneous monitoring of multiple biological pathways in response to sophisticated therapeutic interventions.

Biography

Sergey Suchkov graduated from Astrakhan State Medical University and awarded with MD, then in 1985 main-tained his PhD at the I.M. Sechenov Moscow Medical Academy and in 2001, maintained his Doctorship Degree at the Nat Inst of Immunology, Russia. From 1987 through 1989, he was a senior Researcher, Koltzov Inst of Devel-opmental Biology. From 1989 through 1995, he was a Head of the Lab of Clinical Immunology, Helmholtz Eye Research Institute in Moscow. From 1995 through 2004, a Chair of the Dept for Clinical Immunology, Moscow Clinical Research Institute (MONIKI. Dr Suchkov has been trained at: NIH; Wills Eye Hospital, PA, USA; Univ of Florida in Gainesville; UCSF, S-F, CA, USA; Johns Hopkins University, Baltimore, MD, USA. He was an Exe Secre-tary-in-Chief of the Editorial Board, Biomedical Science, an international journal published jointly by the USSR Academy of Sciences and the Royal Society of Chemistry, UK.

At present, Dr Sergey Suchkov is a Chair, Dept for Personalized Medicine, Precision Nutriciology and Biodesign of the Institute for Biotech & Global Health of RosBioTech and Professor of the Dept for Clinical Allergology & Im-munology of A.I. Evdokimov MGMSU, Russia. He is a member of the: New York Academy of Sciences, USA; American Chemical Society (ACS), USA; American Heart Associa-tion (AHA), USA; EPMA (European Association for Predictive, Preventive and Personalized Medicine), Brussels, EU; ARVO (American Association for Research in Vision and Ophthalmology); ISER (International Society for Eye Research); PMC (Personalized Medicine Coali-tion), Washington, USA.