FIGURE 1

Gα as a regulated molecular signaling nexus. This graphic of the Gα signaling nexus delineates functional elements within the molecule such as nucleotide binding (e.g. NKxD motif, TCAT motif, P-loop) and GPCR-driven nucleotide exchange (α-helix 5, β-strand 6), the different conformations of Gα (i.e. transition and GDP-, GTP-bound states), along with mammalian macromolecules that have been reported to directly interact with Gα. Reported interactions are classified by nucleotide dependence and by functional outcome (GDI, GEF, etc.). The single-headed arrow represents an interaction leading to signaling, the cross represents an interaction that does not lead to signaling, a blunt arrow represents interactions leading to signal termination, while the double-headed arrow represents a neutral physical interaction. While the list of reported interactions is intended to be extensive, it is not intended to be exhaustive, particularly in regard to the GPCRs.

References for the interactions included in the graphic are given below:

Interactions with GPCRs:

Interactions between GPCRs and Gα family members are discussed in the following references: (Juneja and Casey 2009), (Hubbard and Hepler 2006).

Nucleotide-Free State Interactions:

GIV (Gα-interacting vesicle-associated protein) was shown to directly interact with the GDP-bound state of Gαi and to also act as a nonreceptor GEF for the subunit (Garcia-Marcos, Ghosh, and Farquhar 2009; Ghosh et al. 2008; Le-Niculescu et al. 2005). Ric-8A interacted

preferentially with the GDP-bound Gα subunits and catalyzed exchange of GDP for GTP *in vitro* by stabilizing the nucleotide-free conformation (Tall, Krumins, and Gilman 2003; Tall and Gilman 2004; Tall and Gilman 2005; Thomas et al. 2008), while Ric-8B was shown to interact with Gα subunits *in vivo* in a nucleotide-dependent manner (Kerr et al. 2008), and both Ric-8A and Ric-8B were reported to amplify GPCR signaling *in vivo* (Von Dannecker, Mercadante, and Malnic 2005; Fenech et al. 2009).

GDP-Bound State Interactions:

The four families of mammalian proteins that contain GoLoco motifs, which possess a GDI functionality, are reviewed by Siderovski and Willard (Siderovski and Willard 2005).

Transition State Interactions:

The RGS family containing proteins that GAP Gα subunits preferentially interact with the transition state and are reviewed by Siderovski et al. (Siderovski and Willard 2005), Willars (Willars 2006), and Hurst and Hooks (Hurst and Hooks 2009). References for RhoGEF interactions are given in Results and in the Supplemental Discussion in Supplemental File 5. AKAP110 interaction with $G\alpha_{13}$ is reviewed in Niu et al (Niu et al. 2001).

GTP-Bound State Interactions:

Proteins that directly interact with G(12) subunits are reviewed by Kelly et al (Kelly, Casey, and Meigs 2007). The G(q) family subunits are reviewed by Hubbard and Hepler (Hubbard and Hepler 2006).

Nucleotide Independent Interactions:

Direct interactions between $G\alpha_{13}$ and integrins have recently been reported (Gong et al. 2010).

Depalmitoylation has also been reported: (Duncan and Gilman 1998) and (Tsutsumi et al. 2009).

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