Göteborg, 2022

Viral proteins as serological antigens

Development and clinical applications

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i föreläsningssalen, Klinisk Mikrobiologi, Guldhedsgatan 10A, Göteborg, den 17 juni 2022, klockan 13:00

av Linn Persson Berg

Fakultetsopponent:

Överläkare Helena Hervius Askling

Karolinska institutet, Stockholm, Sverige

Avhandlingen baseras på följande delarbeten

I. Thomsson E, **Persson L**, Grahn A, Snäll J, Ekblad M, Brunhage E, Svensson F, Jern C, Hansson G.C, Bäckström M, Bergström T. *Recombinant glycoprotein E produced in mammalian cells in large-scale as an antigen for varicella-zoster-virus serology.* Journal of Virological Methods. 2011;175(1):53-9.

II. **Persson Berg L,** Thomsson E, Hasi G, Bäckström M, Bergström T. *Recombinant Epstein-Barr virus glycoprotein 350 as a serological antigen.* Journal of Virological Methods. 2020;284:113927.

III. **Persson L**, Longhi S, Enarsson J, Andersen O, Haghigi S, Nilsson S, Lagging M, Johansson M, Bergström T. *Elevated antibody reactivity to measles virus N_{CORE} protein among patients with multiple sclerosis and their healthy siblings with intrathecal oligoclonal immunoglobulin G production*. Journal of Clinical Virology. 2014;61(1):107-12.

IV. Jons D, **Persson Berg L**, Sundström P, Haghighi S, Axelsson M, Thulin M, Bergström T, Andersen O. *Follow-up after infectious mononucleosis in search of serological similarities with presymptomatic multiple sclerosis.* Multiple Sclerosis and Related Disorders. 2021;56:103288.

V. **Persson Berg L**, Eriksson M, Longhi S, Kockum I, Warnke C, Thomsson E, Bäckström M, Olsson T, Fogdell-Hahn A, Bergström T. *Serum IgG levels to Epstein-Barr and measles viruses in patients with multiple sclerosis during natalizumab and interferon beta treatment.*
Submitted manuscript.

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Linn Persson Berg

Avdelningen för infektionssjukdomar, Institutionen för biomedicin, Sahlgrenska akademin, Göteborgs universitet, Sverige, 2022.

Abstract

Serological methods are based on the detection of antibodies and antigens in mainly serum but also in other body fluids such as cerebrospinal fluid (CSF). Conventional whole virus antigens are widely used in viral serological assays. These antigens usually contain a mixture of proteins from the virus of interest together with residual cell components from antigen production, which can cause diagnostic problems with cross-reactive antibodies between closely related viruses and antibodies that bind to cellular components. The methods can become more specific by using antigens based on recombinant single viral proteins that differ between closely related viruses but to which the immune system reacts strongly (immunodominant proteins).

The aim of the research has been to develop specific serological assays to detect antibodies to varicella-zoster virus (VZV), Epstein-Barr virus (EBV) and measles virus (MeV). This has been accomplished by recombinantly producing single, specific, immunodominant viral proteins, VZV glycoprotein E (gE), EBV glycoprotein 350 (gp350) and the core part of the MeV nucleocapsid protein (N_{CORE}), for use as serological antigens in enzyme-linked immunosorbent assay (ELISA).

In **Paper I**, we show that VZVgE functions well as ELISA antigen to detect anti-VZVgE IgG antibodies. The antigen has thereafter been used in the routine diagnostics at the Department of Clinical Microbiology, Sahlgrenska University Hospital. In **Paper II**, we demonstrate that EBVgp350 performs well as serological antigen in ELISA for the detection of anti-EBVgp350 IgG. In **Paper III**, we found that patients with multiple sclerosis (MS) and their clinically healthy siblings with similar MS findings in CSF, i.e. a suspect hyperimmune phenotype, still show an increased IgG response to MeV in both serum and CSF compared with healthy controls when the previously used complex MeV whole virus antigen was replaced with MeV N_{CORE}. Our results indicate that the reactivity is indeed specific and not caused by cross-reacting autoantibodies to cellular proteins. In **Paper IV**, patients with MS show higher IgG levels in both serum and CSF to MeV and EBVgp350 compared with healthy controls. In addition, we observed that patients with serologically verified acute infectious mononucleosis have higher serum IgG levels to EBVgp350 at follow-up after 10 years compared with healthy controls, suggesting that EBV-induced mononucleosis affects the immune system in a powerful and long-lasting way. In **Paper V**, patients with MS treated with interferon beta (IFNβ) had higher anti-EBVgp350 and anti-MeV N_{CORE} IgG levels in serum compared with healthy blood donors. Following initiation of treatment with the monoclonal antibody natalizumab, patients' serum IgG levels decreased against both antigens, whereas levels were relatively stable during previous IFNβ treatment. Another finding was that all 728 patients with MS in the study were EBV IgG seropositive while 10 of the 144 blood donors in the control group were EBV IgG seronegative. This finding further strengthens the potential role of EBV in the pathogenesis of MS.

The developed ELISA methods can, through increased specificity, offer new diagnostic possibilities for detecting antibodies to EBV, VZV and MeV in viral infections, for control of immunity after infection/vaccination, in epidemiological investigations and in autoimmune diseases such as MS.

Keywords: Serology, ELISA, IgG, varicella-zoster virus, Epstein-Barr virus, measles virus, viral glycoproteins, multiple sclerosis

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