

Site-specific phosphorylation of paxillin drives autophagy-mediated focal adhesion turnover and cancer cell locomotion

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Abstract

Cancer cell locomotion is a highly regulated process, where focal adhesion (FA) assemble/disassembly cycles are necessary for effective migration. Posttranslational mechanism(s) regulating the dynamics of this FA turnover at focal adhesion sites are not fully understood. In this study, we uncovered a novel direct function of autophagy in the regulation of FA disassembly in breast cancer cells. We established that inhibition of cellular autophagy, either by exposure to chloroquine (CQ) or suppression of autophagosome maturation by Rab7 downregulation, resulted in enhanced FA disassembly along with reduced cell migration. Under similar conditions, we demonstrated that one of the major components of FAs, namely paxillin, accumulated in autophagosomes. Moreover, down-regulation of upstream regulators of autophagy (Atg12) or the endocytic pathway (Rab5) further confirmed the contribution of the autophagic pathway in paxillin removal from FA sites, where phosphorylation of paxillin on tyrosine 118 was required for autophagic targeting and engulfing. Finally, we identified c-Cbl as the major cargo receptor required for paxillin targeting to the LC3 complex, independent of its E3 ubiquitin ligase activity. Together, these results provide new insights into the role of autophagy in the regulation of FA dynamics and cancer cell migration, while providing new therapeutic opportunities for targeting breast cancer progression.