Docking study of LipL32-plasminogen complex: insights contributing to knowledge of the host invasion by pathogenic leptospires

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Leptospirosis is a reemerging zoonosis of endemic behavior and worldwide distribution. The etiological agent of Leptospirosis is the *Leptospira interrogans* bacterium, a spirochetal microorganism with more than 200 serovars or resulting species' varieties from structural heterogeneity in the carbohydrate component of lipopolysaccharide (1; 2). Each serovar is adapted to specific mammals. Because of the large spectrum of mammalian species, both wild and domesticated, might be considered as disease reservoirs. Leptospirosis is considered the most important zoonosis in the world with high rates of death for human species (3; 4). For instance, epidemiological data from 2009 reported more than 100 cases over 100,000 people around the world (www.who.org). Particularly, in South America, the human leptospirosis has reached rates higher than 10 cases over 100,000 people, and continuously it has been reported a growing number of epidemic outbreak along with clinical studies indicating a high frequency of the disease (5).

The poor understanding of the molecular basis of leptospirosis led to deeply address the mechanisms underlying the pathogenesis of this disease. Previous studies have demonstrated that leptospira alters the mammalian proteolytic plasminogen–plasmin system which could promote degradation of ECM (extracellular matrix) components and facilitates the dissemination of the bacteria in the host tissues (7). In 2009, Vieira et al showed that leptospiral species are able to bind to several plasminogen types (PLG1, PLG2, and PLG3) and generate plasmin in presence of an activator (8). By 2010, Vieira et al studied and identified several plasminogen binding receptors, including the major outer membrane antigen expressed during mammalian infection: LipL32 lipoprotein, from the pathogenic bacteria: *Leptospira interrogans* serovar *Copenhageni* (6). More recently, Vieira et al demonstrated the immune evasion from the bacteria along the infection by in vitro evidence for the association bacteria-PLA(plasmin) and the subsequent degradation of main components of the innate immune system (antibodies IgG and C3 opsonins) (9).

LipL32, highly conserved across leptospiral species and serovars (10), is present only in pathogenic Leptospira species and has been shown to be more abundant on the leptospiral surface among all the identified leptospiral lipoproteins (11). LipL32 lipoprotein is the major target of several studies because of its presumable key role in the pathogenesis of Leptospirosis. However, although Vieira and collaborators showed the possible mechanism of evasion by the pathogenic Leptospira against the host immune system and identified to LipL32 protein as a plasminogen binding receptor, the LipL32-plasminogen interaction at the level of individual amino acids is unknown.

As previously reported by Lahteenmaki et al (12), the information on the structural details of the interaction between bacterial PlgRs (Plasminogen binding receptors) and the plasminogen proenzime is important to construct inhibitors of this specific protein-protein interaction that could be allowing the dissemination of the bacteria through the host tissues and invade the host immune system. The investigation of protein interactions with others molecules at level of individual amino acids and its subsequent interference are experimentally difficult to address (12; 7). Computational methods, as the accurate predictive docking, could provide substantial structural knowledge about complexes and
subsequently the binding sites that could be readily mapped, characterized and optimized to be used as output for the design of inhibitors of protein-protein interactions (13). The aim of this study was to generate the 3D structure of LipL32 in complex with Plg (Its five Kringle domains) by molecular docking methods. The resulting complex reveals several binding sites of the LipL32/Plasminogen interaction by lysine residues. Consequently, the final complex contains binding sites that are in agreement with previous experimental work (8). Taking into consideration that binding of plasminogen to a receptor alters its conformation rendering it more susceptible to activation and hence to facilitating the cell migration by degradation of tissue barriers. In conclusion our result provides new insights about the mechanisms of the invasion process and immune evasion of pathogenic leptospires, which is relevant for possible design of synthetic peptides able to inhibit this interaction and prevent the invasion of bacteria in the host system.

References


