INFECTIOUS DISEASES

Two-hit antibody tackles bacteria

With the rise of multidrug-resistant strains of bacteria and a lack of new antibiotic classes in the drug development pipeline, alternative strategies are needed to manage bacterial infections. A recent study reports the development of a bispecific monoclonal antibody (mAb) that targets two surface epitopes on *Pseudomonas aeruginosa* and synergizes with existing antibiotics in mouse models of infection.

P. aeruginosa is a principal cause of hospital-acquired pneumonia and of chronic lung infections in patients with cystic fibrosis. Its large genome and complex regulatory networks provide this pathogen with a substantial capacity to adapt to environmental challenges, such as antibiotics, making effective treatment of infections particularly difficult.

Antibodies against single *P. aeruginosa* epitopes have been investigated but have not shown sufficient protective activity. In the hope that targeting two epitopes could be more successful, in the current study, the authors used a mAb that targets PcrV — a component of a *P. aeruginosa* system for the secretion of virulence factors. Into this antibody they genetically inserted a single-chain variable fragment of a mAb that binds to Psl — an extracellular polysaccharide expressed by the pathogen that is involved in immune evasion and biofilm formation.

Brain light/Alamy

In vitro studies revealed that this bispecific antibody, termed BiS4αPa, potentiated phagocytic clearance, more potently inhibited *P. aeruginosa* attachment to epithelial cells and enhanced cytotoxic activity compared with either or both parent antibodies.

Next, the team tested BiS4αPa in mice against two strains of *P. aeruginosa* — namely, the highly pathogenic 6206 strain and the multidrug-resistant 6077 strain. In both cases, pretreatment with the new antibody provided marked protection relative to monovalent mAb treatment, indicating synergy due to the dual targeting.

Moreover, therapeutic administration of BiS4αPa, 1 hour after infection with strain 6077, conferred potent protection in the murine lethal pneumonia model. Treatment was associated with suppression of bacterial dissemination and reduced pathological markers of pneumonia and cellular damage.

The authors also note that pathogen-specific targeting with therapeutic antibodies, unlike broad-spectrum antibiotics, should leave the beneficial microbiome intact.

On the basis of *in vitro* studies of various bispecific antibody constructs targeting either or both PcrV and Psl, the authors proposed that BiS4αPa enhances activity against the low-abundance PcrV target through high-avidity binding to the abundant Psl target, thereby showing cooperative target engagement.

Last, the team investigated whether BiS4αPa might complement the activity of existing antibiotics. Indeed, subtherapeutic doses of the antibiotics ciprofloxacin or meropenem (which have different mechanisms of action) combined with subtherapeutic doses of BiS4αPa, administered either prophylactically or 4 hours post-infection, synergized to enable mice to survive challenge in the lethal pneumonia model. By contrast, mice receiving control immunoglobulin G (IgG) or monotherapy succumbed after infection.

In addition, the antibiotic tobramycin was rendered effective in treating tobramycin-resistant *P. aeruginosa* when BiS4αPa was administered adjunctively at subtherapeutic doses in the murine acute pneumonia model.

BiS4αPa is a promising clinical candidate (designated MEDI3902) that could provide a valuable new option to treat *P. aeruginosa* infections. More broadly, these findings highlight the bispecific antibody platform as a potential tool to reinvigorate the existing 'battery' of antibiotics against a range of bacterial pathogens.

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ORIGINAL RESEARCH PAPER DiGiandomenico, A. *et al.* A multifunctional bispecific antibody protects against *Pseudomonas aeruginosa*. *Sci. Transl. Med.* **6**, 262ra155 (2014)
FURTHER READING Garber, K. Bispecific antibodies rise again. *Nature Rev. Drug Discov.* **13**, 799–801 (2014)