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Autophagy protease ATG4B as a drug target in cancer

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Autophagy is a catabolic process that encloses cytoplasmic content in a double membrane vesicle, the autophagosome, and degrades it through fusion with the lysosome. The modulation of autophagy has been implicated in multiple diseases including pathogen infection, neuro-degenerative disorders and cancer. Although the main components of the autophagy machinery have been identified by yeast genetics and in mammalian cells, the identification of entry points for drug targeting in this pathway has proven challenging. Recent findings suggest that autophagy protease ATG4B and proteins that regulate ATG4B activity are potential drug targets in cancer. In order to study the regulation of ATG4B, we took advantage of our recently developed assay to measure ATG4B activity in cells by assessing the amount of secreted luciferase in cells expressing the reporter Actin-LC3-DeltaNluciferase. We used this assay to identify small molecule inhibitors of ATG4B that may have therapeutic potential in breast cancer. Further, we used kinase and phosphatase siRNA and cDNA libraries and identified genes that enhance or suppress cellular ATG4B activity. We identified an inhibitory phosphorylation of ATG4B at the forming autophagosome that allows the spatio-temporal control of autophagosome maturation. Finally, we provide preliminary data using CRISPR-Cas9 genome editing to study the function of ATG4 isoforms in mammalian cells. Overall, our results shed light on the complex regulation of ATG4B in cells and will inform therapeutic strategies targeting this protein.

Biography

Robin Ketteler has studied Biochemistry at the Free University Berlin and completed his PhD in 2002 at the Max-Planck Institute for Immunobiology in Freiburg, Germany. He completed his Post-doctoral studies from Massachusetts General Hospital in Boston. Since 2009, he is a Group Leader at the University College London. He is the Manager of the Translational Research Resource Center, a high-content screening facility at University College London, UK.

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