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Assessment of the protective potential of monoclonal antibodies against antigen candidate transferrin binding protein B

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Background

Pathogenic neisserial species utilize nutrient acquisition proteins to thrive and establish infection in humans. One example is transferrin binding protein B (TbpB), a bi-lobed surface lipoprotein that acquires iron from human transferrin (hTf). As TbpB is surface-exposed and essential for colonization, it has been regarded as a vaccine antigen candidate. Previously, our group observed reactivity to both gonococcal and meningococcal strains upon immunization with two gonococcal TbpB variants.

Aim/Methods

To investigate the highly cross-reactive antibody response elicited by the gonococcal TbpB variants, we generated and identified reactive monoclonal antibodies (mAbs) and assessed their protective potential. Over 400 rabbit mAbs against the selected TbpB variants were generated for characterization, including reactivity to a panel of gonococcal and meningococcal TbpB variants. Affinity for the homologous antigen for each mAb was determined with biolayer interferometry. Currently, we are assessing the bactericidal activity and protective potential of these mAbs through serum bactericidal assays (SBA) and passive immunization respectively. In addition, we are mapping their epitopes by x-ray crystallography and cryo-electron microscopy.

Results

We isolated mAbs that could distinguish between conformational epitopes and linear epitopes but also identified mAbs that bound highly cross-reactive epitopes present in the gonococcal and meningococcal variants. The mAbs, selected for their recognition of conformational and/or highly cross-reactive epitopes, were determined to bind to the homologous TbpB with nanomolar affinity. As polyclonal sera from these rabbits were bactericidal against matched gonococcal strains, we are currently assessing the role of individual mAbs in SBAs. The structures of several of the antigen binding fragments (Fabs) of these mAbs were determined. For a select mAb, we obtained a 2.3Å crystal structure of Fab in complex with the full-length homologous gonococcal TbpB. Since it binds the hTf binding interface, we are presently assessing the mAb’s ability to neutralize the transferrin binding capability of TbpB.

Conclusions

We identified mAbs that react to surface-exposed epitopes on both pathogenic Neisseria species, supporting TbpB as a pan-neisserial antigen candidate. To inform both vaccine and potential therapeutic design, we will continue to determine immunologically relevant epitopes on TbpB and assess the bactericidal activity of these cross-reactive mAbs.