UKE Paper of the Month Mai 2017

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SHANK proteins limit integrin activation by directly interacting with Rap1 and R-Ras.

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ABSTRACT:
SHANK3, a synaptic scaffold protein and actin regulator, is widely expressed outside of the central nervous system with predominantly unknown function. Solving the structure of the SHANK3 N-terminal region revealed that the SPN domain is an unexpected Ras-association domain with high affinity for GTP-bound Ras and Rap G-proteins. The role of Rap1 in integrin activation is well established but the mechanisms to antagonize it remain largely unknown. Here, we show that SHANK1 and SHANK3 act as integrin activation inhibitors by sequestering active Rap1 and R-Ras via the SPN domain and thus limiting their bioavailability at the plasma membrane. Consistently, SHANK3 silencing triggers increased plasma membrane Rap1 activity, cell spreading, migration and invasion. Autism-related mutations within the SHANK3 SPN domain (R12C and L68P) disrupt G-protein interaction and fail to counteract integrin activation along the Rap1–RIAM–talin axis in cancer cells and neurons. Altogether, we establish SHANKs as critical regulators of G-protein signalling and integrin-dependent processes.

STATEMENT:
In this study we combine human genetic, protein structural and cell biological data to identify an unexpected binding module for Ras family G-proteins in postsynaptic Shank proteins. Shank mutations found in autism patients disrupt this function, and interfere with a role of Shank in regulating integrin-mediated cell adhesion. Our work not only provides new insight into the cellular mechanisms of autism, but also into the regulation of cancer cell spreading.

BACKGROUND:
This work is an interdisciplinary study, in collaboration with the group of Johanna Ivaska from Turku, Finland, and Igor Barsukov, Liverpool, UK. Work at the UKE was performed at the Institute of Human Genetics, in the group of Hans-Jürgen Kreienkamp. PhD students Victoria Martens and Fatemeh Hassani Nia, and medical student Malte Beifuss contributed to this work. The work was funded by the Dr. Hans and Lieselotte Ritz-Stiftung, DAAD, and the DFG through GRK1459.