Letter to the Editor

Host-Microbiota Interaction is MyD88-Independent in the Intestinal Tract under Physiologic Condition

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Abstract

The role of microbiota in health and disease is the subject of rigorous investigation. Several studies have demonstrated that microbiota and the pattern-recognition receptors contribute to intestinal tumourigenesis; the exact mechanism of which is still obscure. MyD88 is the downstream effector of all Toll-like receptors (TLRs) except TLR3. However, the alternative MyD88-independent pathway is functional downstream of not only TLR3, but also TLR1/2, 2/6, 4, and 5. TLR4 stimulation with intraperitoneal lipopolysaccharide exerts distinct functional effect on the intestinal motility via MyD88-dependent and-independent pathways.

Keywords: Host-microbiota interaction, Intestinal tract, Toll-like receptors

We read with interest the paper entitled "Analysis of gut microbial regulation of host gene expression along the length of the gut and regulation of gut microbial ecology through MyD88" by Larsson *et al* [(1)]. The role of microbiota in health and disease is the subject of rigorous investigation. Several studies have demonstrated that microbiota and the Pattern-Recognition Receptors (PRRs) contribute to intestinal tumourigenesis; the exact mechanism of which is still obscure. Larsson *et al* have studied the effect of microbiota on the intestinal epithelial cell gene expression through a systematically microarray experiment in germfree *vs.* colonised mice. They have discovered that microbiota *per se* alters the intestinal gene expression in colonised mice in comparison to germfree counterparts.

Toll-Like Receptors (TLRs) are a group of PRRs which detect a wide range of stimuli. All TLRs except TLR3 function via MyD88. To address the question on the mechanism of transcriptional effect of microbiota on the intestinal cells, Larsson *et al* conducted the microarray experiment in MyD88$^{-/-}$ mice. If the microbiota effect was largely mediated by TLR signalling, it was expected to discover similar expression patterns in germfree and MyD88$^{-/-}$ mice. However, interestingly germfree mice demonstrate a distinct gene expression pattern compared to MyD88$^{-/-}$ mice. This finding is suggestive of a MyD88-independent mechanism of host-microbiota interaction in the normal intestine. MyD88 is the downstream effector of all TLRs except TLR3. However, the alternative MyD88-independent pathway is functional downstream of not only TLR3, but also TLR1/2, 2/6, 4, and 5 [(2-4)]. It is noteworthy that a distinctive host response to microbiota is observed through activation of different downstream effectors in the TLR pathway; [(5,6)] the implication of which in the intestinal homeostasis and tumourigenesis is still unknown. In addition, other members of PRRs namely, NOD-like receptors and RIG-I-like receptors are potentially

implicated in the physiologic host-microbiota interaction.

TRIF is the main adaptor of the MyD88-independent TLR signalling. MyD88 $^{-/-}$ TRIF$^{-/-}$ mice are completely unresponsive to TLR stimulation [7]. In other words, MyD88 and TRIF exhibit non-redundant effects in TLR signalling. Larsson *et al* have demonstrated that under physiologic condition, the MyD88-independent pathway is an important mechanism of intestinal homeostasis maintenance [1]. In order to fully understand the role of TLR signalling in the normal intestinal homeostasis, it is essential to study the TRIF-dependent pathway in a similar experiment in TRIF$^{-/-}$ *vs.* TRIF$^{+/+}$ mice. It is conceivable that the balance between MyD88-dependent *vs.*–independent pathways can fine-tune the TLR signalling in response to normal and altered microbiota in health and disease.

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