

**P003** Kinase inactivated ULK proteins inhibit autophagy via their conserved C-terminal domain using an Atg13-independent mechanism

**Edmond Y. W. Chan, Nicole McKnight, Sharon A. Tooze**

*London Research Institute*

*Cancer Research UK*

Atg1, a serine-threonine protein kinase, is a key regulatory component of the signalling pathway controlling autophagy in all organisms. In mammals, the homologs ULK1 and ULK2 are required for autophagy, and previous studies have demonstrated that the C-terminal domain (CTD) is required for autophagy and for the localization of the protein. We explored the intra-molecular regulation of the kinase activity to understand the function of these proteins during autophagy. Using kinase-dead ULK1 and ULK2 and CTD deletion constructs we demonstrate that the dominant-negative activity of the kinases requires an eight-residue motif in the CTD. Our data leads to a model in which the activity of ULK1 and 2 is controlled by autophosphorylation and conformational changes regulated by the CTD. The CTD contains distinct regions promoting membrane association, and interaction with the putative mammalian homologue of Atg13, which we have here characterized. Atg13 is required for autophagy, and as shown for ULK1 but not ULK2, is required for mammalian Atg9 trafficking during starvation. Atg13 does not bind the eight-residue motif in the CTD of ULK1 or 2, nor is the inhibitory activity of the CTD rescued by Atg13, suggesting that in mammalian cells the CTD may interact with additional autophagy proteins.