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Review Article

A New Generation of Translational Tools designed to Monitor Multiple Sclerosis (MS) at Clinical and Subclinical Stages

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Abstract

According to tremendous translational researchers, biomarkers as a part of the ligand-receptor tandems have induced an impulse to prompt the evolution of an upgraded concept of the targeted therapy. It is health indicators that justifying the necessity to create targeted drug of the next-step generation to be implemented at the clinical and sub-clinical key stages of the disease process and to get involved into a multi-stage process to get the shifts appeared modified.

There is an evident-based outcome of the latest studies in multiple sclerosis (MS) related fields that illustrates the proved targeted activity of Ab-proteases. High impact of Ab-proteases can be used to monitor both clinical and subclinical courses of chronic autoimmune inflammation (MS) to predict stepwise transformations of the course and to prognosticate the clinical illness finally. In this sense, Ab-proteases can be programmed and reprogrammed to suit the requests and standards of regenerative medicine and re-myelination, in particular. This data makes it possible to design the algorithms for combinatorial (preventive, prophylactic, therapeutic and rehabilitative) treatment, whilst developing unique tools for individually therapy, especially, for autoimmune diseases which holds a particular position.

Introduction

Today, the society objectively requires a new concept to health care, founded on the prevention of diseases, but not on endless and expensive treatment of chronic cases. And those grandiose events that occur today in the world of medical science, once again pay attention to the reconsideration their views on problems related with human health. Thus, an absolutely new model of healthcare service, which includes the principles of Personalized and Precision Medicine (PPM) and integrative medicine and aimed at identifying the disease in early (subclinical) stage, is being created [1].

Meanwhile, to reveal the focus of preclinical pathology, it's imperative to create a special system of preclinical criterions and respective predictive diagnostic tests. What tests will allow us to determine with high authenticity the genetic susceptibility to the oc-

B cells can increase or dampen CNS inflammation, but their proinflammatory effects seem to be more prominent in most patients, as B-cell depletion is a promising therapeutic strategy. Meanwhile, the MS clinical phenotypes, disease courses and responses to treatment that are associated with anti-myelin autoAbs are currently being defined.

Anti-myelin basic protein (MBP) autoAbs have generally been considered to be absent from sera from healthy individuals, but to be detectable in sera from some patients with multiple sclerosis (MS). AutoAb biomarkers are useful in distinguishing subjects with the relapsing-remitting form of MS from those with the secondary progressive subtype.

Myelin basic protein (MBP) is one of the most abundant proteins in CNS. However, its role in MS pathogenesis or prediction of disease progression is still unclear. And anti-MBP autoAbs are a marker for MS-associated demyelination and appears to play a significant role in the etiology of multiple sclerosis.

Similar to MBP, the pathogenic role of MOG Abs has been debated intensely, whilst demonstrating their pathogenic potential.

Abs against myelin oligodendrocyte glycoprotein (MOG-Abs) are associated with demyelinating syndromes of the CNS. Most patients with MOG-Ab-associated disorders have favourable outcomes, but a subset is left with permanent disability, usually as a result of the initial attack. Many MOG-Ab-positive MS patients develop relapsing disease; relapses usually involve optic neuritis and often occur during steroid weaning or soon after steroid cessation, suggesting that a longer initial treatment duration is required.

Analysis of serum autoAbs against MOG and MBP in patients with a clinically isolated syndrome is a rapid, inexpensive, and precise method for the prediction of early conversion to clinically definite MS. This finding may be important for the counselling and care of patients with a first demyelinating event suggestive of MS.

Although, in general, autoAbs against myelin are neither a specific nor a diagnostic feature of MS, it seems that specific demyelinating Abs are involved in the immunopathogenesis of the disorder in at least a subgroup of patients. And the analysis of those Abs can be used to estimate roughly the individual risk of an early first relapse and therefore of clinically definite MS.

Which, in turn, would drive the demyelination and thus the disease progression.

Today, a spectrum of myeline-associated autoAbs occurring in patients with MS has been confirmed to be very large. The versatility of Abs is demonstrated by the various functions that they mediate such as neutralization, agglutination, fixation with activation of complement and activation of effector cells. In addition to this plethora of functions, some Abs express enzymatic activity [4, 5].

According to classical conception, Abs are specific proteins produced by the immune systems with exclusive function of Ag binding. But Abs against chemically stable analogues modelling the transition states of chemical reaction can catalyze many different reactions and were thus called *catalytic Abs* or *abzymes* (derived from *Ab* and *enzymes*),which thus to belong to Abs with a feature of *functionality* [6].

