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Targetting T6SS of Klebsiella pneumoniae for Assessment of Immune Response in Mice for Therapeutic Lead Development

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Abstract : Klebsiella pneumoniae bacteria is a global threat to human health due to an increase in multi-drug resistance among strains. The hypervirulent strains of Klebsiella pneumoniae is a major trouble due to their association with life-threatening infections in a healthy population. One of the major virulence factors of hyper virulent strains of Klebsiella pneumoniae is the T6SS (Type six secretary system) which is majorly involved in microbial antagonism and causes interaction with the host eukaryotic cells during infections. T6SS mediates some of the crucial factors for establishing infection by the bacteria, such as cell adherence, invasion, and subsequent in vivo colonisation. The antibacterial activity and the cell invasion property of the T6SS system is a major requirement for the establishment of K. pneumoniae infections within the gut. The T6SS can be an appropriate target for developing therapeutics. The T6SS consists of an inner tube comprising hexamers of Hcp (Haemolysin -regulated protein) protein, and at the top of this tube sits VgrG (Valine glycine repeat protein G); the tip of the machinery consists of PAAR domain containing proteins which act as a delivery system for bacterial effectors. For this study, immune response to recombinant VgrG protein was generated to establish this protein as a potential immunogen for the development of therapeutic leads. The immunogenicity of the selected protein was determined by predicting the B cell epitopes by the BCEP analysis tool. The gene sequence for multiple domains of VgrG protein (phage_base_V, T6SS_Vgr, DUF2345) was selected and cloned in pMAL vector in E. coli. The construct was subcloned and expressed as a fusion protein of 203 residue protein with mannose binding protein tag (MBP) to enhance solubility and purification of this protein. The purified recombinant VgrG fusion protein was used for mice immunisation. The antiserum showed reactivity with the recombinant VgrG in ELISA and western blot. The immunised mice were challenged with K. pneumoniae bacteria and showed bacterial clearance in immunised mice. The recombinant VgrG protein can further be used for studying downstream signalling of VgrG protein in mice during infection and for therapeutic MAb development to eradicate K. pneumoniae infections.

Keywords : immune response, Klebsiella pneumoniae, multi-drug resistance, recombinant protein expression, T6SS, VgrG
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