Review

Molecular mechanisms mediating the G protein-coupled receptor regulation of cell cycle progression
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Abstract

G protein-coupled receptors are key regulators of cellular communication, mediating the efficient coordination of a cell’s responses to extracellular stimuli. When stimulated, these receptors modulate the activity of a wide range of intracellular signalling pathways that facilitate the ordered development, growth and reproduction of the organism. There is now a growing body of evidence examining the mechanisms by which G protein-coupled receptors are able to regulate the expression, activity, localization and stability of cell cycle regulatory proteins that either promote or inhibit the initiation of DNA synthesis. In this review, we will detail the intracellular pathways that mediate the G protein-coupled receptor regulation of cellular proliferation, specifically the progression from the G1 phase to the S phase of the cell cycle.

Background

An efficient system of cellular communication has evolved to ensure the ordered development, growth, maintenance and reproduction of multicellular organisms. This allows cells to respond to environmental stimuli as well as to each other by integrating the numerous extracellular and intercellular cues that they are constantly receiving into a coordinated response. Central to cellular signalling are the G protein-coupled receptors (GPCRs). The human genome is estimated to encode 800 to 1000 of these seven-transmembrane spanning proteins [1,2]. Activated GPCRs promote a wide spectrum of intracellular biochemical changes resulting in the modulation of many aspects of physiology, growth, development and disease control [3]. GPCRs have long been known to mediate mitogenic signals leading to cellular proliferation [4] and the overexpression or mutation of many GPCR subtypes in numerous cell types is thought to contribute to deregulated growth and tumour development [5,6].

Eukaryotic cell cycle progression is driven by a coordinated series of phosphorylation events, chiefly mediated by the cyclin-dependent kinase (CDK) family of serine/threonine kinases. The activity of the CDKs is, in turn, regulated by their phosphorylation status as well as by their interaction with numerous activating and inhibitory binding proteins. Active CDK complexes drive the cell cycle through its phases by phosphorylating downstream proteins [7]. During the G1 phase of the cell cycle, these CDK-driven events are responsive to extracellular cues. It is during this period of the cell cycle that GPCR-induced signal transduction pathways are able to affect, either negatively or positively, cell cycle progression. In this review we will examine the ability of GPCRs to modulate the activity of intracellular pathways that connect activation at the cell membrane to cellular proliferation.
**Heterotrimeric G proteins**

GPCRs predominantly, although not exclusively [8], exert their effects by activating heterotrimeric G proteins. This promotes the release of free Ga and Gβγ subunits, which then initiate intracellular signal transduction. GPCRs preferentially couple to heterotrimeric G proteins that are grouped into four classes, known as Gaαq/11, Gaαi/o, Gaαs and Gaα12/13 [9]. Members of all four classes of Ga subunit have been shown to be involved in the regulation of cell growth and proliferation by virtue of the fact that constitutively active Ga mutants have been found in numerous tumours. The gsp oncogene (for Ga protein) is a mutationally active form of Gaα detected in pituitary and thyroid tumours that promotes cell growth by constitutively activating adenyl cyclase (AC). The gip2 oncogene (for Ga protein) promotes tumour growth by activating mitogen-activated protein kinase (MAPK) pathways [10], while mutationally activated forms of Gaαs, Gaαq, Gaα12 and Gaα13 are able to generate transformed phenotypes [10,11].

Numerous GPCRs utilize heterotrimeric G proteins to modulate cellular proliferation. Direct evidence of the involvement of Gaαi/o proteins has been obtained by the use of pertussis toxin (PTX) to block Gaαi/o-mediated signalling. For example, melatonin acting on Gaαi/o-coupled MT1 receptors expressed in MCF-7 breast cancer cells suppresses estrogen and glucocorticoid-induced cell proliferation [12], possibly by inhibiting the steroid receptor-induced transcription of the cyclin D1 gene [13,14]. These effects of melatonin are entirely blocked by PTX. The use of PTX has also indicated that Gaαi/o proteins mediate the promotion of DNA synthesis by α1-adrenergic receptors in osteoblasts [15], κ-opioid receptors in C6 glioma cells [16] and lysophosphatidic acid (LPA) receptors in human fibroblasts [17]. Further examples of GPCR utilization of Gaαi/o proteins in proliferative responses can be found in Table 1.

The involvement of Gaαs proteins in a few GPCR-initiated responses has been determined using cholera toxin (CTX), which constitutively activates Gaαs subunits, preventing further activation by GPCRs. Glucagon-like peptide 2 (GLP-2) acts as a potent mitogen at Caco-2 intestinal epithelial cells but pretreatment of cells with CTX significantly reduces GLP-2-induced DNA synthesis [18]. Likewise, CTX blocks the LPA-induced proliferation of retinal pigment epithelial cells [19], although the relative contribution of LPA receptor activation of Gaαi/o and Gaαs proteins in these responses was not determined. Other Gaαs-coupled GPCRs also play significant roles in promoting or inhibiting cell cycle progression, as witnessed by their effects on downstream effectors (see Table 1 and below).

While there is much compelling evidence that proves the involvement of Gaαq/11 and Gaα12/13-activated signalling pathways in cell cycle control (discussed in more detail below), direct experimental evidence of the GPCR activation of these G proteins for the purposes of cell cycle control is generally absent. A notable exception, however, is a study of NIH3T3 fibroblasts transfected with Gaα12. In the presence of LPA, these cells synthesize DNA and proliferate much more rapidly than untransfected cells, indicating that the LPA effects are mediated by the LPA receptor coupled to Gaα12 [20].

**cAMP/PKA/CREB**

Cyclic AMP (cAMP) is generated from ATP by the AC family of enzymes. ACs are activated by Gaαq subunits while most isoforms are inhibited by Gaαi/o subunits. Gβγ dimers can either negatively or positively regulate AC isoforms. cAMP activates protein kinase A (PKA), which not only phosphorylates transcription factors, including the cAMP response element binding protein (CREB) and AP1 family members, but also modulates the activity of other signalling pathways (Fig. 1 and [21]).

Parathyroid hormone (PTH) receptor activation in UMR-106 osteoblast cells inhibits the progression of cells into S phase. This blockage is accompanied by increases in p27Kip1, an inhibitor of the cyclin-CDK complexes necessary for the G1 to S phase transition [7]. As PTH is a Gaαs-coupled receptor, a cell permeable cAMP analogue mimicked the effects of PTH while a PKA inhibitor abolished the increases in p27Kip1 levels [22]. In complete contrast, activation of the thyroid stimulating hormone (TSH) receptor, also Gaαs-coupled, induced G1 to S phase progression in rat thyroid cells. The TSH-induced progression and increased DNA synthesis was associated with increases in the levels of c-Fos [23], a binding site for which is found in the promoter region of cyclin D1 [14], as well as increases in the levels of two G1 cyclins, D1 and E [24]. These effects were mimicked by a cAMP analogue [24] and cells containing a dominant negative mutant of CREB, which also activates the cyclin D1 promoter, had reduced levels of TSH-induced DNA synthesis and an increased cell cycle length [25]. Similarly, estrogen and 17β-estradiol (E2) are thought to act, in part, as ligands for the orphan GPCR GPR30 [26]. The E2-induced proliferation of keratinocytes is accompanied by increases in the levels of cyclin D2, a key mediator of G1 to S phase progression in skin cells [27], and increases in the activity of cyclin D2-CDK4 or 6 complexes [28]. E2 increased the amount of active CREB, a transcriptional activator of the cyclin D2 gene, and this, as well as the increased levels of cyclin D2 and proliferation, were reversed by a PKA inhibitor [28].