Abzymes can catalyze many different chemical reactions and are ultra-new biological catalysts that have attracted much attention in recent years.

CatAbs is well positioned to performing almost any type of reaction with high selectivity and stereo-specificity and like enzymes process their substrates through a Michaelis complex in which the chemical transformation occurs, followed by product dissociation [7].

"Naturally occurring" CatAbs dispose of metabolic products, thus indicating an intrinsic protective role for Abs under physiologically normal conditions. This role does not correlate with the ability of Abs to neutralize circulating exogenous Ags, unburden their endocytosis by Ag-presenting cells (APCs), and participate in their elimination from the body [8].

Abs with enzymatic properties have previously been described in human autoimmune manifestations in various diseases, such as

autoimmune thyroiditis, systemic red fever (SCD), scleroderma, rheumatoid arthritis (RA), and acquired hemophilia (AI). Abs detected in the above diseases was capable of specifically hydrolyzing thyroglobulin, DNA, RNA, and factor VIII (FVIII) or factor IX (FIX), respectively. The variety of data accumulated in the course of research on natural catalytic autoAbs indicate that production scales up markedly in pathological abnormalities. DNA- and RNA-hydrolyzing Abs (DNA- and RNA-abzymes) have been identified in the serum of patients with such systemic autoimmune diseases as systemic lupus erythematosus (SLE), scleroderma, and rheumatoid arthritis (RA) [9].

Historically, abzymes were first used in pathological conditions in patients with bronchial asthma, when abzymes were able to cleave vasoactive intestinal peptide (VIP) [10].

Being specific for thyroglobulin (Tg) proteolytic Abs have been found in patients with thyroiditis. Recently, IgM-Abs that hydrolyze amyloid b peptide (Ab) have been found in the sera of patients with Alzheimer's disease (AD) [11].

The appearance of CatAbs in pathological conditions is far from clear. It is assumed that the disease-associated CatAbs were induced by Ag. Second, the increased number of CatAbs under pathological conditions may be the result of a loss of repressive control over CatAbs-producing clones spontaneously produced under physiological conditions. Moreover, a third explanation for the occurrence of CatAbs is based on an idiotypical network and exacerbated self-recognition in autoimmune diseases.

Proteases have evolved multiple times, and different classes of protease can perform the same reaction by completely different catalytic mechanisms [8]. So, Proteases are known to precisely control certain physiological processes and therefore could potentially serve as targets for targeted drugs.

The precise pathogenesis and etiology of MS as a complex autoimmune disease are still a mystery. Despite many studies that have been aimed to identify biomarkers, no marker has yet been approved for MS. And as it is known, canonical autoAbs play neither predictive nor discriminative role to affect the pre-early and/or subclinical stage of MS. Therefore, biomarkers that could clarify the pathology in the pre-early stage, manifestation of the disease, response to treatment, and prognosis in MS are extremely necessary. Immunomic analysis is a set of powerful tools to identify putative and novel candidate biomarkers. Human biomolecular research using proteomics, cytomics, and bioinformatics has provided state-of-the-art information to further clarify MS pathology, understand pathogenesis, find fundamentally new targets, and monitor treatment response [3]. Based on the above, omics technologies can improve various therapeutic and diagnostic aspects of MS, from the discovery of biomarkers to the implementation of new tools in the daily practice of physicians.

Briefly! CatAbs are multivalent Ig, presumably of the IgG isotype, endowed with the ability to hydrolyze the Ag substrate. This property is inherent in the Fab-fragment of the Ig molecule and appears to be a functional property of the Ab molecule. In this sense, proteolytic Abs (or Ab proteases), as a significant part of the large family of Abzymes, are Abs endowed with the ability to exert a directed proteolytic action.

Abs against the major myelin/MBP protein with proteolytic activity demonstrating sequence-specific MBP cleavage are of great importance for monitoring demyelination during MS. Ab-protease activity was first recorded in subclinical stages 1-2 years before clinical disease. At the same time, it was recorded that Ab-protease activity correlates with the extent of demyelination and disability of patients (Fig. 4A-C) [4].

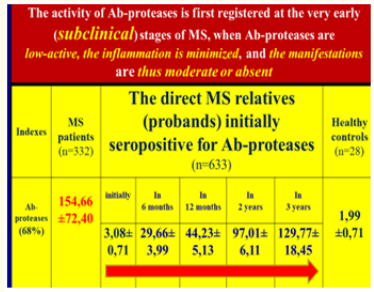

Figure 4A: The evolution of the activity of MBP-targeted Ab-proteases at healthy persons, pre-early (*subclinical*) and *clinical* stages of MS.

