Fingerprinting disease by mass spectrometry

Manfred WUHRER [1],

[1] Center for Proteomics and Metabolomics, Leiden University Medical Center, Leiden, Netherlands

m.wuhrer@lumc.nl

Most diseases affect glycosylation at the tissue as well as serum level. Glycosylation changes are modulating protein function in cancer, infection and immunity. Mass spectrometry is a powerful technique to unravel tissue- and protein-specific glycosylation changes as exemplified for disease- and antigen-specific antibody responses.

Antibodies have key roles in adaptive immune responses. They exert their function via antigen binding as well as effector functions mediated by Fc receptors. Antibody function is strongly influenced by glycosylation of the constant region as well as the antigen-binding region. In the case of immunoglobulin G (IgG), the absence of fucose on the highly conserved N-linked glycan in the IgG-Fc domain strongly enhances IgG binding to Fc gamma receptors and activation of myeloid and NK cells.

Recent studies have shown a massive skewing of antibody glycosylation in infectious diseases and vaccination towards low fucosylation in the case of plasma membrane-associated antigens. In malaria infections, antibodies against parasite-infected erythrocytes show markedly low levels of fucosylation which may be important for development of natural immunity to the parasite. In contrast, in COVID-19 afucosylated IgG responses may induce aggravated immunopathology.

Bibliographic references:

Immunoglobulin G1 Fc glycosylation as an early hallmark of severe COVID-19. Pongracz et al, EBioMedicine. 2022, 78:103957

Affinity capillary electrophoresis - mass spectrometry permits direct binding assessment of IgG and FcγRIIa in a glycoform-resolved manner. Gstöttner et al, Front Immunol. 2022 13:980291.

Afucosylated IgG characterizes enveloped viral responses and correlates with COVID-19 severity. Larsen et al, Science. 2021, 371(6532):eabc8378.