Due to the differential expression patterns and levels of AC isoforms, the multiplicity of phosphodiesterases that can degrade cAMP and the regulation of ACs by Ca2+/calmodulin and a variety of kinases [21], it is perhaps not
Table 1: GPCR-mediated activation of signalling pathways leading to cell cycle modulation

| GPCR                  | Intracellular Pathway                          | Cell Cycle Effect                  | References |
|-----------------------|------------------------------------------------|------------------------------------|------------|
|                       |                                                |                                    |            |
| **G<sub>i</sub>-coupled** |                                                |                                    |            |
| α<sub>1</sub>-adrenergic | ↑Src/C3G/Rap-1/B-Raf/ERK                       | ↑DNA synthesis                      | [15]       |
| Adenosine A<sub>3</sub>  | ↑PI3K/Akt/ERK                                 | ↑Proliferation                      | [77]       |
| CXCR1/2               | ↑MMP/EGFR/ERK                                 | ↑Proliferation                      | [40]       |
| CXCR3                 | ↑ERK, ↑p38                                    | ↑DNA synthesis                      | [99]       |
| CXCR4                 | ↑Pyk2/PI3K/ERK                                 | ↑DNA synthesis                      | [71]       |
| Dopamine D<sub>2</sub> | ↑PKC/NF-κB                                    | ↑p21<sup>Cip1</sup>, ↑p27<sup>Kip1</sup> | [60]       |
|                       | ↑Src/C3G/Rap-1/B-Raf/ERK                       | ↑Proliferation                      | [77]       |
| Dopamine D<sub>4</sub> | ↑Src/SHC/Ras/ERK                              | ↑DNA synthesis                      | [78]       |
| Sphingosine 1-phosphate EDG-1 | ↑p70<sub>erk</sub>              | ↑Cyclin D1                          | [96]       |
|                       | ↑PDGFβ/ERK                                    | ↑Proliferation                      | [100]      |
| κ-opioid              | ↑PLC/PKC/Ras/ERK                              | ↑DNA synthesis                      | [16]       |
| Lyosphosphaticid acid LPA |                                                | ↑DNA synthesis                      | [17]       |
| Melatonin MT<sub>1</sub> | ↓ERα/glucocorticoid receptor                  | ↓Cyclin D1                          | [12, 13]  |
| Serotonin SHT<sub>1E</sub> | ↑Src/C3G/Rap-1/B-Raf/ERK                       | ↑Proliferation                      | [77]       |
| Somatostatin SST<sub>14/5</sub> | ↑ERK                                 | ↑p21<sup>Cip1</sup>, ↑p27<sup>Kip1</sup> | [50]       |
| Somatostatin SST<sub>2</sub> | ↑PI3K/Ras/Rap-1/B-Raf/ERK                     | ↑p27<sup>Kip1</sup>                | [90]       |
| Somatostatin SST<sub>2a</sub> | ↑p38                                     | ↑p21<sup>Cip1</sup>                | [91]       |
| Somatostatin SST<sub>2b</sub> | ↑PI3K/p70<sub>erk</sub>/Akt                   | ↑Proliferation                      | [91]       |
| **G<sub>s</sub>-coupled** |                                                |                                    |            |
| Dopamine D<sub>1</sub> | ↑PLC/β/↓Raf-1                                 | ↓Cyclin D1/↑p27<sup>Kip1</sup>     | [101]      |
| Glucagon-like peptide GLP-1 | EGFR/PI3K                              | ↑Proliferation                      | [42]       |
| Glucagon-like peptide GLP-2 |                                                | ↑DNA synthesis                      | [18]       |
| GPR30                 | ↑PKA/CREB                                     | ↑Cyclin D2/CDK4-6 complex formation | [27, 28]  |
| Lyosphosphaticid acid LPA |                                                | ↑Proliferation                      | [19]       |
| Melanocortin MC<sub>5</sub> | ↑JAK/STAT                                   | ↑Proliferation                      | [82]       |
| Parathyroid PTH       | ↑cAMP/PKA                                     | ↑p27<sup>Kip1</sup>                | [7, 22]    |
|                       | ↑cAMP/Epac/Rap-1/B-Raf/ERK                    | ↑Proliferation                      | [51]       |
|                       | ↑cAMP/↑PKA/↓Raf-1                             | ↓Proliferation                      | [51]       |
|                       | ↑MKP-1/↓ERK                                   | ↓Cyclin D1, ↑p21<sup>Cip1</sup>    | [52]       |
| Thyroid stimulating hormone TSH | ↑cAMP/CREB/c-Fos           | ↑DNA synthesis, ↑Cyclins D1/E       | [14, 23-25]|
|                       | ↑PKA/Ras/PI3K                                 | ↑DNA synthesis                      | [102]      |
| **G<sub>q</sub>-coupled** |                                                |                                    |            |
| α<sub>1B</sub>-adrenergic | ↑PKC/Raf-1/ERK                               | ↑Proliferation                      | [34]       |
|                       | ↑JNK, ↑p38                                    | ↓Proliferation                      | [55]       |
|                       | ↑Src/Dbs/cdc42/MKK4/JNk                        | ↓Proliferation                      | [76]       |
| Angiotensin II        | ↑MMP/EGFR/ERK                                 | ↑Cyclin D1                          | [39]       |
A selection of examples is presented that demonstrate the involvement of GPCR-mediated intracellular signalling pathways in the regulation of cell cycle progression. ↑, indicates an increase in protein levels or activity; ↓, indicates a decrease in protein levels or activity.

