

Abstract

Signalling through the EGF receptor is subject to a complex and multilayered regulation. One such mode of regulation is through control of ligand production which plays an important role in fine-tuning EGF receptor activation. In mammals, the production of soluble, biologically active forms of EGF receptor ligands relies on ADAM metalloproteases, predominantly ADAM10 and ADAM17. Recently, a pseudoprotease from the rhomboid-like family of intramembrane proteases, iRhom, emerged as a key positive regulator of ADAM17. However, *Drosophila* iRhom has also been implicated in the negative regulation of EGF receptor signalling by promoting the degradation of precursors of its ligands. Cell culture based assays suggest that mammalian iRhoms might also be involved in a similar process. In this thesis, the effect of mammalian iRhom overexpression on the levels of EGF receptor ligands has been investigated. Contrary to previous findings, the data presented in this thesis suggest that the observed effect might not be entirely iRhom specific, for the inactive mutants of rhomboid proteases also diminish the levels of EGF receptor ligands. Nor do we find the effect to be specific to EGF receptor ligands, as unrelated transmembrane proteins were also depleted by iRhom overexpression. The coexpression of ADAM17 was able to prevent the depletion of EGF receptor ligands by iRhom overexpression but only in HEK cells lacking endogenous iRhom protein. The loss of EGF receptor ligands does not appear to be caused by canonical degradation pathways, for neither lysosomal nor ERAD pathway inhibitors reversed the effect of iRhom overexpression.

Key words: regulation of EGF receptor signalling, iRhom, ADAM17, quantitative immunoblotting