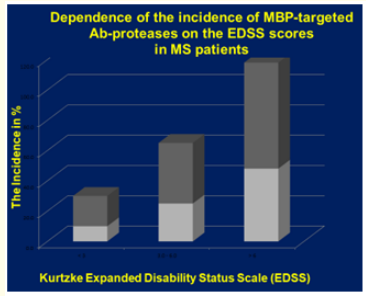

Figure 4B: Dependence of the incidence of MBP-targeted Ab-proteases on the EDSS score in MS patients.

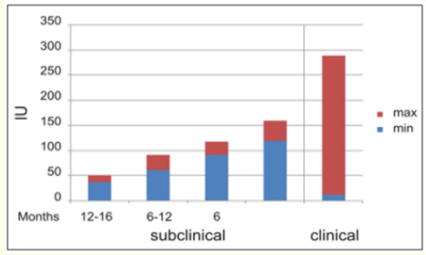

Figure 4C: The evolution of the activity of MBP-targeted Ab-proteases at subclinical and clinical stages of MS.

Sequence-specific Ab-proteases have proved to be greatly informative and thus valuable as biomarkers to monitor MS at both subclinical and clinical stages! Therefore, the proposed predictive value of MBP-targeted Ab-proteases for the development of MS is being challenged! So, the activity of Ab-proteases and its dynamics tested would confirm a high *subclinical* and *predictive* value of the tools as applicable for monitoring protocols [12].

Ab-proteases affecting the remodeling of tissues with multilevel architectonics such as myelin are of significant practical importance. By changing the sequence specificity, it is possible to achieve a decrease in the frequency of negative proteolytic effects in the myelin sheath and thus minimize the extent of demyelination.

Targeted Ab-mediated proteolysis could be also applied to isolate from Ig molecules catalytic domains directed against encephalitogenic autoepitopes or domains containing segments to exert proteolytic activity. So, further studies on Ab-mediated MBP degradation and other targeted Ab-mediated proteolysis may provide biomarkers of new generations and thus a supplementary tool for assessing

the disease progression and predicting disability of the patients and persons-at-risks.

As stated at the beginning, to implement PPM principles requires creating a new thinking strategy based on the identification and monitoring of the latest generation of biomarkers. In this sense, CatAbs (abzyme) is a type of Abs with catalytic activity being found not only in healthy humans and but also in patients with autoimmune diseases. Studying abzymes can provide important insights into enzyme reaction mechanisms and the immune system itself.

Discussion

What does arise in response to «a call» of this kind of information received? Naturally, it is the emergence of nanotechnology, specifically, the design of new diagnostic tools and new targeted therapeutics based on principles of artificial biocatalysts and drug design. The traditional goal of Ab engineering is to combine various Ab domains to generate customized Abs that show specialized binding properties, optimal half-lives and desirable effector functions. Abs can be engineered to produce proteins with higher affinity or smaller molecular variants that can retain or modify the functional properties of the original Abs. So, biomarkers and integration of diagnostics with therapeutics are becoming important for the selection and monitoring of individualized treatments [13].

The translational potential of Ab-proteases and the knowledge is in the rational design of new diagnostic tools and new therapeutics based on principles of artificial biocatalysts and biodesign. In addition, the traditional goal of AB engineering is to combine different Ab domains to create individual Abs that are characterized by binding specificity, optimal half-life, and desirable effector functions. Abs can be engineered to produce proteins with higher affinity or smaller molecular variants that can retain or modify the functional properties of the original Abs [14].

Neurodegenerative diseases are promisingly suited models for PPM because of the rapidly expanding Hi-Tech innovations and translational resources including ABZYMES technologies and the development of biomarkers and the potential modifying treatments. And Personalized Precision Neurology (PPN) is the application of principles of PPM.

Several biotechnologies are being integrated to develop PPM and PPN. Besides BASICS, post genomic technologies such as nano-immunotechnology are also used. So, biomarkers and integration of diagnostics with therapeutics are becoming important for the selection and monitoring of individualized treatments to get neurodegenerative disorders cured. And accurate and precise prediction is crucially vital for prevention of autoaggression, and the targeted preventive, therapeutic and rehabilitative treatment could thus be given to those individuals who are most likely to develop the disease [15].