| GPCR-mediated activation of signalling pathways leading to cell cycle modulation (Continued) |
|---------------------------------------------------------------|
| ↑Ras/ERK/c-Fos/c-Jun  | ↑Cyclin D1, ↑pRB phosphorylation  | [48] |
| ↑p125FAK/Rac1/JNK  | ↑p125FAK/Rac1/JNK  | ↑Proliferation  | [67] |
| Bombesin  | ↑MMP/EGFR/PI3K  | ↑Cyclins D1/E  | [41] |
|   | ↑PKD  | ↑Proliferation  | [58] |
| Bradykinin  | ↑MMP/EGFR/PI3K  | ↑Cyclins D1/E  | [41] |
| Endothelin  | ↑MMP/EGFR/ERK  | ↑DNA synthesis  | [39] |
|   | ↑PLC/Cal2+/Src/ERK  | ↑Proliferation  | [74] |
|   | ↑Src/Rho/p125FAK/paxillin  | ↑DNA synthesis  | [70] |
|   | ↑Pyk2/ERK  | ↑DNA synthesis  | [70] |
| Gastrin-activated CCK2  | ↑Rho/integrin/p125FAK/paxillin  | ↑Proliferation  | [68,69] |
|   | ↑PKC/Src/p38  | ↑Proliferation  | [75] |
|   | ↑JAK/STAT  | ↑Proliferation  | [80] |
| Lysophosphatidic acid LPA  | ↑MMP/EGFR/ERK  | ↑cyclin D1  | [39] |
| Muscarinic M1  | ↑PKC/Raf-1/ERK  | ↑Proliferation  | [34] |
| Muscarinic M2  | ↑JNK/c-Jun/SP-1  | DNA synthesis, ↑p21Cip1/CDK2, ↓pRb phosphorylation  | [56] |
| Muscarinic M3  | ↑Ras/Rac/JAK/STAT  | ↑Proliferation  | [81] |
| Muscarinic M5  | ↑Src/ERK/CREB  | DNA synthesis  | [103] |
| Platelet-Activating Factor receptor  | ↑MMP/EGFR/ERK  | ↑Proliferation  | [104] |
| Purinergic P2Y2/4  | ↑PKC/Raf/MAPK  | DNA synthesis  | [49] |
| Substance P (NK-1)  | ↑Src/PKCδ/ERK  | ↑Proliferation  | [72] |
| Thrombin  | ↑MMP/EGFR/ERK  | DNA synthesis  | [39] |
|   | ↑RhoA/PI3K/Akt  | p27Kip1, ↑Cyclin D1/CDK4  | [92-94] |
|   | ↑ERK  | CDK2 nuclear translocation  | [95] |
|   | ↑PI3K/Akt  | Proliferation  | [58] |
| Vasopressin V1a  | ↑PKD  | Proliferation  | [58] |
|   | ↑Ca2+/PI3K/PKC/ERK  | G1-S phase  | [105] |
|   | ↑EGFR/Pyk2/Src/ERK/PI3K  | Proliferation  | [106] |
| G<sub>12/13</sub>-coupled  | | |
| Lysophosphatidic acid LPA  | ↑DNA synthesis, ↑Proliferation  | [20] |
|   | ↑EGFR/Rho/ROCK  | Cyclins A/D1, ↑p21Cip1, ↓p27Kip1  | [43,45] |
|   | ↑JNK  | Cyclin A  | [20,54] |

A selection of examples is presented that demonstrate the involvement of GPCR-mediated intracellular signalling pathways in the regulation of cell cycle progression. ↑, indicates an increase in protein levels or activity; ↓, indicates a decrease in protein levels or activity.
It is not yet clear whether G\textsubscript{i/o}-coupled GPCR-induced reductions in basal cAMP levels can independently affect cell cycle progression but it is likely that intracellular cAMP levels are the product of competing signals from G\textsubscript{s} and G\textsubscript{i/o} proteins. There are examples of G\textsubscript{i/o}-coupled receptors modulating cell cycle progression, e.g. the melatonin MT\textsubscript{1} receptor-mediated inhibition of proliferation in rat uterine cells [31], however these effects are likely to be mediated by a variety of other intracellular pathways (see following sections) rather than by the inhibition of AC activity.

**MAPK pathways**

Mammalian cells express three major classes of MAPKs, the extracellular signal-regulated kinases (ERK), \textit{c-Jun N-terminal kinase/stress-activated protein kinases (JNK/}

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**Figure 1**

Modulation of intracellular cAMP levels by GPCR-coupled mechanisms affects cell cycle progression. Agonist activation of G\textsubscript{s}-coupled receptors promotes increased AC activity and cAMP accumulation. Subsequent PKA activation leads to the activation of the transcription factor CREB and the regulation of the expression of cyclins and the CDK inhibitor p27\textsuperscript{Kip1}. The resulting effect on cell cycle progression is dependent on a number of factors, including the concentration of cAMP generated. PKA can also regulate, positively or negatively, other mitogenic pathways, particularly those leading to the activation of MAPKs, (see text for further details). Activation of the AC/cAMP/PKA axis can be antagonized by the activation of GPCRs coupled to G\textsubscript{i/o}-family proteins. However, the definitive involvement of these MAPK and G\textsubscript{i/o}-coupled pathways in regulating proliferation has not been established (indicated by dashed lines).

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SAPK) and p38 kinases, the activation of which results in the stimulation of transcription factors and the regulation of the expression of cell cycle proteins [32,33]. GPCRs activate MAPKs via several distinct mechanisms, i.e. by using β-arrestin/endocytotic pathways, transactivating RTKs or by second messenger activation. The β-arrestin pathway generally results in the retention of MAPKs in the cytoplasm and transient MAPK activity, limiting their role in the activation of nuclear substrates and proliferation (discussed in [34]). However, GPCR activation of β-arrestin dependent pathways does not exclude the possibility of sustained ERK activation [35] or of nuclear translocation of ERK activity and the promotion of proliferation, as demonstrated for the neurokinin NK-1 receptor [36]. In contrast, RTK-mediated and second messenger activation of MAPK pathways generate the sustained MAPK activity that is often thought critical to the GPCR regulation of cell cycle progression [32].

**RTK transactivation**

It is often observed that GPCR-mediated proliferation is the result of the Gα or Gβγ subunit transactivation of RTKs [37,38]. Ligands for the LPA, endothelin-1 and thrombin receptors all promote S phase entry and DNA synthesis in Rat-1 fibroblasts by transactivating the epidermal growth factor receptor (EGFR, an RTK). Such transactivation requires the activation of matrix metalloproteases (MMPs) to release EGF from its membrane bound form, which then stimulates the EGFR and downstream ERK pathways (Fig. 2 and [39]). The same study also demonstrated that LPA and angiotensin II promoted cyclin D1 accumulation in the G1 phase of kidney cancer cells via the same MMP/EGFR/ERK pathway [39], while a similar proliferative pathway is activated by G<sub>12/13</sub>-coupled CXCR1/2 receptors in Caco-2 cells [40]. However, in Swiss 3T3 cells bradykinin and bombesin promote cyclin D1 and E expression in mid to late G1 in an EGFR-dependent but ERK pathway-independent manner [41]. This ERK-independent pathway may involve the RTK activation of phosphatidylinositol 3-kinase (PI3K)/Akt cascades (see below and Figs. 2 and 6), as might the G<sub>c</sub>-coupled GLP-1 receptor promotion of proliferation in β-cells [42].

As for receptors acting via G<sub>12/13</sub> heterotrimeric, LPA receptors stimulate Rho, a member of the Ras superfamily [43], and its effector Rho kinase (ROCK; [44]) utilizing EGFRs. This potentially leads to the stimulation of several signal transduction pathways and the regulation of the levels of cyclins A and D1 as well as the CDK inhibitors p21<sub>Cip1</sub> and p27<sub>Kip1</sub> (Fig. 2 and [45]).

A number of other proliferation-inducing RTKs are also transactivated by GPCRs (reviewed in [46]). It is not yet clear whether activation of these RTKs requires GPCR-induced cleavage of membrane-bound RTK ligands by MMPs or whether this requirement can be bypassed by the GPCR-induced Src family tyrosine kinase activation of RTKs (Fig. 2 and [46]). It is also yet to be determined what role GPCR/EGFR activation of JNK and p38 play in proliferative responses [38]. It has, however, been reported that G<sub>q/11</sub>-coupled GPCR-induced JNK activity can be synergistically increased upon EGF co-stimulation, although this may not necessarily require transactivation [47].

