

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

Shirin Moossavi¹ and Nima Rezaei^{2,3,4*}

1. Digestive Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran

2. Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

3. Molecular Immunology Research Center, Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

4. Department of Infection and Immunity, School of Medicine and Biomedical Sciences, University of Sheffield, Sheffield, UK

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.

References

1. Larsson E, Tremaroli V, Lee YS, Koren O, Noo-kaew I, Fricker A, et al. Analysis of gut microbial regulation of host gene expression along the length of the gut and regulation of gut microbial ecology through MyD88. *Gut* 2012;61(8):1124-1131.
2. Gao Q, Qi L, Wu T, Wang J. Clostridium butyricum activates TLR2-mediated MyD88-independent signaling pathway in HT-29 cells. *Mol Cell Biochem* 2012;361(1-2):31-37.
3. Biswas SK, Bist P, Dhillon MK, Kajiji T, Del Fresno C, Yamamoto M, et al. Role for MyD88-independent, TRIF pathway in lipid A/TLR4-induced endotoxin tolerance. *J Immunol* 2007;179(6):4083-4092.
4. Choi YJ, Im E, Chung HK, Pothoulakis C, Rhee SH. TRIF mediates Toll-like receptor 5-induced signaling in intestinal epithelial cells. *J Biol Chem* 2010;285(48):37570-37578.
5. Zughair SM, Zimmer SM, Datta A, Carlson RW, Stephens DS. Differential induction of the toll-like receptor 4-MyD88-dependent and -independent signaling pathways by endotoxins. *Infect Immun* 2005;73(5):2940-2950.
6. Buchholz BM, Billiar TR, Bauer AJ. Dominant role of the MyD88-dependent signaling pathway in mediating early endotoxin-induced murine ileus. *Am J Physiol Gas-trointest Liver Physiol* 2010;299(2):G531-G538.
7. Gavin AL, Hoebe K, Duong B, Ota T, Martin C, Beutler B, et al. Adjuvant-enhanced antibody responses occur without toll-like receptor signaling. *Science* 2006;314 (5807):1936-1938.

* Corresponding author:

Nima Rezaei, M.D., Ph.D., Children's Medical Centre Hospital, Tehran 14194, Iran

Tel: +98 21 66929234

Fax: +98 21 66929235

E-mail: rezaei_nima@tums.ac.ir; shirin.moossavi@gmail.com

Received: 5 Aug 2012

Accepted: 30 Aug 2012