The application of the newest and upgraded translational applications to the treatment and prevention of neurodegenerative disorders appear to be highly promising in contrast to the traditional “one-drug-fits-all” approach. And Ab-based therapeutics are entering the key stage of drug discovery (Fig. 5).

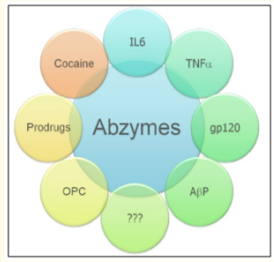

Figure 5: Perspectives of artificial (engineered) biocatalysts ***in vitro IL,*** interleukin; ***TNF,*** tumor necrosis factor; ***gp120,*** a glycoprotein exposed on the surface of the HIV envelope. ***OPC,*** oligodendrocyte precursor (progenitor) cell; ***AβP,*** anti-amyloid beta protein Abs [16].

As a result of a major shift in focus of many biopharma companies. For instance, prodrug activation by CatAbs conjugated with targeted Abs, called Ab-directed abzyme prodrug therapy (ADAPT), might be proposed as a strategy for site-specific drug delivery systems for myelin degradation preventing drugs. To achieve ADAPT, one should focus on individual criteria for prodrugs and CatAbs, the stability of prodrugs with respect to enzyme systems, and the applicability of abzymes to a wide range of prodrugs. As an example, CatAbs formed by immunization with a transient state analog of vitamin B6 phosphonate can be considered. The induced Abs were found to hydrolyze several anti-inflammatory prodrugs with the vitamin B6 promoter, on the one hand, and to protect the Ab catalyzed prodrugs, on the other. Thus, the combination of CatAbs and prodrugs masked by target bioactive ingredients will allow the use of target drugs [17].

Another example is artificial CatAbs on a platform of well-defined peptide-modified metal clusters called *clusterbodies*, which have favorable complex characteristics such as selected ultra-small size, intrinsic fluorescence, and enzyme-like catalytic and selective recognition properties not available for traditional Abs. Consequently, fluorescence measurements and the catalytic chemiluminescence method of metal clusters can be used in quantitative analysis with high accuracy and sensitivity. This framework has potential applications for the analysis of protein biomarkers with a low concentration range (including target Ags and Abs) in complex biological matrices, which is important for autoimmune conditions in subclinical stages. Thus, it inspires accurate cluster-body-based bioprobes with personal structure and integrative functions for advanced quantitative biosensing [18, 19]. In this context, the development in neurology of a PPM approach could represent an excellent possibility to identify subclinical stages of disease, make adequate differential diagnosis and provide timely and optimal treatments instead of the traditional treatments which are utilized at later stage of disease. With advances in our knowledge of the functions and properties of Ab-proteases, combined with advances in immune and protein engineering, we can predict that highly effective therapeutic Ab-proteases will gain regulatory approval and make significant contributions to health care in the near future.

Utilizing globally PPM in MS requires 3 crucial components:

(i) Assessment of prognosis soon after diagnosis;
(ii) Considering an early therapeutic plan based on risk benefit and patient predilections;
(iii) A pre-early assessment of response to therapy and taking alternative therapies in the case of failure.

And thus biomarkers are important for understanding MS patient disease profile, prognosis, diagnosis, and disease course prediction. They are also critical in identifying the benefits and side effects of new therapies on patients (therapy-oriented) and/or persons-at-risk (preventively oriented).

We would stress that the future biomarkers' discovery and execution will face numerous challenges. And consequently, serious cooperative attempts among biodesigners, translational researchers, clinicians, and bioindustry are needed. Presumably, this collaboration will move us one step forward from expectation to ultimate goal. We hope that the standardization of critical elements of proteomics research as well as immunomics signatures will soon provide insight into the pathogenesis of MS and definitely valuable clinical and translational applications that will be further validated.

Conclusion

We are witnessing the rapid development of personalized medicine, primarily through next-generation biotechnology. In this sense, neurodegenerative diseases are promisingly suited models for PPM because of the rapidly expanding Hi-Tech innovations and translational resources including ABZYMES Technologies and the development of biomarkers and the potential modifying treatments. In this context, the development in neurology of a PPM approach could represent an excellent possibility to identify subclinical stages of disease, make adequate differential diagnosis and provide timely and optimal treatments instead of the traditional treatments which are utilized at later stage of disease [20].

Further studies on Ab-mediated MBP degradation and other targeted Ab-mediated proteolysis may provide biomarkers of the next step generations and thus supplementary tools for assessing the disease progression and predicting disability of the patients and persons-at-risks.

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