**Second messengers**

GPCRs can also promote the MAPK-dependent transcription of cell cycle proteins without transactivating RTKs [33]. Mitogenic pathways activated by different Gα families have been described in detail. Angiotensin II promotes DNA synthesis and proliferation in many cell types by activating the G<sub>q</sub>-coupled AT<sub>1</sub> receptor. AT<sub>1</sub> receptor activity in human adrenal cells induces Ras-dependent ERK activity, leading to increased levels of c-Fos and c-Jun transcription factors and increases in cyclin D1 promoter activity, cyclin D1 protein levels and pRB hyperphosphorylation (Fig. 3 and [48]). Other mitogenic GPCRs, including M<sub>1</sub> muscarinic and α<sub>1b</sub>-adrenergic and purinergic receptors, induce ERK activity via the Ras-independent PKC phosphorylation and activation of Raf-1 [34,49]. However, there are reports of GPCRs using seemingly similar ERK pathways to promote G1 phase arrest. For example, several of the G<sub>q/11</sub>-coupled somatostatin receptors inhibit cell cycle progression in a variety of cell types by promoting accumulation of the CDK inhibitors p27<sub>Kip1</sub> and p21<sub>Cip1</sub> (Fig. 3 and [50]).

G<sub>c</sub>-coupled GPCRs utilize the Epac/Rap-1/B-Raf pathway to activate MAPK cascades and proliferation. In bone cells expressing B-Raf, PTH promotes cAMP accumulation, which binds directly to the Rap-1 guanine nucleotide exchange factor Epac. Epac in turn activates Rap-1, a Ras family GTPase, which activates the kinase B-Raf, triggering ERK cascades [51]. Alternatively, PKA may directly activate Rap-1 (Fig. 3 and [34]). Interestingly, it now seems clear that in cells lacking B-Raf, GPCR-mediated activation of AC leads to the PKA phosphorylation and inhibition of Raf-1 [34], and/or the antagonism of the Ras activation of Raf-1 by Rap-1 [51]. Therefore, in cells with reduced levels of B-Raf, G<sub>c</sub>-coupled receptor activation leads to the inhibition of the canonical Ras/Raf/ERK mitogenic pathway. This inhibition may be reinforced by the induction of MAPK phosphatase-1 (MKP-1), which dephosphorylates and inactivates ERKs. In bone cells this may account for the PTH-induced inhibition of the ERK-mediated expression of cyclin D1, arresting cells in G1 phase [52]. The ability of G<sub>q/11</sub>-coupled receptors to utilize Rap-1/B-Raf pathways to modulate proliferation is not yet clear but the potential for such a pathway to operate is apparent as dopamine D<sub>2</sub> receptors are able to use G<sub>q</sub> proteins as intermediaries to activate B-Raf [53].
The JNK and p38 kinases do not seem to be as commonly involved in the transduction of GPCR-induced proliferative signals, yet JNKs do mediate the LPA-induced proliferation of NIH3T3 cells transfected with Gα12 [20], possibly via the induction of cyclin A at the G1-S phase transition [54]. In fact, JNKs and p38 kinases seem adept at mediating antiproliferative signals. In HEK293 cells, α1B-adrenergic receptor stimulation inhibited cell proliferation in a JNK- and p38-dependent manner [55]. In Chinese hamster ovary cells, activation of the Gq-coupled muscarinic M3 receptors caused a G1 phase arrest and inhibited DNA synthesis by increasing the expression levels p21Cip1 and p27Kip1 delays S phase entry. Dashed lines also identify the probable involvement of multiple, unidentified intermediates in the transcriptional regulation of cell cycle proteins.

**Figure 2**

**GPCR transactivation of EGFR leads to the activation of multiple mitogenic pathways.** GPCR/G protein activity of many families of G protein promotes the activity of MMPs via PLCβ-dependent, or possibly Src-dependent (indicated by dashed lines – see text for further details), mechanisms. MMP activity releases EGF in its soluble form. The resulting EGFR activity promotes the formation of a signalling complex and the activation of PI3K, MAPK and ROCK kinases in a GPCR and cell type specific manner. The increased expression of cyclins promotes progression into S phase, while the upregulation of CDK inhibitors p21Cip1 and p27Kip1 delays S phase entry. Dashed lines also identify the probable involvement of multiple, unidentified intermediates in the transcriptional regulation of cell cycle proteins.

As well as its documented role in activating Raf-1 (see above), PKC also acts as a key mediator of a number of other GPCR-induced proliferative pathways. PKC isoforms, as well as DAG, are able to activate the protein kinase D (PKD) family of serine/threonine kinases [57]. Indeed, the proliferation of Swiss 3T3 cells in response to the activation of Gq-coupled bombesin or vasopressin receptors is greatly potentiated by the overexpression of PKD [58]. The pathways connecting GPCR activation to
the control of cell cycle progression have not yet been outlined but it is known that PKD can activate ERK pathways and phosphorylate c-Jun (Fig. 4 and [57]).

PKC also activates the NF-κB transcription factors by initiating a series of phosphorylation and degradation events [59]. In mouse embryonic cell lines expressing both dopamine D₁ (Gₛ-coupled) and D₂ (Gᵢ/o-coupled) receptors, the administration of dopamine resulted in a PKC-dependent increase in NF-κB DNA binding activity, along with increases in the levels of p21cip₁ and p27kip₁ and an inhibition of DNA synthesis [60]. However, in an embryonic fibroblast model NF-κB binds to and activates the cyclin D1 promoter region, leading to G1 to S phase progression (Fig. 4 and [61]). Other GPCRs, including the Gₛ-coupled μ-opioid receptor [62], the somatostatin SST₂ receptor acting via Go₁₄ [63] and the adenosine A₁ receptor acting via Go₁₆ [64] also promote NF-κB activation. This activity appears to be mediated by numerous intracellular pathways, including those dependent on PKC, ERK, Src, PI3K, JNK, and PLCβ, although the role of Gᵢ/o-coupled receptor activation of these pathways in NF-κB mediated cell cycle progression is yet to be investigated.

**Src family tyrosine kinases**

Members of this family of kinases are firmly embedded in signal transduction pathways activated by diverse extracellular stimuli [65]. They also play a significant role in the crosstalk between many pathways. We have already seen that Src kinases play a part in the GPCR-induced transactivation of RTKs (see preceding discussion and Fig. 2). The GPCR/Src/RTK sequence of events is poorly under-
stood, involving either \( \alpha \) or \( \beta \gamma \) subunit stimulation of Src or Src-activating pathways [46]. GPCRs can also transactivate focal adhesion complexes consisting of integrin heterodimers that act as extracellular matrix receptors. The transactivation is Src-dependent and leads to the formation of a signalling platform that includes Src, the focal adhesion kinase p125FAK or its homologue Pyk2, paxillin, as well as the adaptor proteins required to promote Ras family-dependent signalling pathways, particularly those that use MAPKs and PI3Ks as intermediates (reviewed in [66]). Angiotensin II utilizes just such a p125FAK/Rac1/JNK pathway to promote the proliferation of vascular smooth muscle cells [67]. Gastrin and other neuropeptides, through their agonistic effect on \( G_{q} \) and \( G_{12/13} \)-coupled GPCRs, are also thought to promote G1 to S phase transition, in part, via their activation of similar Rho/integrin/p125FAK/paxillin signalling complexes [68,69]. This would include the endothelin receptors, which promote DNA synthesis in primary astrocytes using a combination of an adhesion dependent Src/Rho/p125FAK/paxillin and an apparently Rho/adhesion-independent Pyk2/ERK pathway [70]. The \( G_{q/14} \)-coupled CXCR4 receptor promotes DNA synthesis via a Pyk2/PI3K/ERK pathway (Fig. 5 and [71]).

