Supplementary material: The ERBB pathway that regulates the G1/S transition

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October 23, 2012

Edge (1): ERBB weakly activates PI3K kinase which phosphorylates AKT [3]

Edge (2): ERBB phosphorylates ERK by activating RAF/MEK/ERK pathway [15].

Edge (3): There are several possible mechanisms by which ERK pathway may regulate the activity of ERBB receptors. One such mechanism involves the Eearly Growth response genes such as EGR-1. In response to EGFR, ERK pathway activates the transcription of EGR-1. EGR1 can directly bind to the promoter of TGF-α [25] which activates ERBB, thus forming a positive feedback loop. These feedback loops are known as autocrine loops and implicated for drug resistance in many different cancer cells [24]. In another mechanism, EGR-1 binds directly to the promoter of the EGFR gene and inhibits its transcription, thus forming a negative feedback loop[1] (not shown in the paper).

Edge (4): AKT, a downstream kinase of ERBB, inhibits ADAM17 which activates TGF-α[12].

Edge (5): Regulation of Retinoblastoma protein by ERBB in an AKT and ERK independent manner, possibly via JNK pathway [10].

Edge (6): p27 can be regulated by ERBB in an ERK or AKT independent manner, possibly via Src [7].

Edge (7): CDK2/Cyclin-A complex phosphorylates and activates CDC25 [20] which is a phosphatase of ERK [28].

Edge (8): ERK phosphorylates and inhibits the activity of IRS [11] which is a key adapter protein for ERBB mediated AKT activation [3] .

Edge (9): AKT is found to stabilize Cyclin D1, since inhibiting PI3K decreases the half-life of Cyclin D1 [8].

Edge (10): ERK pathway transcriptionally activates Cyclin-D1 [29]

Edge (11): ERK pathway regulates C-MYC expression [17] and C-MYC functionally antagonizes the action of p27 [18].

Edge (12): ERK pathway regulates the activity of CDK2 in many different ways. ERK positively regulates the expression of Cyclin D and E which binds with CDK2 and induces its kinase activity [16]. ERK also induces the nuclear localization of CDK2 and phosphorylates it at the activating site Thr160 [16].

Edge (13): PI3K pathway regulates the protein stability of C-MYC [26] and C-MYC functionally antagonizes the action of p27 [18].

Edge (14): PI3K pathway regulates the protein stability of C-MYC [26] and C-MYC inhibits p21 [22].

Edge (15): p21 binds to the promoter region of CDC25A and inhibits its transcription [27]. CDC25A acts as a phosphatase and dephosphorylates ERK [28].

Edge (16): ERK pathway regulates C-MYC expression [17] and C-MYC inhibits p21 [22].

Edge (17): p21 activates PDK1 which mediates the expression of Cyclin D1 [2].

Edge (18): CDK4 regulates the nuclear translocation and kinase activity of CDK2 [30].

Edge (19): p27 inhibits the activity of CDK2 [5].

Edge (20): p27 inhibits the activity of CDK4 [5].

Edge (21): p21 inhibits the activity of CDK4 [14].

Edge (22): p21 inhibits the activity of CDK2 [14].

Edge (23): The growth factor activation of Cyclin D/CDK4 complex sequesters unbound p21 and inhibits its inhibitory effect of Cyclin E/CDK2 complex.

Edge (24): The growth factor activation of Cyclin D/CDK4 complex sequesters unbound p27 and inhibits its inhibitory effect of Cyclin E/CDK2 complex.

Edge (25): Cyclin D1 binds to CDK4 to activate its kinase activity [21].

Edge (26): Cyclin E/CDK2 complex phosphorylates p27 and promotes its degradation.

Edge (27): CDK2/Cyclin-E complex phosphorylates pRB1 [13].

Edge (28): CDK4/Cyclin-D complex phosphorylates pRB1 [13].

Edge (29): pRB phosphorylation activates E2F transcription factors which activate ARF. ARF regulates p53 protein [23]. p53 inhibits the translation of the CDK4 protein [9] forming a feedback loop.

Edge (30): pRB phosphorylation activates E2F transcription factors which directly binds to the promoters of CDK2 [4].

Edge (31): Cyclin D1 binds to CDK6 to form a heterodimer. The heterodimer complex phosphorylates pRB.

Edge (32): pRB phosphorylation activates E2F transcription factors which binds to AKT1 promoter and activates its transcription [6].

Edge (33): CDK2 regulates apoptin which modulates the activity of AKT by regulating its subcellular localization.

Edge (34): pRB phosphorylation activates E2F transcription factors, E2F transcriptionally activates PAC1 which dephosphorylates ERK [31] completing a negative feedback loop.

Edge (35): ERK phosphorylates and activates MDM2 [19] which binds with pRB and modulates its activity [23].

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