et al. 2008). Many pathogens need host proteins as cofactors for their disease-causing activity. For example, exoenzyme S from *Pseudomonas aeruginosa*, an opportunistic bacterium that causes pneumonia, needs to interact with host 14-3-3 proteins to be able to transfer an ADP-ribose moiety from NAD^+ to small G proteins like Ras (Fu et al. 1993).

Many cellular functions like motility, e.g., in the context of angiogenesis, are related to functional changes in the cytoskeleton. The dynamic assembly and disassembly of actin filaments are based on the interaction of actin with itself and the binding to protein partners like cofilin and profilin (Bernstein and Bamburg 2010). Biological (surface) recognition, like in the immune system, is also mediated by PPIs as in the case of binding of LFA-1 (*l*ymphocyte *f*unction-associated *a*ntigen *1*) presented on the surface of immune cells to ICAM-1 (*i*ntracellular *a*dhesion *m*olecule *1*) found on the surface of endothelial cells (Lawson and Wolf 2009). This interaction enables immune cells to attach to the walls of blood vessels and to migrate into neighboring tissue to initiate inflammation.

2 Physiological Regulation of PPIs

Given the importance and number of PPIs in the living cell, it is no surprise that they have to be tightly regulated in a precise spatial and temporal manner. The occurrence and perseverance of PPIs are in general governed by the local concentration of the binding partners and the intrinsic binding energy of their interactions (Nooren and Thornton 2003). The first is regulated by (epi)genetic control and translational mechanisms, subcellular localization, proteolytic degradation, and temporary storage. The second is modulated by covalent modifications like phosphorylation, by changes in pH, ionic strength, and temperature. Furthermore, additional PPIs can influence binary interactions. These can lead to inhibition when, e.g., the interaction interface of one partner is masked by binding to the same interface or by simple sterical hindrance. PPIs can also be just induced by a further protein, for example, when the third interacting protein binds simultaneously to both protein partners. Such a "bridging" or "assembly platform" function has been described for the *A-k*inase *a*nchoring *p*roteins (AKAPs) (Wong, and Scott 2004) and the *k*inase *s*uppressor of *R*as (KSR) (Clapéron and Therrien 2007). It is clear that the local architecture of such signaling complexes is one of the keys to understand regulation and specificity of signaling events, and small-molecule intervention of these processes holds great promises for the development of novel therapeutic agents.

3 Small-Molecule Modulation of PPIs: Inhibition

An early example of an FDA-approved (1999) PPI inhibitor is **tirofiban** (trade name Aggrastat®, Merck & Co.) (Hartman et al. 1992; Springer et al. 2008). Tirofiban was designed as an RGD tripeptide mimic that binds to the integrin