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ENA/VASP and Homer scaffolding proteins compete for the EVH1 binding site of the hFat1 cadherin

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The intracellular domain of the human transmembrane protocadheriun Fat1 (hFat1) is involved in actin cytoskeleton regulation by the interaction of its class I EVH1 binding domain (4437FPPPP) with Ena/Vasp. We have identified the scaffolding proteins Homer-3 and Homer-1 as binding partners of hFat1 by pull-down experiments and mass spectrometry. Homer proteins are known to form complexes with several actors at critical key points of signalling pathways, such as the metabotropic glutamate receptors, IP3-dependent Ca2+ and transient receptor potential ion channels, small GTPases, cytoskeletal proteins, and transcription factors. Homer proteins play essential roles in the development of spines and synapses. They are linked to cocaine-induced neurological effects and may be involved in the pathogenesis of schizophrenic disorders. Transfection of HeLa cells with transmembrane forms of hFat1 enhances the formation of cellular protrusions and hFat1 is predominantly located at the tips of these protrusions in co-localisation with Homer.

In vitro binding and mutation analyses showed that Homer proteins interact with the sequence 4440PPEDF which represents a class II EVH1 binding site. The interaction domains in hFat1 for ENA/VASP and Homer proteins are different but overlapping, and consequently binding of hFat1 to Homer proteins competes with binding to mammalian Ena and vice versa. Although the EVH1 domains of Homer proteins are highly homologous, stronger binding of Homer-3 compared to that of Homer-1 was observed. Since binding of Homer-3 to hFat1 appears to be very strong, the interaction is also expected to compete with the binding of other ligands of its EVH1 domain.

Following stimulation of T-cells, Homer-3 is translocated to the nucleus and affects serum response element – dependent transcription by binding to and inactivating C/EBP. We have recently shown that hFat1 undergoes proteolytic processing in response to unknown stimuli. The released intracellular domain is subsequently translocated to the nucleus and apparently also affects specific transcription processes. The mechanisms, however, are indirect. With respect to interaction between hFat1 and Homer proteins and the links between Homer proteins and psychic disorders, the recently reported link between the susceptibility to familial bipolar disorder and mutations in the genomic locus encoding the EVH1 binding site of hFat1 appears to be of special interest.