The Function of Toll-like receptor 2 in Infection and Inflammation

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2021, Leiden

Colophon

Title: The Function of Toll-like receptor 2 in Infection and Inflammation

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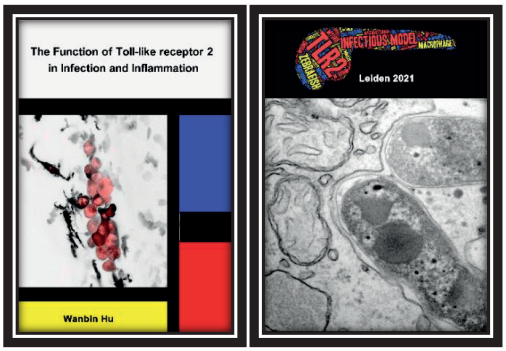
Ph.D. thesis, University of Leiden, Leiden, The Netherlands

ISBN: 978-94-92597-88-5



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Cover Front: The design was inspired by the painting “Composition with red, yellow and blue” (by Piet Mondriaan). The confocal picture in the middle box shows the co-localization of macrophages (black) with clusters of *Mycobacterium avium* bacteria (red) in infected zebrafish larvae at 4 days post infection.
Cover back: Word cloud in the shape of a 1 day post fertilization zebrafish larva. The font size in the word cloud is based on its occurrence frequency in the thesis. The transmission electron microscope image shows two *Mycobacterium avium* bacteria inside a phagosome. The image was taken from zebrafish larva tail fin infected with *Mycobacterium avium* strain MAC101. The transmission electron microscope image was taken by Gerda Lamers.

Printing company: Printsupport4U

The studies described in this thesis were performed at the Institute of Biology Leiden, Leiden University.
The work was supported by a grant from the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) under the RespiriNTM project (Grant No. 853932) and the China Scholarship Council (CSC no. 201708210177).
The publication of this thesis was financially supported by Leiden University.

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Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op 16 december 2021
klokke 15.00 uur

door

Wanbin Hu

geboren te Luoyang, Henan, China

op 8 mei 1991

Promotores:	Prof. Dr. H. P. Spaink
	Prof. Dr. F. J. Verbeek
Promotiecommissie:	Prof. Dr. G. P. van Wezel
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路漫漫其修远兮，吾将上下而求索。

The road ahead is long and has no ending; yet high and low I will search with my will unbending.

——Qu Yuan

For my family and friends

献给远方的家人和所有的朋友

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Scope of this thesis

Innate immunity is considered as the first line in defense against microbial invasion and it is also involved in responses to tissue injury [1-3]. The innate immune system consists of physical/chemical barriers, humoral components, innate immune cells, and innate signaling molecules [1]. The host maintains its homeostasis and initiates adaptive immune responses by modulating the innate immune system [1, 2]. Innate immune disorders can increase the susceptibility of hosts to invading pathogen infections [4]. Thus, better comprehension of events involved in innate immunity is essential for understanding human pathogenesis and the subsequent discovery of new targets for therapeutic applications.

Toll-like receptor (TLR) signaling, as a crucial part of the innate immune system, has been widely investigated after its initial discovery in *Drosophila* [5, 6]. TLR2, which is conserved in most vertebrates, is one of the most crucial toll-like receptors because its function in microbial defense is the broadest, and the most promiscuous [7]. It has been reported that TLR2 is involved in the immune modulation during infectious diseases [8, 9], chronic and acute inflammatory diseases [10, 11], cancers [12], and even metabolic disorders [13]. At present, the function of TLR2 is still controversial in some studies and its role in several diseases is still inconclusive [7]. It is clear that TLR2 is a promising therapeutic target, but its dual role in both activation and suppression of innate immune responses makes further clinical research challenging [14]. Thus, further studies on the function of toll-like signaling and TLR2 in the innate immune system are necessary.

In this thesis, the functions of toll-like signaling in infection and inflammation are studied by using the zebrafish larval model. Firstly, we studied the function of Toll-like signaling in the absence and presence of pathogenic microbial infection at the transcriptome level. Then, we studied the role of Toll-like signaling on the regulation of leukocyte migration in response to tissue damage and infection, respectively. For this, sophisticated cell tracking and mathematic analyses were performed using fluorescent live imaging based on a confocal laser scanning microscopy. In the end, we set up a comparative zebrafish infection model and found specialized roles of the *tlr2* gene in defense against various mycobacterial species. This thesis provides better understanding of the functions of TLR2 in innate immune responses and provides a large amount of data for future mathematical modeling and deep learning, which makes further *in silico* biological studies possible.

In the general introduction, we address the current cell biological knowledge about the function of TLR2 that makes it a promising therapeutic target for combatting infectious and inflammatory diseases. Subsequently, we discuss the advantages of transparent zebrafish larvae for cell tracking methods to uncover new functions of TLR2.