In the absence of RTK transactivation, Src activity is required for GPCR-induced proliferation of a number of alternative pathways. The \( G_{q} \)-coupled substance P receptor (NK-1) promotes the proliferation of human glioblastoma cells in a Src-dependent manner. Inhibition of Src activity prevents the phosphorylation and activation of PKC\( \delta \) and ERK in these cells [72]. ERKs are known substrates of PKC\( \delta \) [73]. The mitogenic \( G_{q} \)-coupled endothelin receptors activate ERKs via a Src-dependent pathway.

Figure 4
Further PKC-dependent cell cycle regulation. \( G_{aq} \), \( G_{q} \) and \( G_{s/o} \)-family coupled GPCRs can activate PLC\( \beta \) and PKC activity via \( \alpha \) or \( \beta \gamma \) subunits. Activated PKC can phosphorylate and activate PKD, leading to the activity of ERK-dependent proliferative pathways. PKC is also able to initiate a series of events that promotes the transcriptional activity of NF-\( \kappa \)B. NF-\( \kappa \)B activates the promoter regions of cyclin D1 as well as those of \( p21^{Cip1} \) and \( p27^{Kip1} \), causing S phase entry or delay. Dashed indicators identify the probable involvement of multiple, unidentified intermediates.
that requires the Gαq-subunit activation of PLCβ and Ca2+ release [74]. A similar pathway was identified in CHO cells expressing the gastrin-activated CCK2 receptor, where proliferation was mediated by a PKC/Src activation of p38 MAPK [75]. In contrast, the anti-proliferative effects of the α1B-adrenergic receptor in HEK293 cells are Src family kinase dependent. Such activity stimulates a Rho family GEF, Dbs, and cdc42, a Rho family member, activating a MAPK kinase, MKK4, and JNK (Fig. 5 and [76]).

Other studies have shed light on the Gαi/o-coupled GPCR activation of Src-mediated proliferation. Serotonin 5HT1E, dopamine D2, and α2C-adrenergic receptors all promote the proliferation of NIH3T3 cells via the Gαi-subunit activation of Src, which activates C3G, a RapGEF. As was discussed above, RapGEFs, including Epac, activate Rap-1/B-Raf/ERK pathways leading to proliferation (Fig. 5 and [77]). Alternatively, the dopamine D4 receptor promotes DNA synthesis via Src/Src homology 2-containing protein (SHC)/Ras/ERK pathway [78]. The precise mechanism of Gαi activation of Src is still under investigation but both Gαi and Gαs directly bind to and activate Src family kinases [79].

Activation of MAPKs is not the only consequence of the GPCR-induced activation of Src family kinases. An increasing number of GPCRs activate the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways as a means to modulate cell cycle progression. The gastrin-activated CCK2, muscarinic M5, and α1B-adrenergic Gq-coupled receptors, as well as the Gq-coupled...
melanocortin MC₅ receptor induce increases in cell proliferation by activating JAK and STAT family members [80-82]. The definitive involvement of Src in these pathways has not been established and it is possible that a combination of the direct activation by Src kinases and Ras-dependent MAPK pathways is required for full STAT transcriptional activation [83]. Interestingly, the promiscuously coupled Gα₁₄ and Gα₁₆ subunits are similarly able to mediate the activation of Src and JAK/STAT pathways following activation of several GPCRs [84-86], although whether this leads to the modulation of cell cycle progression is not yet known. The ability of Gα₁₀ subunits to promote the Src-mediated activation of STATs is well documented [83]. What is less clear is the role of Gα₁₀-coupled GPCRs in controlling cell cycle progression via these pathways. Intriguingly, in NIH3T3 cells, Gα₁₂ mediates the Src activation of STAT3, and this may promote the expression of cyclin D1 (Fig. 5 and [87]).

### PI3K/Akt pathways

Extracellular signals transduced by both RTKs and GPCRs converge upon the activation of a family of PI3Ks. Activation of these lipid kinases by GPCRs is thought to be dependent on the direct binding of Gβγ subunits and Ras to PI3Ks [88]. PI3K activation initiates a phosphorylation cascade leading to the activation of Akt (also termed protein kinase B) and its downstream kinases phosphoinositide-dependant kinase 1 (PDK1), glycogen synthase
kinase 3 (GSK3), p70 ribosomal protein S6 kinase (p70S6K), mammalian target of rapamycin (mTOR) and others [89]. In addition, we have already seen how GPCRs can activate PI3K pathways via RTK or integrin transactivation [41,42,66]. Following direct or indirect GPCR-induced PI3K activation, cell cycle progression is regulated by the effect of PI3K-activated kinases on the expression and stability of cell cycle proteins, or by the modulation of the activity of other signal transduction pathways. For example, somatostatin SST2 receptors expressed in Chinese hamster ovary cells (CHO) inhibit proliferation by activating a PI3K-dependent Ras-Rap1/B-Raf/ERK pathway, resulting in an increase in the levels of p27Kip1 protein (Fig. 6 and [90]). It has also been shown that sustained activation of p38 by activation of the SST2a receptor subtype leads to upregulation of p21Cip1 and cell cycle inhibition. However, this can be antagonized by activation of SST2b receptor, which activates PI3K, p70S6K, Akt and proliferation (Fig. 6 and [91]). This suggests that the final outcome of a signalling event relies on the balance of several competing mechanisms.

Several studies have shed further light on the effect of the activation of GPCR/PI3K pathways on cell cycle proteins. For example, thrombin receptor activation in vascular smooth muscle cells leads to reduced levels of p27Kip1 and increased cellular proliferation [92], while in embryonic fibroblasts the evidence suggests that thrombin receptor activation of PI3K/Akt pathways promotes cyclin D1 accumulation, cyclin D1-CDK4 activity and cell cycle progression [93,94]. Furthermore, it has been postulated that thrombin receptor activation of ERK activity ultimately leads to enhanced translocation of CDK2 into the nucleus and fibroblast proliferation [95]. Moreover, sphingosine 1-phosphate activation of the EDG-1 receptor activates p70S6K, promoting cyclin D1 expression and proliferation (Fig. 6 and [96]). The reduction in p27Kip1 levels and the upregulation of cyclin D protein are thought to be the primary cell cycle effects of PI3K activation by RTKs [89]. The cyclin D1 protein is stabilized by the Akt-mediated inactivation of GSK3, which normally phosphorylates and promotes the degradation of cyclin D1. Akt also phosphorylates and inactivates forkhead (FH) transcription factors, which bind to and activate the p27Kip1 promoter. PI3K pathways may also reduce the stability of p27Kip1, and Akt phosphorylation of p27Kip1 adversely affects its nuclear localization. Akt-induced phosphorylation of the tumour suppressor TSC2 (also known as tuberin) causes the dissociation of TSC2 and TSC1 (also known as hamartin), relieving their inhibition of mTOR kinase. Increased mTOR activity reduces the stability of p27Kip1 (Fig. 6 and [89]). Some GPCRs have now been shown to couple to this PI3K/tuberin system [97], although the significance for cellular proliferation has not been established.

