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Review

Pathogenesis of leptospirosis: Cellular and molecular aspects

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ABSTRACT

Leptospirosis is arguably the most widespread zoonosis; it is also a major cause of economic loss in production animals worldwide. At the level of the host animal or human, the progression of infection and the onset of disease are well documented. However, the mechanisms of pathogenesis at the cellular and molecular level remain poorly understood, mainly as a result of the lack of modern genetic tools for mutagenesis of pathogenic *Leptospira* spp. The recent development of transposon mutagenesis and the construction of a very small number of directed leptospiral mutants have identified a limited number of essential virulence factors. Perhaps surprisingly, many leptospiral proteins with characteristics consistent with a role in virulence have been shown to not be required for virulence in animal models, consistent with a high degree of functional redundancy in pathogenic *Leptospira*. A large number of putative adhesins has been reported in *Leptospira*, which interact with a range of host tissue components; however, almost none of these have been genetically confirmed as having an essential role in pathogenesis.

Contents

1. Introduction

Leptospirosis caused by pathogenic species of *Leptospira* is arguably the most widespread zoonosis both in terms of geographical region and animal species that are susceptible to acute disease or can serve as renal carriers. The clinical aspects and progression of disease in humans and domestic animals are well understood (Elllis, 2014; Haake and Levett, 2014). However, knowledge of specific virulence mechanisms and host factors that determine the outcome of infection is limited. When considering the pathogenesis of leptospirosis at the cellular and molecular level, our understanding of the processes and interactions between bacteria and host lags some way behind what is known for most other bacterial species and indeed for infections caused by other spirochete genera (Adler and de la Peña Moctezuma, 2010; Adler et al., 2011; Ko et al., 2009).

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The main reason has been the lack of tools for the genetic manipulation of pathogenic *Leptospira*. However, in the past few years, random transposon mutagenesis methods for pathogenic leptospires have been developed (Bourhy et al., 2005; Murray et al., 2009a). The ensuing analysis of defined mutants has identified a small number of genes and proteins with defined roles in virulence. Targeted mutagenesis in pathogenic *Leptospira* spp. is possible, but is very inefficient and is at present not suitable for routine use. Indeed, only a very small number of genes have been reported as inactivated by this approach in pathogenic leptospires (Croda et al., 2008; Liao et al., 2009; Kassegne et al., 2014; Zhang et al., 2012). Perhaps surprisingly, a number of genes/proteins with predicted virulence attributes, such as cellular location and presence in only pathogenic *Leptospira* spp., have been shown by mutagenesis studies to be not required for virulence, at least in the most commonly used animal models for acute infection (hamster) or for renal colonisation (rat, mouse) (Adler et al., 2011; Murray, 2014). Most surprising amongst these factors have been the most abundant cellular leptospiral protein LipL32 and the surface exposed LigB and LipL41 proteins; all are expressed *in vivo*, are conserved and unique to pathogenic *Leptospira* spp., but are dispensable for virulence, at least in the animal models tested (Croda et al., 2008; King et al., 2013; Murray, 2013). The basis for this degree of functional redundancy at great metabolic cost to the bacteria remains unexplained.

2. Entry, adhesion, invasion and dissemination

Leptospires gain entry to the body *via* mucous membranes or through skin where integrity has been compromised by damage (cuts, abrasions) or by immersion in water. Haematogenous spread follows rapidly; in experimental animals, leptospires can be detected in blood and tissues with 10 min of intraperitoneal, intradermal or intraocular inoculation. Adhesion to host tissues would seem to be a prerequisite for successful infection and indeed both intact leptospiral cells and a plethora of leptospiral proteins have been shown *in vitro* to adhere to a range of host components (Table 1). Many leptospiral proteins are reported to interact with multiple host components. In almost all cases, the experiments have involved recombinant proteins expressed in a heterologous host, usually *E. coli*. While these *in vitro* interactions are clearly real and appear specific, the sheer numbers reported must raise some questions about their biological significance, even taking into account the

Table 1
Adhesion and putative adhesins of pathogenic *Leptospira*.

Leptospiral serovar	Leptospiral component	Host component	Reference
Copenhageni	Viable leptospires	L929 fibroblasts	Vinh et al. (1982)
Copenhageni	Viable leptospires	Primary renal epithelial cells	Ballard et al. (1986)
Ballum			
Copenhageni	Viable leptospires	L929 fibroblast ECM	Ito and Yanagawa (1987)
Canicola			
Pomona			
Icterohaemorrhagiae	Viable leptospires	Vero fibroblasts	Merien et al. (1997)
		J774A.1 macrophages	
Icterohaemorrhagiae	Unidentified 36 kDa protein	Fibronectin	Merien et al. (1997)
Copenhageni	Recombinant Lsa24	Laminin	Barbosa et al. (2006)
Copenhageni	Recombinant LigA, LigB	ECM, fibronectin	Choy et al. (2007)
Copenhageni	Recombinant LenA (LfhA, Lsa24), LenBCDEF	Laminin, fibronectin	Stevenson et al. (2007)
Copenhageni	Recombinant Lsa21	Laminin, collagen IV, fibronectin	Atzingen et al. (2008)
Manilae	Recombinant LipL32	Laminin, collagen I, collagen V	Hoke et al. (2008)
Copenhageni	Recombinant LipL32	Fibronectin, collagen IV	Hauk et al. (2008)
Pomona	Recombinant LigB fragment	Elastin, tropoelastin	Lin et al. (2011)
Copenhageni	Recombinant Lsa27	Laminin	Longhi et al. (2009)
Copenhageni	Recombinant Lp95	Laminin, fibronectin	Atzingen et al. (2009)
Copenhageni	Viable leptospires	Chondroitin sulfate B	Breiner et al. (2009)
Canicola			
Copenhageni	Recombinant Lsa63	Laminin	Vieira et al. (2010b)
Copenhageni	Recombinant OmpL37	Elastin, fibronectin, fibrinogen, laminin	Pinne et al. (2010)
Copenhageni	Recombinant Lipl32, LIC12730, LIC10494, Lp29, Lp49, LipL40, MPL36, LIC12238	Plasminogen	Vieira et al. (2010a)
Copenhageni	Recombinant LigB fragment	Fibronectin, collagen III	Choy et al. (2011)
Copenhageni	LigA and LigB expressed in *L. biflexa*	MDCK cells, fibronectin, laminin	Figueira et al. (2011)
Copenhageni	Recombinant Lsa66	Fibronectin, laminin, plasminogen	Oliveira et al. (2011)
Copenhageni	Recombinant Lsa20	Laminin, plasminogen	Mendes et al. (2011)
Copenhageni	Recombinant Lsa25, Lsa33	Laminin	Domingos et al. (2012)
Copenhageni	Recombinant Lsa30	Plasminogen	Souza et al. (2012)
Copenhageni	OmpL1	Fibronectin, laminin, plasminogen	Fernandes et al. (2012)
Copenhageni	Recombinant elongation factor Tu LIC12875	Collagen, fibronectin, laminin, elastin, fibrinogen	Wolff et al. (2013)
Copenhageni	Recombinant LIC12238, Lsa33, Lsa30, OmpL1, LIC11360, LIC11975	Fibrinogen	Oliveira et al. (2013)
Copenhageni	Viable leptospires	Cadherin	Evangelista et al. (2014)
Copenhageni	Recombinant Lsa44, Lsa45	Laminin	Fernandes et al. (2014)
Manilae	LMB216 expressed in *L. biflexa*	Fibronectin	Toma et al. (2014)