Autoantibodies in the nervous system

09.

Valorization

Chronic disorders are defined as persistent lifelong health conditions that usually require ongoing clinical support. They significantly affect the activity and daily life of the patients and their families. Examples of the most common chronic diseases in the world include Alzheimer's disease, cancer, coronary heart disease, autoimmune diseases such as diabetes, rheumatoid arthritis, multiple sclerosis, and mental disorders. These diseases usually affect different parts of the body and develop in waves, with periods of remission and relapse that can vary in intensity. Enormous progress has been made in the diagnostics, monitorization and treatment of these disorders. While symptoms can partially be suppressed and sometimes even eliminated, no cure exists to date. Besides the consequences of the disability experienced by the patients and the societal burden, chronic disorders represent a stunning economic affliction on society and health care resources.

Importantly, the immune system plays a crucial role in a significant number of chronic disorders, while in many others its contribution is still under investigation. The studies described in this dissertation have mainly focused on the potential role of the immune system in psychotic disorders, the pathogenic mechanisms and the efficacy of novel therapeutic strategies in myasthenia gravis.

It is estimated that 1 in 5 adults is suffering from a mental illness, and a total cumulative of 43% of the population experience a form of mental illness at least once in their lifetime [1,2]. The spectrum of mental disorders is extremely diverse and the underlying pathogenic mechanisms remain a mystery, making the diagnosis and treatment extremely difficult. Antipsychotics and mood stabilizers focus on the suppression of the symptoms but are not efficient at reducing the cognitive decline experienced by many patients or at stagnating disease progression. Besides long-term periods where medication is required, sometimes for life, the treatment-associated side effects and the lack of treatment efficacy which in some cases leads to institutionalization is very common in the active phases of the disease. The public stigmatization and the negative connotation associated to these disorders challenges the integration of these individuals into society, meaning that they can experience difficulties finding and maintaining a job and and also struggle to live an independent life.

It has been demonstrated that there is a clear link between the immune system and mental disorders [3]. Its exact role, however, is not yet well-defined. In autoimmune encephalitis antibodies against neuronal surface channels and receptors trigger neuropsychiatric manifestations which could, in some cases, be incorrectly diagnosed as schizophrenia or bipolar disorder.

Lately, the prevalence of antibody-mediated autoimmune disorders, those caused by antibodies that mistakenly recognize and attack organs, tissues and cells of the body, is increasing significantly [4, 5]. Nowadays, 2.5% of the global population suffer from an antibody-mediated autoimmune disease [6].

Some of the most common are multiple sclerosis, diabetes, systemic lupus erythematous, celiac disease, psoriasis and myasthenia gravis. Myasthenia gravis is a neuromuscular disorder characterized by fluctuating muscle weakness and fatigue. Antibodies against different proteins of the neuromuscular junction are the direct cause of the disease, and the underlying pathogenic mechanisms have been intensively studied.

In this dissertation, I have reviewed the literature on psychotic disorders (including schizophrenia and bipolar disorder) and the potential role of the immune system in the development of these disorders. Interestingly, the methodological differences among the different screening assays raised a controversial variability in the prevalence of these autoantibodies in psychotic disorders. Thanks to the dissemination of scientific studies, patients with a subtle and uncommon disease course, treatment resistance or relapses and/or subtle neurological abnormalities, where the probability of autoimmunity is enhanced, are nowadays diagnosed in most of the cases. The use of standardized detection assays, and the analysis of cerebrospinal fluid, along with an extensive neurological examination indicate that the percentage of patients with pure psychosis and an autoimmune origin is very low. Early diagnosis and treatment are essential for a complete and fast recovery of the patients. However, it is important to be critical when it comes to the analysis of the results, since treatment administration could also have severe consequences for the patient when the disease is not correctly diagnosed.

Including different detection assays, I was able to identify novel autoantibodies in a young adult with Hashimoto's thyroiditis, progressive cognitive complaints and subtle neurological abnormalities. After testing negative for neuronal surface autoantibodies by the commercial kit, I revealed the presence of coexistent autoantibodies against a protein expressed in the brain, specifically, in the membrane of pyramidal hippocampal neurons. Although I have not been able to identify the target yet, the clinical response to immunosuppressive IVIG treatment suggests but does not prove that these novel autoantibodies may induce the encephalopathy. Even though this is a single case report and the expected prevalence of autoimmunity in these patients is very low, reporting our findings could help other researchers to identify similar cases. In an extended cohort of newly recruited patients with a recent onset of psychosis, 7% of the patients presented neuronal autoantibodies. Thanks to the extensive neuropsychiatric description, I was able to identify the phenotype of these patients, characterized by severe manifestations and impairment of cognitive functioning and, interestingly, a shorter time between the last psychotic episode and the moment of the visit. This will help to narrow the characteristics of these patients with higher probabilities to have an underlying autoimmune cause and facilitate their diagnosis and further treatment.

