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Absolute Quantification of the Bexsero Vaccine Component Factor H Binding Protein (fHbp) by Selected Reaction Monitoring: The Contribution of Mass Spectrometry in Vaccinology

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Abstract : The gram-negative bacterium Neisseria meningitidis serogroup B (MenB) is an exclusively human pathogen representing the major cause of meningitides and severe sepsis in infants and children but also in young adults. This pathogen is usually present in the 30% of healthy population that act as a reservoir, spreading it through saliva and respiratory fluids during coughing, sneezing, kissing. Among surface-exposed protein components of this diplococcus, factor H binding protein is a lipoprotein proved to be a protective antigen used as a component of the recently licensed Bexsero vaccine. fHbp is a highly variable meningococcal protein: to reflect its remarkable sequence variability, it has been classified in three variants (or two subfamilies), and with poor cross-protection among the different variants. Furthermore, the level of fHbp expression varies significantly among strains, and this has also been considered an important factor for predicting MenB strain susceptibility to anti-fHbp antisera. Different methods have been used to assess fHbp expression on meningococcal strains, however, all these methods use anti-fHbp antibodies, and for this reason, the results are affected by the different affinity that antibodies can have to different antigenic variants. To overcome the limitations of an antibody-based quantification, we developed a quantitative Mass Spectrometry (MS) approach. Selected Reaction Monitoring (SRM) recently emerged as a powerful MS tool for detecting and quantifying proteins in complex mixtures. SRM is based on the targeted detection of ProteoTypicPeptides (PTPs), which are unique signatures of a protein that can be easily detected and quantified by MS. This approach, proven to be highly sensitive, quantitatively accurate and highly reproducible, was used to quantify the absolute amount of fHbp antigen in total extracts derived from 105 clinical isolates, evenly distributed among the three main variant groups and selected to be representative of the fHbp circulating subvariants around the world. We extended the study at the genetic level investigating the correlation between the differential level of expression and polymorphisms present within the genes and their promoter sequences. The implications of fHbp expression on the susceptibility of the strain to killing by anti-fHbp antisera are also presented. To date this is the first comprehensive fHbp expression profiling in a large panel of Neisseria meningitidis clinical isolates driven by an antibody-independent MS-based methodology, opening the door to new applications in vaccine coverage prediction and reinforcing the molecular understanding of released vaccines.

Keywords : quantitative mass spectrometry, Neisseria meningitidis, vaccines, bexsero, molecular epidemiology
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