Novel regulators of endosome dynamics, MHCII antigen presentation and chemosensitivity

Wijdeven, R.H.M.

An introduction before the Introduction

During the last years I have worked on defining various factors in control of vesicle transport and MHC class II antigen presentation, as well as resistance to anti-cancer drugs. This yielded various chapters describing the role of cholesterol, the ER and membrane contact sites in the control of endosome and autophagosome transport and the elucidation of the role of a novel protein, RNF26, regulating positioning of the entire endosomal system (Chapter 2 and 3). In Chapter 4 and 5 I have focussed on an enzyme class that removes ubiquitin modifications from proteins and used RNAi screening to identify two controllers of endosomal motility and MHC class II expression. We subsequently performed several experiments to dissect the corresponding cell biology, which is work that is still ongoing.

Chapter 6 is an introduction to Chapter 7 that describes a series of experiments where we tried to integrate chemical and genetic data to define novel target-lead combinations in control of MHC class II expression. Using this approach we identified two novel proteins, Keap1 and p62, and two drugs, dimethylfumarate (DMF) and arsenite, that coordinate interferon-γ induced MHCII expression. This system induces the expression of MHC class II in non-hematopoietic cells and may be critical for MHC class II upregulation in inflamed tissue. Interestingly, DMF is already used in the clinic to treat auto-immune diseases.

Chapter 8 continues on drugs, and more specifically the anthracycline cancer drugs. It reviews the current understanding of these anti-cancer drugs as well as their mechanisms of resistance. This is explored further in Chapter 9, where we describe the use of genome-wide screening systems to determine novel factors in control of resistance to the anthracycline doxorubicin, a drug extensively used in anti-cancer treatment. We also delved into the corresponding cell biology and showed that the most prevailing pathway identified revolves around DNA double stranded break repair.

The thesis is wrapped up with a discussion of the different chapters, which in combination cover the cell biology of endosomal transport and the utilization of drugs in control of MHC class II transcription and anti-cancer responses.