Insight into the pathogenic mechanisms of psychotic disorders will help to understand the role of the different components involved in the disease. Autoantibodies could then be used as biomarkers that could serve not only for diagnosis but also to monitor the disease progression and might be instrumental in developing specific therapies that will not only mask the symptoms but treat the disease at the source. If successful, this will cause a true landslide in psychiatry with genuine healing effects on patients. The impact on patients, their families, society and economy would be substantial.

Even though antibody-mediated autoimmune disorders, especially myasthenia gravis, are better characterized and we know more about the disease mechanisms, important gaps remain in our understanding of the disease.

Using an animal model for myasthenia gravis, I showed that changes in the expression of Dok7, involved in the clustering of the acetylcholine receptors (AChRs), essential for the correct muscle contraction, directly affects the disease susceptibility. Elucidating the role of the different proteins involved in the disease not only answers a basic research question about the pathogenic mechanisms, but also would be most helpful for designing new therapies. In the case of agrin, a protein involved in the upstream activation of MuSK via its interaction with LRP4, the administration of an agrin fragment has shown binding to LRP4 and stimulation of the neuromuscular junction. Together with Dok7 and rapsyn, they assure the correct anchoring and dense clustering of the AChRs at the membrane, essential for a correct neuromuscular transmission. Manipulating the signalling path of these proteins by enhancing MuSK activation, one could improve the motor function and correct neuromuscular defects not only in myasthenia gravis but also in many other disorders of the neuromuscular junction such as amyotrophic lateral sclerosis, spinal muscular atrophy, nerve injury and sarcopenia. In combination with other disease-modifying therapies, they can help to reduce the damage at the neuromuscular junction and accelerate its recovery.

Antibody-mediated autoimmune diseases are in most cases successfully treated with broad-spectrum immunosuppressive drugs, known as first line therapeutic strategies. However, the lack of complete remission, the presence or development of treatment-resistance and the high incidence of unwanted side effects reinforce the unmet medical need to find and design novel therapeutic strategies. Using myasthenia gravis as a template, I described the novelties in the field of pharmacological intervention and highlight the relevance of treatment combination. Interlacing different drugs can enhance the effect or reduce the side effects. An additional value comes from the bivalency aspect of the newly developed therapies, which could also apply to other disorders where the immune system is involved such as cancer. Treatment strategies are moving towards personalized treatment, i.e. an exhaustive study of the disease mechanisms developed in each patient and the subsequent selection of the most

efficient therapies that alone or in combination, following a specific timeline, will help patients to reach disease remission that will be maintained over their lifetime.

Besides the design of novel drugs, this knowledge gives new opportunities to use drugs already available on the market, whose effects can be beneficial for other pathologies. Proteasome inhibitors, initially developed to treat multiple myeloma, a plasma cell malignancy, not only eliminate malignant plasma cells but all plasma cells. Plasma cells produce high amounts of antibodies and are significantly involved in antibody-mediated autoimmune disorders. However, they are rather insensitive to regular immunosuppressant therapies. I proved the therapeutic effect of ixazomib, a second generation proteasome inhibitor, in various models of myasthenia gravis. Additionally, no signs of neurotoxicity were observed, which was one of the bottlenecks of previous proteasome inhibitors. Animal research is essential for the application of novel or repurposed human therapies as they provide mechanistic information and give evidence of the safety and effectiveness in different diseases. These results are the proof of principle used to develop a clinical trial with ixazomib in patients with myasthenia gravis. Eliminating the plasma cells is a step further towards the cure of not only myasthenia gravis, but many other antibody-mediated autoimmune diseases since these cells are responsible for the antibody production and in consequence are responsible for the development of the disease.

All in all, the studies described in this dissertation are relevant for a substantial proportion of society considering the patients who currently have or will develop mental illnesses or autoimmune disorders which also have impact on members of their family. The results presented will influence the diagnostics and treatment of these patients with a direct impact in health care costs and new opportunities for pharmaceutical industries.

References

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