**Conclusion**

It is a common finding that GPCRs regulate cell cycle progression. The final effect on cellular proliferation is likely to be the result of the combined action of different GPCRs simultaneously activating several different G protein families, each of which affects the activity of multiple intracellular signalling pathways that modulate the expression, activity and stability of key proteins of the cell cycle machinery. Restrictions on GPCR-induced effects may arise from factors such as the expression and accessibility of signalling components as well as the magnitude and duration of the intracellular response. Yet to be studied in depth is the combined effect of GPCR activation along side the mitogenic effects of other classes of signalling molecules. Nevertheless, there is much hope that the targeted modulation of GPCR activity will reveal strategies for the treatment of medical conditions that arise due to deregulated cell growth and proliferation.

**Competing interests**

The author(s) declare that they have no competing interests.

**Authors’ contributions**

YHW conceived of the review and revised it critically for important intellectual content. DCN drafted the manuscript.

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**References**

1. Marchese A, George SR, Kolakowski LF Jr, Lynch KR, O’Dowd BF: Novel GPCRs and their endogenous ligands: expanding the boundaries of physiology and pharmacology. Trends Pharmacol Sci 1999, 20:370-375.
2. Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, Smith HO, Yandell M, Evans CA, Holt RA, et al.: The sequence of the human genome. Science 2001, 291:1304-1351.
3. Pierce KL, Premont RT, Lefkowitz RJ: Seven-transmembrane receptors. Nature Rev Mol Cell Biol 2002, 3:639-650.
4. Moolenaar WH: G-protein-coupled receptors, phosphoinositide hydrolysis, and cell proliferation. Cell Growth Differ 1991, 2:359-64.
5. Li S, Huang S, Peng SB: Overexpression of G protein-coupled receptors in cancer cells: involvement in tumor progression. Int J Oncal 2005, 27:1329-1339.
6. Schoneberg T, Schulz A, Bieberrnan H, Hermsdorff T, Rompler H, Sangkuhl K: Mutant G-protein-coupled receptors as a cause of human diseases. Pharmacol Therapeut 2004, 104:173-206.
7. Malumbres M, Barbadic M: Mammalian cyclin-dependent kinases. Trends Biochem Sci 2005, 30:630-641.
8. Kristiansen K: Molecular mechanisms of ligand binding, signaling, and regulation within the superfamily of G-protein-coupled receptors: molecular modeling and mutagenesis approaches to receptor structure and function. Pharmacol Therapeut 2004, 103:21-80.
9. Simon Ml, Strathmann MP, Gautam N: Diversity of G proteins in signal transduction. Science 1991, 252:802-808.
10. Radhika V, Dhanasekaran N: Transforming G proteins. Oncogene 2001, 20:1607-614.
11. Wong YH, Chan JS, Yung LY, Bourne HR. Mutant α subunit of Gα transforms Swiss 3T3 cells. Oncogene 1995, 10:1927-1933.

12. Kiefer TL, Lin Y, Yuan L, Dong C, Burrow MH. Differential regulation of estrogen receptor α, glucocorticoid receptor and retinoic acid receptor α transcriptional activity by melatonin is mediated via different G proteins. J Pineal Res 2005, 38:231-239.

13. Cini G, Neri B, Pacini A, Cesati V, Sassoli C, Quattrone S, D’Apollito M, Fazio A, Scapagnini G, Provenzani A, Quattrone A. Antiproliferative activity of melatonin by transcriptional inhibition of cyclin D1 expression: a molecular basis for melatonin-induced oncostatic effects. J Pineal Res 2005, 39:12-20.

14. Pastell RG, Albanese C, Reuter AD, Segal JE, Lee RJ, Arnold A. The cyclins and cyclin-dependent kinase inhibitors in hormonal regulation of proliferation and differentiation. Endocrine Rev 1999, 20:501-534.

15. Suzuki A, Palmer G, Bonjou P, Caverzasio J. Catecholamines stimulate bone collagenase and alkaline phosphatase activity of MC3T3-E1 osteoblast-like cells. Bone 1999, 23:197-203.

16. Bohn LM, Belcheva MM, Coscia CJ. Mitogenic signaling via endogenous κ-opioid receptors in C6 glialoma cells: evidence for the involvement of protein kinase C and the mitogen-activated protein kinase signaling cascade. J Neurochem 2000, 74:564-573.

17. van Corven EJ, Groenink A, Jalink K, Eicholtz T, Moelenen WH. Lysophosphatidate-induced cell proliferation: identification and dissection of signaling pathways mediated by G proteins. Cell 1989, 59:45-54.

18. Rocha FG, Shen KM, Jasleen J, Tavakkoli-zadeh A, Zinner MJ, Wang EE, Ashley SW. Glucagon-like peptide-2: divergent signaling pathways. J Surg Res 2004, 121:5-12.

19. Thoresen WB, Khandalavala BN, Mahanan RG, Poljak IA, Liu JL, Chacko DM. Lysophosphatidic acid stimulates proliferation of human retinal pigment epithelial cells. Curr Eye Res 1997, 16:698-702.

20. Radhika V, Hee Ha J, Jayaraman M, Tsim ST, Dhanasekaran N, Tavakkoli-Zadeh A, Zinner MJ, Yuan L, Dong C, Burow ME, Hill SM. Radhika V, Hee Ha J, Jayaraman M, Tsim ST, Dhanasekaran N, Tavakkoli-Zadeh A, Zinner MJ, Yuan L, Dong C, Burow ME, Hill SM. Gravity and light induce oncostatic effects. J Pineal Res 2005, 39:12-20.

21. Kranenburg O, Moolenaar WH. New mechanisms in heptahelial receptor signaling to mitogen activated protein kinase cascades. Oncogene 2001, 20:1532-1539.

22. Lattrell JM. Activation and targeting of mitogen-activated protein kinases by G protein-coupled receptors. Can J Pharmacol 2002, 80:375-382.

23. Gesty-Palmer D, Chen M, Fazio A, Scapagnini G, Provenzani A, Quattrone A. Antiproliferative activity of melatonin by transcriptional inhibition of cyclin D1 expression: a molecular basis for melatonin-induced oncostatic effects. J Pineal Res 2005, 39:12-20.

24. Pastell RG, Albanese C, Reuter AD, Segal JE, Lee RJ, Arnold A. The cyclins and cyclin-dependent kinase inhibitors in hormonal regulation of proliferation and differentiation. Endocrine Rev 1999, 20:501-534.

25. Suzuki A, Palmer G, Bonjou P, Caverzasio J. Catecholamines signal via endogenous κ-opioid receptors in C6 glioma cells: evidence for the involvement of protein kinase C and the mitogen-activated protein kinase signaling cascade. J Neurochem 2000, 74:564-573.

26. Schafer B, Gschwind A, Ullrich A. Multiple G-protein-coupled receptor signals converge on the epidermal growth factor receptor to promote migration and invasion. Oncogene 2004, 23:991-999.

27. Ohtsru H, Dempsey PJ, Eguchi S. ADAMs as mediators of EGF receptor transactivation by G protein-coupled receptors. Am J Physiol – Cell Physiol 2006, 291:C1-10.

