Example of proteins with many identifiable domains From Gomperts, "Signal Transduction"

Mechanism of GTPase activation

In trying to understand the mechanism of activation of the intrinsic GTPase activity of Ras by GAP proteins, two main ideas have been examined.[110] First, there is the possibility that the GAP acts simply by driving the Ras protein into a conformation active for GTP hydrolysis, without itself forming a part of the active site. In this case, the action of GAP on Ras would be catalytic and hence non-stoichiometric. Now, however, it is thought that the RasGAP interacts with the Ras stoichiometrically, contributing cationic residues (arginine) that stabilize the transition state of

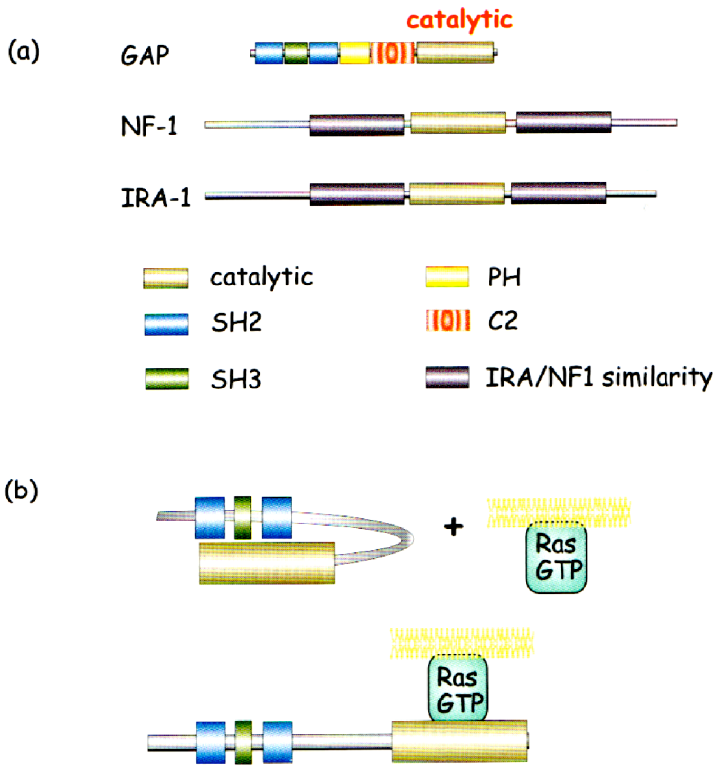

Figure 4.16 The domain organization of RasGAP and related GTPase activating proteins.

GAPs and effectors

Does RasGAP do more than regulate GTPase activity? Is it, like the effectors of heterotrimeric G-proteins, also an effector of downstream processes?[109] The fact that RasGAP interacts only with Ras.GTP, not with Ras.GDP, is certainly consistent with the idea of an effector function. Furthermore, the interaction is mediated through its contact with the effector domain of Ras (Figure 4.16b). Some (though not all) mutations in this domain prevent the interaction with GAP. Against this is the finding that RasGAP suppresses the transformation of fibroblasts induced by over-expression of normal wild-type Ras. Here, the GAP appears to play the role of a negative regulator, simply accelerating the rate of GTP hydrolysis.

An alternative possibility would be that Ras GAP might be the mediator of just a subset of Ras functions, the rest of which are linked to other effector proteins. For instance, it can stimulate transcription of the c-*fos* promoter[110] but here its catalytic domain plays no part since deletion mutants comprising only the SH2 and SH3 domains are equally effective.