Nature Reviews Molecular Cell Biology | AOP, published online 18 August 2010; doi:10.1038/nrm2966

CELL MIGRATION

ESCRTing integrin degradation

> ubiquitylation of α5 integrin mediates the proper migration of fibroblast cells

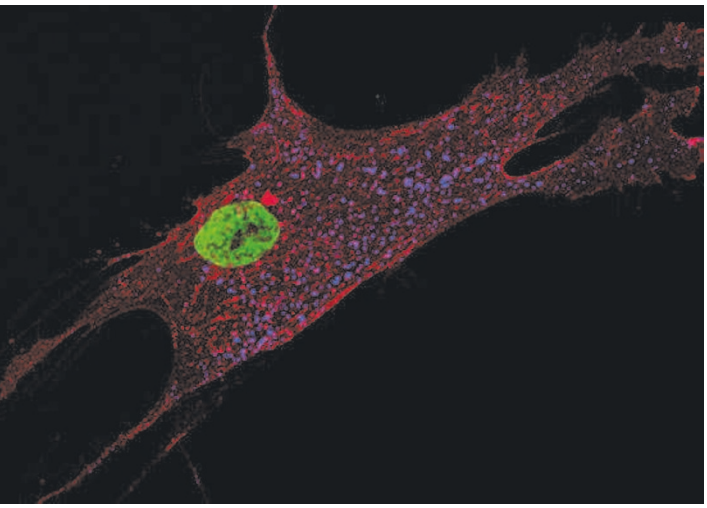
Integrin endocytosis and recycling are important during cell migration, but it is not known whether integrins need to be degraded. In *Developmental Cell*, Stenmark and colleagues now report that the ubiquitylation of α5 integrin and the binding of fibronectin to α5β1 integrin mediates lysosomal degradation of both proteins by the endosomal sorting complex required for transport (ESCRT) machinery, and that this process is required for cell migration.

The authors first showed that a portion of α5 integrin colocalizes with fibronectin in the multivesicular endosomes (MVEs) of human fibroblasts. This suggests that fibronectin and a fraction of α5β1 integrin are trafficked together from endosomes to lysosomes for degradation. Furthermore, they found that endogenous α5 integrin is ubiquitylated at cytoplasmic Lys residues in response to fibronectin binding and that mutation of these residues reduces the degradation rate of α5 integrin, showing that fibronectin-mediated ubiquitylation of α5 integrin promotes its lysosomal degradation.

The authors also saw that both α5 integrin and β1 integrin localize to the lumen of MVEs on fibronectin binding, and that this sorting required α5 integrin ubiquitylation. Importantly, wild-type α5 integrin colocalized with 'active' β1 integrin inside the lumen of the MVEs, indicating that endocytic sorting of integrin proteins depends on ligand binding. Moreover, depletion of α5 integrin inhibited sorting of fibronectin to the MVEs and this could not be restored by expression of a mutant α5 integrin. Thus, fibronectin and its receptor α5β1 integrin traffic together and this depends on ubiquitylation of α5 integrin.

Ubiquitylated proteins directly interact with the components of the ESCRT machinery and, indeed, the authors found that inhibition of the ESCRTs resulted in accumulation of ubiquitylated α5β1 integrin on endosomal compartments, and this was enhanced in the presence of fibronectin. Furthermore, fibronectin degradation was also dependent on the ESCRT machinery. Consistent with these results, immuno-electron microscopy showed that fibronectin and α5 integrin colocalize in enlarged early endosomes in ESCRT-depleted cells and that their levels were regulated by the ESCRT machinery. Finally, live-cell time-lapse imaging showed a reduced cell migration speed in the absence of α5 integrin; transfection with small interfering RNA-resistant wild-type α5 integrin restored the migration speed, whereas expression of the mutant α5 integrin did not have any effect. Taken together, these results show that ubiquitylation of α5 integrin mediates the proper migration of fibroblast cells through the trafficking and degradation of fibronectin-bound α5β1 integrin by the ESCRT pathway. Further research will help elucidate the role of integrin degradation in cancer cell migration.

Iley Ozerlat, Assistant Editor,
Cell Migration Gateway



A substantial fraction of α5β1 integrin (red) is transported to late endosomes or lysosomes (colocalization with lysosomes is shown in magenta; the nucleus is stained in green). Image courtesy of H. Stenmark, Department of Biochemistry, Institute for Cancer Research, Oslo University Hospital, Norway.

ORIGINAL RESEARCH PAPER Lobert V. H. *et al.* Ubiquitination of α5β1 integrin controls fibroblast migration through lysosomal degradation of fibronectin–integrin complexes. *Dev. Cell* **19**, 148–159 (2010)