28. Schafer B, Marg B, Gschwind A, Ullrich A. Distinct ADMET metalloproteinases regulate G protein-coupled receptor-induced cell proliferation and survival. J Biol Chem 2004, 279:47929-47938.

29. Itoh Y, Joh T, Tanida S, Sasaki M, Katoaka H, Itoh K, Oshima T, Ogawara N, Toyaga S, Wada T, Kubota H, Mori Y, Ohara H, Nomura T, Higashiyama S, Itoh M. IL-8 promotes cell proliferation and migration through metalloproteinase-cleavage proH-B-EGF in human colon carcinoma cells. Cytokine 2005, 29:275-282.

30. Santiskulvong C, Sinnott-Smith J, Rozengurt E. EGFR receptor function is required in late G1 for cell cycle progression induced by bombesin and bradykinin. Am J Physiol – Cell Physiol 2001, 281:C886-899.

31. Buteau J, Foisy S, Joly E, Prentki M. Glucagon-like peptide 1 induces pancreatic β-cell proliferation via transactivation of the epidermal growth factor receptor. Diabetes 2003, 52:124-132.

32. Gohl A, Harhammer R, Schultz G. The G-protein G12, but not G13 mediates signaling from lysophosphatic acid receptor via epidermal growth factor receptor to Rho. J Biol Chem 1998, 273:4653-4659.

33. Cechin SR, Dunkley PR, Rodnight R. AMNI: an extracellular ATP: a growth factor for vascular smooth muscle cells. Gen Pharmacol 1998, 31:1-8.

34. Derfoul G, Bosquet C, Cordelier P, Benali N, Lopez F, Rochaix P, Bousquet C, Cordelier P, Benali N, Lopez F, Rochaix P, Bousquet C. New signaling pathway for parathyroid hormone and cyclic AMP action on extracellular-regulated kinase and cell proliferation in bone cells. Checkpoint of modulation by cyclic AMP. J Biol Chem 2002, 277:22191-22200.

35. Qin L, Li X, Ko JK, Partridge NC. Parathyroid hormone uses multiple mechanisms to arrest the cell cycle progression of osteoblastic cells from G1 to S phase. J Biol Chem 2005, 280:3104-3111.
53. Antonelli V, Bernasconi F, Wong YH, Vallar L: Activation of B-Raf and regulation of the mitogen-activated protein kinase pathway by the Gq alpha chain. Mol Biol Cell 2000, 11:1219-49.
54. Mitsuhi H, Tsuchiya N, Kurokawa K, Etoh JH, Tsuchiya Y: Dependence of activated Gq alpha 11 to S phase cell cycle progression on both Ras/mitogen-activated protein kinase and Ras/Raf/1-Jun N-terminal kinase cascades in NIH3T3 fibroblasts. J Biol Chem 1997, 272:4904-4910.
55. Yamauchi J, Itoh H, Shinoura H, Miyamoto Y, Hirasewa A, Kato Y, Tsujimoto G: Involvement of c-Jun N-terminal kinase and p38 mitogen-activated protein kinase in alpha1B-adrenergic receptor(Gr alpha 11)-induced inhibition of cell proliferation. BiochemBiophys Res Comm 2001, 281:1019-1023.
56. Burdon D, Patel R, Challiss RA, Blank EJ: Growth inhibition by the muscarinic M3 acetylcholine receptor: evidence for p21(Cip1/Waf1) involvement in G1 arrest. Biochem J 2002, 367:549-559.
57. Liu AM: PKD at the crossroads of DAG and PKC signaling. Trends Pharmacol Sci 2006, 27:317-323.
58. Zhukova E, Sennett-Smith J, Rozengurt E: Protein kinase D potentiates DNA synthesis and cell proliferation induced by bombesin, vasopressin, or phorbol esters in Swiss 3T3 cells. J Biol Chem 2001, 276:40298-40305.
59. Spitaler M, Cantrell DA: Protein kinase C and beyond. Nature Immunol 2004, 5:785-790.
60. Lee MY, Heo JS, Han Hj: Dopamine regulates cell cycle regulatory proteins via a cAMP, Ca(2+)/PKC, MAPKs, and NF-kB in cerebellar embryonic stem cells. J Cell Physiol 2006, 208:399-406.
61. Guttridge DC, Albanese C, Reutter JY, Pestell RG, Baldwin AS Jr: NF-kB controls cell growth and differentiation through transcriptional regulation of cyclin D1. Mol Cell Biol 1999, 19:5787-5796.
62. Liu AM, Wong YH: ,alpha- opioid receptor-mediated phosphorylation of IkB kinase in human neuroblastoma SH-SY5Y cells. NeuroSignals 2005, 14:136-142.
63. Liu AM, Wong YH: Activation of nuclear factor-xB by somatostatin type 2 receptor in pancreatic acinar AR42J cells involves Gq alpha 11 and multiple signaling components: a mechanism requiring protein kinase C, calmodulin-dependent kinase II, ERK, and c-Src. J Biol Chem 2005, 280:36417-36425.
64. Liu AM, Wong YH: Gq alpha 11-mediated activation of nuclear factor-xB and the adenosine A1 receptor involves c-Src, protein kinase C, and ERK signaling. J Biol Chem 2004, 279:53196-53204.
65. Parsons SJ, Parsons JT: Src family kinases, key regulators of signal transduction. Oncogene 2004, 23:7906-7909.
66. Luttrell DK, Luttrell LM: Not so strange bedfellows: G-protein-coupled receptors and Src family kinases. Oncogene 2004, 23:7969-7978.
67. Sundberg Lj, Galante LM, Bill HM, Mack CP, Taylor JM: An endogenous inhibitor of focal adhesion kinase blocks Rac1/JNK but not Ras/ERK-dependent signaling in vascular smooth muscle cells. J Biol Chem 2003, 278:29788-29791.
68. Yu HG, Schaffer H, Mergler S, Murer KT, Schrader C, Toker A, Hocker M, Herzig KH, Schmidt WE, Schmitz FA, Vallee BL: Alpha2-adrenergic G protein-coupled receptor activates mitogen-activated protein kinase in human glioblastoma cells: roles for Src and PKC delta. Cancer Chemother Pharmacol 2005, 56:585-93.
69. Czifa G, Tobi IB, Marinics R, Juhaz I, Kovacs I, Acz P, Kovacs L, Blumberg PM, Biro T: Insulin-like growth factor-I-coupled mitogenic signaling in primary cultured human skeletal muscle cells and in C2C12 myoblasts. A central role of protein kinase C alpha. Cell Signal 2006, 18:1461-1472.
70. Chrambach A, Schrenk K, Hockmeyer A, Boning H, Breit A, Picker A, Ludstrom MJ, Muller-Esterl W, Schroeder C: Coupling of endothelin receptors to the ERK/MAPK kinase pathway. Roles of palmitoylation and Gr alpha 11. Eur J Biochem 2001, 286:5449-5459.
71. Dehez S, Daunha L, Kowalski-Chauvel A, Fourmy D, Pradayrol S, Seva C: Gastrin-induced DNA synthesis requires p38-MAPK activation via PKC/Ca(2+) and Src-dependent mechanisms. FEBs Lett 2001, 496:25-30.
72. Yamauchi J, Hirasewa A, Miyamoto Y, Kobuk I, Nishii H, Okamoto M, Itoh H: Role of this big sister in the anti-mitogenic pathway from alpha1B-adrenergic receptor to c-Jun N-terminal kinase. Biochem Biophys Res Comm 2002, 296:85-92.
73. Weissman JT, Ma JN, Essex A, Gao Y, Burstein ES: G-protein-coupled receptor-mediated activation of the GTPase characterisation of a novel Gr alpha 11 regulated pathway. Oncogene 2004, 23:241-249.
74. Zhen X, Zhang J, Johnson GP, Friedman E: Delta2 dopamine receptor differentially regulates Akt/nuclear factor-xB and extracellular signal-regulated kinase signal-regulated cell cycle pathways in D12MN9D cells. Mol Pharmacol 2001, 60:857-864.
75. Ma YC, Huang XY: Novel regulation and function of Src tyrosine kinase. Cell Mol Life Sci 2002, 59:456-462.
76. Ferrand A, Kowalski-Chauvel A, Bertrand C, Escrieu C, Mathieu A, Poisson G, Pradayrol S, Fourmy D, Dufrasne M, Seva C: A novel mechanism for JAK2 activation by a G protein-coupled receptor, the CCK2R: implication of this signaling pathway in pancreatic tumor models. J Biol Chem 2005, 280:10710-10715.
77. Burstein ES, Hesenberg DJ, Gudkina JS, Brann MR, Currier EA, Messier TL: The ras-related GTase rac regulates a proliferative pathway selectively utilized by G-protein coupled receptors. Oncogene 1998, 17:1617-1623.
78. Buggy JJ: Binding of G(alpha) -melanocyte-stimulating hormone to its G-protein-coupled receptor on B-lymphocytes activates the JAK/STAT pathway. J Biol Chem 1999, 274:1211-216.
79. Ram PT, Iyengar R: G protein coupled receptor signaling through the Src and Stat3 pathway: role in proliferation and transformation. Oncogene 2004, 20:1601-1606.
80. Lo RK, Wong YH: Signal transduction and activation of transcription 3 activation by the -opioid receptor via Gr alpha 11 involves multiple intermediates. Mol Pharmacol 2004, 65:1427-1439.
81. Lo RK, Cheung H, Wong YH: Constitutively active Gr alpha 11 stimulates STAT3 via a c-Src/JAK- and ERK-dependent mechanism. J Biol Chem 2004, 279:52154-52165.
82. Wu EH, Lo RK, Wong YH: Regulation of STAT3 activity by Galpha11-coupled receptors. Biochem Biophys Res Comm 2003, 303:920-925.
83. Corre I, Baumann H, Hermouet S: Regulation by Galpha isoforms of v-fms-induced proliferation and transformation via Src kinase and STAT3. Mol Cell Biol 2001, 21:6353-6360.
84. Schwindender WF, Robishaw JD: Heterotrimic G-protein beta, gamma dimers in growth and differentiation. Oncogene 2001, 20:1653-1660.
85. Liang J, Slingerland JM: Multiple roles of the PI3K/PKB (Akt)/ mammalian target of rapamycin signaling in cell cycle progression. Cell Cycle 2003, 2:339-345.
86. Mahmoud S, Noccherini A, Giralt JA, Adamson P, Slosberg AD, Couraud PO: Growth factor activity of endothelin-1 in primary astrocytes mediated by adhesion-dependent and -independent pathways. J Neurosci 1997, 17:6203-6212.
87. Bertotto A, Barbero S, Bonavia R, Piccioli P, Pirani P, Florio T, Schettini G: Stromal cell-derived factor-1 induces astrocyte proliferation through the activation of extracellular signal-regulated kinases 1/2 pathway. J Neurochem 2001, 77:1226-1236.
88. Yamaguchi K, Richardson MD, Bigner DD, Kustner GM: Signal transduction through substance P receptor in human glioblastoma cells: roles for Src and PKCdelta. Cancer Chemother Pharmacol 2005, 56:585-93.
arrestin1-dependent and -independent mechanisms, and only the sustained Akt phosphorylation is essential for G1 phase progression. J Biol Chem 2002, 277:18640-18648.

