Studies on Intracellular Logistics

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Scope of Thesis

This thesis contains research pertaining to several aspects of cellular biology. This led to a title which matched such a wide range of cellular domains.

In **chapter one,** Studies on Intracellular Logistics will start with a perspective on current treatments for lung cancer and the possibility of the immunoproteasome as potential novel target. In this perspective we discuss a study relating to the poor outcome of non-small cell lung cancer in relation to lower expression of immunoproteasomal subunits. We discuss the possibilities of modulating immunoproteasomal subunit expression as a tool to assist in cancer therapies, such as tumor infiltrating lymphocyte therapy and checkpoint inhibition.

Following this discussion; **chapter two** will delve into basic biology by studying a mechanism which appears to be responsible for ensuring the correct segregation of soluble proteins in the cytosol and the nucleus following mitosis. With special focus on the (immuno)proteasome, due to its size and intracellular localization characteristics. These data show evidence for an elegant physical event responsible for maintaining the separation of soluble proteins between the cytosol and the nucleus following mitosis.

Chapter three will discuss current understanding on the spatiotemporal pathway following endocytosis. We use EGFR and its ligand EGF as example of how a receptor becomes activated and endocytosed. Following these events, we describe the range of proteins and events needed for endosomes to mature properly, leading to the disposal of EGF and EGFR.

Next, in **chapter four**, we discuss our study regarding the influence of the endosomal population on ER architecture. Here, we show that various endosomal populations exert influence on the ER architecture through endosomal mobility. Our data suggests that late endosomes cause a significant amount of ER movement due to the relatively large number of interactions between endosomes and the ER. Alterations in endosomal movement are shown to have a direct effect on the complexity of the ER architecture. Sequestering endosomes to a specific location subsequently resulted in a marked decrease in ER complexity. Just as disrupting contacts sites between the ER and lysosomes led to a similar effect. This led us to conclude that movement of the late endosomal / lysosomal

populations assist in maintaining ER architecture.

In **chapter five**, we discuss data on MOSPD2. Our data shows MOSPD2 as a novel MSP-domain containing protein with strong ties to lipid metabolism. Depleting MOSPD2 from the cellular repertoire led to alterations in lipid content, predominantly in Ceramide synthesis. We found that MOSPD2 interacts with the enzyme UGCG, which glucosylates ceramides. Furthermore, we discovered that, due to its involvement in glucosylceramide synthesis, MOSPD2 may play a role in the formation of alpha-synuclein aggregate formation. These aggregates are thought to play an important role in Parkinson's disease pathology.

With **chapter six**, I summarize and conclude Studies on Intracellular Logistics.