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Two-step proteolytic cleavage of the human protocadherin Fat1 and translocation of the intracellular domain to the nucleus

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The giant member of the protocadherin family, hFat1, is of pivotal importance during embryonal and fetal development of various organs including frontal brain. hFat1 is also essential in podocyte and slit membrane formation of renal glomeruli. In cultured cells, the transmembrane form of hFat1 is located at lamellipodial edges and filopodial tips. Its involvement in the regulation of actin cytoskeleton dynamics by interacting with mammalian Ena/Vasp proteins has been reported. In HEK293 cells we have expressed a transmembrane construct of hFat1 comprising the extracellular EGF-like domains and the intracellular domain. The localization pattern of the construct agrees with that of endogenous hFat1. Our data also suggest that the transmembrane form of hFat1 undergoes a regulated two step proteolytic process similar to that described for other members of the cadherin family. Apparently, the cleavages occurs spontaneously in some cell lines. In a first step, the extracellular domain is cleaved and released into the culture medium. A subsequent cleavage process releases the intracellular domain. The intracellular domain is predominantly translocated to the nucleus. This is partly due to the unmasking of a N-terminal nuclear localisation sequence but additional effects, such as binding to nuclear proteins may also contribute.