PMC534114

**Gab1 binds PI-3 kinase.**

Gab1 is a docking protein that recruits phosphatidylinositol-3 kinase (PI-3 kinase) and other effector proteins in response to the activation of many receptor tyrosine kinases (RTKs).

Gab1 contains a number of tyrosine residues that could serve as potential binding sites for the SH2 domain containing proteins Grb2, PI-3 kinase, and the protein tyrosine phosphatase Shp2.

**Gab1 phosphorylated on tyrosine binds PI-3 kinase.**

EGF stimulation leads to tyrosine phosphorylation of Gab1 enabling recruitment and activation of PI-3 kinase by the three canonical pYXXM motifs on Gab1.

**Gab1 binds Shp2.**

- Gab1 contains a number of tyrosine residues that could serve as potential binding sites for the SH2 domain containing proteins Grb2, PI-3 kinase, and the protein tyrosine phosphatase Shp2.

- Complex formation between Gab1 and the protein tyrosine phosphatase Shp2 negatively regulates Gab1 mediated PI-3 kinase and Akt activation following EGF-receptor stimulation.

- Gab1 thus acts as a docking protein facilitating the recruitment of a multi-protein signaling complex including the EGFR, p85 and Shp2 in response to EGF treatment.

**Gab1 binds p85.**

* Gab1 is essential for EGF stimulation of PI-3 kinase and Akt in these cells and that these responses are mediated by complex formation between p85, the regulatory subunit of PI-3 kinase, and three canonical tyrosine phosphatase sites on Gab1.
* Gab1 thus acts as a docking protein facilitating the recruitment of a multi-protein signaling complex including the EGFR, p85 and Shp2 in response to EGF treatment.
* The binding of p85 is absolutely required for Gab1-mediated activation of PI-3 kinase and Akt following EGF treatment.
* The PI-3 kinase holoenzyme consists of a regulatory subunit (p85) and a catalytic p110 subunit. The regulatory subunit contains two SH2 domains that bind specifically to pYXXM motifs in a variety of cellular proteins, including receptor tyro- sine kinases such as the PDGF (platelet-derived growth factor) receptor, and c-kit and docking proteins such as IRS (insulin receptor substrate) 1, IRS2 and Gab1. Shp2 may specifically dephosphorylate the tyrosine phosphorylation sites on Gab1 that bind to p85.

**Shp2 dephosphorylates Gab1.**

- Shp2 may act to dephosphorylate Gab1 at one or both of the p85 binding sites.

**Shp2 dephosphorylates Gab1 on tyrosine.**

* Shp2 may specifically dephosphorylate the tyrosine phosphorylation sites on Gab1 that bind to p85.

PMC3178447

**BRAF binds BRAF.**

**CRAF binds CRAF.**

**BRAF binds CRAF.**

- BRAF and CRAF kinases form homo- and heterodimers on RAS activation.

**RAF binds RAF.**

- RAF isoforms form dimers in cells.

**RAF-bound RAF activates RAF.**

- Transactivation of wild-type RAF requires dimerization and depends on RAS activity.

**CRAF activates BRAF.**

- Transactivation from CRAF to BRAF can occur as well.

PMC4345513

**MEK phosphorylates ERK1 and ERK2 on threonine and tyrosine.**

- MEK is a dual-specificity protein kinase that phosphorylates Erk1/2 (p42/ p44 MAP kinase) on both threonine and tyrosine in a con- served Thr-X-Tyr motif

**Active ERK phosphorylates RSK.**

- Activated Erk phosphorylates several cytosolic signaling molecules, including p90 ribosomal S6 kinase (RSK).

**MKP dephosphorylates MAPK at threonine and tyrosine.**

- MAPK phosphatase (MKP) belongs to the dual-specificity phosphatase (DUSP) family that functions as a negative regulator of MAPK activity by dephosphorylating both the phospho- threonine and phosphotyrosine residues in the Thr-X-Tyr motif of MAPKs.

**Akt phosphorylates RAF on Ser-259.**

Akt can inhibit Raf through phosphorylation on Ser-259.

PMC1234335

**Estradiol phosphorylates SRC-3.**

- Estradiol (E2) induces SRC-3 phosphorylation at all six sites, while tumor necrosis factor alpha (TNF-alpha) induces phosphorylation of all but the serine-860 (S860) site.

**Estradiol phosphorylates SRC-3 that is bound to ER-alpha.**

**-** E2-induced SRC-3 phosphorylation requires a direct interaction between SRC-3 and ER-alpha.

**Estradiol phosphorylates SRC-3.**

**-** In cells that express ER-alpha, E2 induces SRC-3 phosphorylation at all six phosphorylation sites identified.

**Estradiol phosphorylates SRC-3.**

**-** Estradiol-induced SRC-3 phosphorylation requires the presence of ER.

**Estradiol phosphorylates SRC-3 at Thr24, S505, S543, S857 and S867.**

- E2 induced SRC-3 phosphorylation at all six sites (T24, S505, S543, S857, S860, and S867)

**Estradiol phosphorylates SRC-3.**

- It has been shown that E2 and the synthetic androgen R1881 can induce SRC-3 phosphorylation in the presence of ER and androgen receptor.