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Mechanism of NSP – Cas modules in Cell Signaling

Stefan J. Riedl

Max Plank Institute for Biochemistry, Munich

The formation of multiple domain signaling protein complexes is a central paradigm in cell pathway regulation. The two protein families comprised of NSP (novel SH2-containing proteins) and Cas (Crk-associated substrates) are an emerging class of regulators that form such signaling nodes mediated by their distinct C-terminal domains. Arguably the NSP protein BCAR3 and the Cas protein p130Cas (BCAR1) constitute the most prominent members of these protein families. As indicated by their dedications, both proteins were identified as significant breast cancer anti-estrogen resistance factors able to function synergistically to augment cancer drug resistance. Further important functions of these proteins and other NSP/CAS family members have come to light implicating them in the regulation of such processes as angiogenesis, the immune response, and neuronal development. Despite the emerging importance of these protein families, detailed insight into the nature of their interaction regions and their signaling nodes have remained elusive. To elucidate this enigma we have solved the crystal structures of BCAR3 as well as the NSP3/p130Cas complex. These structures combined with biochemical and biological analysis show a surprising new mode of module formation in which a central enzymatic domain used in classical Ras GTPase signaling has been redirected to function as an exceptional cellular signaling entity. Together these findings explain the biology of NSP-Cas modules in signaling and also serve as a basis for potential efforts targeting NSP-Cas dependent pathways.

Biography

Dr. Riedl obtained his Ph.D. in 2002 with Nobel Laureate Dr. Robert Huber at the Max Plank Institute for Biochemistry in Munich. After postdoctoral research at Princeton University he started his own research group in 2006 at The Sanford|Burnham Medical Research Institute where he is currently an assistant professor in the Cancer Center. Throughout his career Dr. Riedl has made several key contributions in the field of cell death and cancer signaling complexes.