95. Knecht SM, Bellone C, Baldassare JJ: Cyclin-dependent kinase 2 nucleocytoplasmic translocation is regulated by extracellular regulated kinase. J Biol Chem 2001, 276:22404-22409.

96. Kluk MJ, Hta T: Role of the sphingosine 1-phosphate receptor EDG-1 in vascular smooth muscle cell proliferation and migration. Circulation Res 2001, 89:496-502.

97. Wu EH, Wong YH: Involvement of G1n proteins in nerve growth factor-stimulated phosphorylation and degradation of tuberin in PC-12 cells and cortical neurons. Mol Pharmacol 2005, 67:195-1205.

98. Merighi S, Benini A, Mirandola P, Gessi S, Varani K, Leung E, Maclennan S, Borea PA: A1 adenosine receptor activation inhibits cell proliferation via phosphatidylinositol 3-kinase/Akt-dependent inhibition of the extracellular signal-regulated kinase 1/2 phosphorylation in A375 human melanoma cells. J Biol Chem 2005, 280:19516-19526.

99. Aks oy MO, Yang Y, Ji R, Reddy P, Shahabuddin S, Litvin J, Rogers TJ, Kelsen SG: CXCR3 surface expression in human airway epithelial cells: cell cycle dependence and effect on cell proliferation. Am J Physiol – Lung Cell Mol Physiol 2006, 290:l909-918.

100. Waters C, Pyne S, Pyne NJ: The role of G-protein coupled receptors and associated proteins in receptor tyrosine kinase signal transduction. Seminars Cell Development Biol 2004, 15:309-323.

101. Zhang L, Bai J, Undie AS, Bergson C, Lidow MS: D1 dopamine receptor regulation of the levels of the cell-cycle-controlling proteins, cyclin D, p27 and Raf-1, in cerebral cortical precursor cells is mediated through cAMP-independent pathways. Cerebral Cortex 2005, 15:74-84.

102. Ciullo I, Diez-Roux G, Di Domenico M, Migliaccio A, Avvedimento EV: cAMP signaling selectively influences Ras effectors pathways. Oncogene 2001, 20:1186-1192.

103. Zhao WQ, Alkon DL, Ma W: c-Src protein tyrosine kinase activity is required for muscarinic receptor-mediated DNA synthesis and neurogenesis via ERK1/2 and c-AMP-responsive element-binding protein signaling in neural precursor cells. J Neurosci Res 2003, 72:334-342.

104. Marques SA, Dy LC, Southall MD, Yi Q, Smietana E, Kapur R, Marques M, Thayer JS, Spandau DF: The platelet-activating factor receptor activates the extracellular signal-regulated kinase mitogen-activated protein kinase and induces proliferation of epidermal cells through an epidermal growth factor-receptor-dependent pathway. J Pharmacol Exp Ther 2002, 300:1026-1035.

105. Thibonnier M, Conarty DM, Pleasnicher CL: Mediators of the mitogenic action of human V1 vascular vasopressin receptors. Am J Physiol – Heart Circ Physiol 2000, 279:H2529-2539.

106. Ghosh PM, Mikhailova M, Bedolla R, Kreisberg JJ: Arginine vasopressin stimulates mesangial cell proliferation by activating the epidermal growth factor receptor. Am J Physiol – Renal Physiol 2001, 280:F972-979.