Supplementary information S4 | RAS interaction with GEF effectors

There are two ways small GTPases have been reported to interact with GEFs, either as substrates of GEFs for the GDP/GTP exchange reaction (pictured in the bottom structures), or with GEFs acting as effectors of their GTP-bound form. This dual situation is illustrated here. The top views depict modeled structures of Ras-GTP in complex with the RA domain of RalGDS, a GEF for Ral, and with the RBD domain of Tiam1, a Rac1 GEF. These interactions may regulate effector function, in part, by release of autoinhibitory interactions in the GEFs and/or promotion of their association with the plasma membrane, and hence stimulate the activation of Ral by the CDC25 domain of RalGDS, or Rac by the DH-PH domains of Tiam1. These pathways are used by Ras to promote tumorigenesis, which could be explored as novel sites of pharmacological intervention. For illustration, the structures of RAS•RBD (top right) and RAL•RALGDS (bottom left) are represented by the related structures of RAP1•RAF (PDB id. 1CY1) and RAS•SOS (PDB id. 1BKD), respectively. The determined structures of RAS•RALGDS RA domain and TIAM1•RAC1 are PDB id. 1LFD and 1FOE, respectively. These pathways are used by Ras to promote tumorigenesis, which could be explored as novel sites of pharmacological intervention.