

Toll-Like Receptor-5 and the Innate Immune Response to Bacterial Flagellin

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The innate immune system identifies the presence of infection by detecting structures that are unique to microbes and that are not expressed in the host. The bacterial flagellum (Latin, a whip) confers motility on a wide range of bacterial species. Vertebrates, plants, and invertebrates all have evolved flagellar recognition systems that are activated by flagellin, the major component of the bacterial flagellar filament. In mammals, flagellin is recognized by Toll-like receptor-5 and activates defense responses both systemically and at epithelial surfaces. Here, we review the role for Toll-like receptor-5 in mediating the mammalian innate immune response to flagellin, and how this provides for defense against infections caused by many different species of flagellated bacteria.

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1 Introduction

The innate immune system rapidly mobilizes defenses to respond effectively to threats posed by a multitude of different microbes. The discovery of the Toll-like receptor (TLR) family has provided great insight into how the innate immune

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system recognizes microbes and initiates inflammatory signaling. Receptors of the innate immune system have been selected to identify microbial components that are distinctly non-self (MEDZHITOV and JANEWAY 1997). The TLR family of innate immune receptors is utilized by a vast array of multicellular eukaryotic organisms, ranging from insects to plants to humans (ADEREM and ULEVITCH 2000; MEDZHITOV 2001). Toll-like receptors detect a wide range of microbial products, including lipopolysaccharide (LPS), peptidoglycan, yeast cell wall, lipoteichoic acid, bacterial lipoproteins, bacterial heat shock proteins, mycobacterial phosphoinositol mannosides, bacterial CpG-DNA, double-stranded RNA, and bacterial flagellin (UNDERHILL and OZINSKY 2002). Once engaged, these receptors activate host cells, initiate local and systemic inflammatory responses, and drive the differentiation of antigen presenting cells to promote an adaptive immune response (AKIRA et al. 2001; MEDZHITOV 2001).

Over the past few years, it has been determined that bacterial flagella activate host innate immune defenses, both in white blood cells (monocytes and macrophages), and in epithelial cells. Recently, we have determined that TLR5 mediates the innate immune response to flagella through recognition of flagellin, the major constituent of the bacterial flagellar filament (HAYASHI et al. 2001). In this review, we will discuss how TLR5 activation by flagellin may mediate innate immune defense against many different species of flagellated bacteria.

2 Bacterial Flagellin

Flagella are responsible for bacterial motility and are regulated to produce directed movement under the control of sensors that detect environmental cues. It is presumed that the ability to approach nutrients and to avoid noxious surroundings confers a strong survival advantage that has led to the evolutionary conservation of structures required for flagellar assembly in many different bacterial species. The concerted action of more than 50 genes is required for eubacterial flagellar regulation and assembly (CHILCOTT and HUGHES 2000). Flagella are composed of three major components: a rotary motor (the basal body complex) that is inserted in a ring structure in the peptidoglycan and LPS cell wall layers, a flexible universal joint (the hook) and a whip-like filament (Fig. 1). The hook and filament are extracellular structures. The motor converts chemical energy into the mechanical force that rotates the hook. The hook is an approximately 55nm long flexible structure that transmits torque to the filament (HIRANO et al. 1994). The filament, which can be up to 15 μ m long, is made almost entirely from polymerized flagellin subunits. The filament is assembled with 11 flagellin monomers being stacked per two turns like bricks forming a spiral staircase-like cylinder. The filament also has a cap complex that functions as a chaperone to facilitate filament assembly (Fig. 1). The ability of the flagellum to generate motility depends on the direction of rotation of the flagellar motor, which, by switching its rotation in