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Abstract (oral session)

Antibodies against a putative type 4 secretion system channel protein are broadly cross-protective among multi-resistant Gram-positive pathogens

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Multiresistant gram-positive bacteria are a continuing and rising threat in hospitals worldwide. Complex mechanisms enable these pathogens to exchange genetic information, especially the distribution of resistance determinants leads to their propensity to cause hospital outbreaks as well as endemic spread. Here, we report that one of the very factors responsible for genetic exchange, namely a specific protein of the so-called type 4 secretion systems, represents an Achilles heel that can be harnessed to fight these often untreatable infections. A prototypical gram-positive type 4 secretion system is present on plasmid pIP501, and several proteins of the transfer region have been expressed in E. coli. Rabbit sera were raised against two proteins, i.e. ORF10 and ORF13, that code for an ATPase and a putative channel component. The rabbit sera were used in an opsonophagocytic assay and sera raised against ORF13 showed 77% killing of the homologous strain at a dilution of 1:10. Using absorption of the sera with increasing amounts of purified protein this killing could be inhibited by up to 44.5%. Testing of a larger collection of strains from different species revealed that 3/4 (75%) E. faecalis, 2/4 (50%) E. faecium, and 5/5 (100%) S. aureus were effectively killed by anti-ORF13 at a dilution of 1:10, including one vancomycin-resistant S. aureus strain and several USA300 CA-MRSA. Western Blot analysis demonstrated cross-reactive protein bands in 2 of 3 tested E. faecalis-, 3 of 4 E. faecium and a total of 5 S. aureus strains, respectively. The homologous strain E. faecalis JH2-2pIP501 (expressing protein Orf13) shows a band at 37.5 kDa. Using a mouse bacteremia model, significant reductions in colony counts were seen in animals that had received anti-ORF13 as compared to animals that had received antisera against ORF10 and were challenged with the homologous E. faecalis, as well as with an E. faecium and a CA-MRSA strain. Animals infected with the homologous E. faecalis that were not carrying plasmid pIP501 were not protected. These data demonstrate that ORF13 is the target of opsonic and protective antibodies and may therefore be a promising and broadly cross-protective vaccine candidate targeting multi-resistant gram-positive pathogens.