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EDITORIAL

Monoclonal antibodies and bacterial virulence

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This issue of *Virulence* features an article entitled "Antibodies to *Staphylococcus aureus* capsular polysaccharides 5 and 8 perform similarly *in vitro* but are functionally distinct *in vivo*"[1] which describes the evaluation of mAbs (monoclonal antibodies) against *S. aureus* CP5 and CP8 for their specificity in binding to a wide variety of encapsulated clinical isolates and their ability to mediate *in vitro* opsonophagocytic bacterial killing. In particular, the authors assessed protection against bacteremia that is provoked by both serotype 5 and 8 *Staphylococcus aureus*, and discovered that serotype 8 *Staphylococcus aureus* clinical isolates release soluble CP8 during culture and infection. The release of soluble CP8, reducing the *in vivo* efficacy of passively administered capsular antibodies (polyclonal or mAbs), may contribute to the inability of CP8 vaccines or antibodies to protect against experimental bacteremia provoked by clinical CP8+ *Staphylococcus aureus* strains staphylococcal infections.

Staphylococcus aureus is a gram-positive bacterium, mostly originating from environment and foods, that causes a wide range of illnesses in humans, ranging from skin infections to bacteremia, sepsis, and endocarditis.[2] Treatment of *Staphylococcus aureus* infections can be difficult, particularly for the frequent rising of antibiotic-resistant strains such as methicillin-resistant (MRSA) and vancomycin-resistant *Staphylococcus aureus* (VRSA). So far, efforts to produce an effective vaccine have failed[3] but immunotherapy with mAbs seems to be effective just as for other pathogen bacteria. Currently, the emergence of multi-drug resistant forms of new and old pathogens and the growingly number of immunocompromised people (pathologies related to immunodeficiency, patients undergoing chemotherapy etc.), has provided an unprotected population from which combinations of complex infections are emerging. The increasing prevalence and rising cost of resistant infections in both nosocomial and community settings emphasizes the need to develop new strategies for controlling infections. Antibodies are widely used in oncology and clinical immunology, and recently have been considered again for other uses, mostly against infectious diseases.[4] New antibody therapeutics, in particular mAbs, seem to be the best strategy in both treating and preventing new drug resistant infectious diseases.[5]

Many infections from a variety of pathogens can be treated with antibody therapies, including viral, bacterial, fungal, and prion-mediated infections, showing great differences in pathology and virulence. In general, highly virulent and acute infections are more likely to require and well respond to the fast protection provided by antibody treatments.[6] A variety of mechanisms allows antibodies to fight different pathogens, including antibody dependent cellular cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), opsonization, immunomodulation.

Both polyclonal and monoclonal antibodies can be used in immunotherapy. Polyclonal immunotherapy uses immune sera-derived immunoglobulins that are polyclonal preparations consisting of many types of antibodies of which only a minute fraction is specific for the intended microbe. On the other hand, mAbs usually include just one type of immunoglobulin with a defined specificity and a single isotype. This represents both an advantage and a disadvantage compared to polyclonal preparations. The obvious disadvantage is that diagnosis must be certain and specific to allow the use of monoclonal preparation, and the infection should be caused by a single kind of microbe. However, advantages of mAbs are crucial. The first advantage is that mAbs, because they are chemically defined reagents, exhibit relatively low lot-to-lot variability in contrast to polyclonals, which can differ over time and by source of origin since different hosts show different antibody responses. Another main advantage for mAbs is a much greater activity per mass of

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protein, because all the immunoglobulin molecules are specific for the real target of the immunotherapy.[7] Moreover, the ability to specifically target microbial populations that cause disease without producing a selection for resistance makes mAb therapy potentially superior to broad spectrum antibiotics that are generally used in therapy, at least for microbial diseases caused by single microbes. It is also evident that treatment of an infectious disease with multiple mAbs could probably provide a better protection. While mAb cocktails are developed to address this problem, another approach may be the use of antibody therapy in association with antimicrobials. Therefore, protocols for clinical development of new antibody therapies for infectious diseases could require clinicians to include the current therapies which in many cases are based on antibiotics. Antibody acts in synergy with antibiotics to provide increased protection against infection. However, naturally resistant bacteria can be rendered susceptible to antibiotics by mAb therapy, thereby decreasing the likelihood of escape mutants.[8]

Very recent studies confirm the efficacy of monoclonal antibodies therapy with new specific applications, on the same side of Liu's study featured in this Virulence issue and detailed at the beginning of this editorial. For example, Aguilar et al.[9] demonstrated that passive immunization with a combination of mAb-4G3 and mAb-5G4, two mAbs that do not compete for epitope(s) on Staphylococcal Enterotoxin K (SEK), significantly enhance survival in a murine model of SEK-induced toxic shock which causes severe shock also in humans. Similarly, passive immunization with the mAb 2H7 confers protection against murine sepsis and peritonitis caused by Methicillin-resistant *Staphylococcus aureus* challenges.[10] Use of mAbs has been recently considered and improved also for other pathogen microorganisms. In particular, another recent study have shown high protective efficacy of humanized version of mAb specific for the conserved LPS O-antigen of *Klebsiella pneumoniae* endotoxin.[11]

In conclusion, with the emergence of new drug resistant bacterial strains, investment in the development of therapeutic antibodies may improve our clinical preparedness to combat these emerging threats. Now, more than ever, research on the use and specific effects of mAbs is necessary in order to advance our knowledge and deploy new effective therapeutic tools against aggressive bacteria.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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