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Leptospira Lipl32-Specific Antibodies: Therapeutic Property, Epitopes Characterization and Molecular Mechanisms of Neutralization

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Abstract : Leptospirosis is a globally neglected disease that continues to be a significant public health and veterinary burden, with millions of cases reported each year. Early and accurate differential diagnosis of leptospirosis from other febrile illnesses and the development of a broad spectrum of leptospirosis vaccines are needed. The LipL32 outer membrane lipoprotein is a member of Leptospira adhesive matrices and has been found to exert hemolytic activity to erythrocytes in vitro. Therefore, LipL32 is regarded as a potential target for diagnosis, broad-spectrum leptospirosis vaccines, and for passive immunotherapy. In this study, we established LipL32-specific mouse monoclonal antibodies, mAbLPF1 and mAbLPF2, and their respective mouse- and humanized-engineered single chain variable fragment (ScFv). Their antibodies' neutralizing activities against Leptospira-mediated hemolysis in vitro, and the therapeutic efficacy of mAbs against heterologous Leptospira infected hamsters were demonstrated. The epitope peptide of mAb LPF1 was mapped to a non-contiguous carboxy-terminal β-turn and amphipathic α-helix of LipL32 structure contributing to phospholipid/host cell adhesion and membrane insertion. We found that the mAbLPF2 epitope was located on the interacting loop of peptide binding groove of the LipL32 molecule responsible for interactions with host constituents. Epitope sequences are highly conserved among Leptospira spp. and are absent from the LipL32 superfamily of other microorganisms. Both epitopes are surface-exposed, readily accessible by mAbs, and immunogenic. However, they are less dominant when revealed by LipL32-specific immunoglobulins from leptospirosis-patient sera and rabbit hyperimmune serum raised by whole Leptospira. Our study also demonstrated an adhesion inhibitory activity of LipL32 protein to host membrane components and cells mediated by mAbs as well as an anti-hemolytic activity of the respective antibodies. The therapeutic antibodies, particularly the humanized-ScFv, have a potential for further development as non-drug therapeutic agent for human leptospirosis, especially in subjects allergic to antibiotics. The epitope peptides recognized by two therapeutic mAbs have potential use as tools for structure-function studies. Finally, protective peptides may be used as a target for epitope-based vaccines for control of leptospirosis.

Keywords : leptospira lipl32-specific antibodies, therapeutic epitopes, epitopes characterization, immunotherapy
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