Manipulating endosomal systems: the molecular mechanisms of transport decisions and Salmonella-induced cancer

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ISBN: 978-90-903-2558-3

Cover: Manipulation of endosomes by a regulatory mechanism. The colors represent the fluorescent labels that are used to detect endosomes marked by different endosomal proteins during confical microscopy experiments. Design: Jeroen Bakker.

The research on which this thesis is based was performed at the department of Cell Biology II, Netherlands Cancer Insttute, Amsterdam, the Netherlands, as well as at the department of Chemical Immunology, Leiden University Medical Center, Leiden, the Netherlands.

Financial support for printing this thesis was provided by the Leiden University Medical Center (LUMC)

Printed by: Printenbind

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Proefschrift

Ter verkrijging van de graad van Doctor aan de Universiteit Leiden, op gezag van Prof. Mr. Carl Stolker, Rector Magnificus & voorzitter college van bestuur volgens besluit van het College voor Promoties te verdedigen op donderdag 12 december 2019 om 15:00 uur

Door

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Geboren te Amsterdam

Op 6 augustus 1985

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Scope of this thesis

This thesis describes the work I performed to study the mechanisms behind endocytosis from 2 different angles. The first part of this thesis focusses on the molecular systems by which a cell controls positioning of intracellular vesicles and how this affects handling of their associated cargoes, while the second part describes the manipulation of the host cell by *Salmonella* bacteria and the potential harm this interference could do.

In chapter 1 I will introduce the general mechanisms behind endocytosis and the role these processes play in the life of a cell. To further elaborate these mechanisms chapter 2 uses the example of EGFR trafficking to showcase the multiple molecular pathways involved in receptor endocytosis. In addition to this, chapter 3 describes a novel regulatory system involved in a crucial event in endosomal maturation: GTPase exchange. In more detail, chapter 3 describes a handover system that exchanges the late endosomal Rab GTPase Rab7 upon activation of Arl8b, by recruitment of Rab7GAP through the HOPS complex. This exchange is important in the proper segregation of Arl8b associated late endosomes and the retrieval of its cargo from the Rab7-positive endosomal compartment.

In chapter 4 I will introduce the second part of this thesis. I will explain how pathogens use the molecular mechanisms of its host cell, including endosomal transport, to facilitate their own growth and survival. I will also highlight the dangers of these invasive mechanisms for the host by showing the role bacterial infections can play in host maladies, such as cancer. Chapter 5 and 6 show a first report of a causal link between salmonella and cancer. This section focusses on how salmonella's usage of the host alters intracellular signaling events in pretransformed cells, with the potential to cause cancer. In vivo, ex vivo and in vitro systems are used to show the, non-immune related, oncogenic capacities of Salmonella and the molecular events that lie behind this effect.

Finally, in chapter 7 I will encapsulate all observations from this thesis with a summary and a discussion that places the findings of this thesis in perspective with the aim to provide deeper insights in the meaning of these results and how it can implicate further research on these topics.