

Dual role of GRK5 in cancer development and progression

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Abstract - GRK5 is a multifunctional protein that is able to move within the cell in response to various stimuli to regulate key intracellular signaling from receptor activation, on plasmamembrane, to gene transcription, in the nucleus. Thus, GRK5 is involved in the development and progression of several pathological conditions including cancer. Several reports underline the involvement of GRK5 in the regulation of tumor growth even if they appear controversial. Indeed, depending on its subcellular localization and on the type of cancer, GRK5 is able to both inhibit cancer progression, through the desensitization of GPCR and non GPCR-receptors (TSH, PGE2R, PDGFR), and induce tumor growth, acting on non-receptor substrates (p53, AUKA and NPM1). All these findings suggest that targeting GRK5 could be an useful anti-cancer strategy, for specific tumor types. In this review, we will discuss the different effects of this kinase in the induction and progression of tumorigenesis, the molecular mechanisms by which GRK5 exerts its effects, and the potential therapeutic strategies to modulate them.

Keywords: GRK5, GPCR, cancer

I. INTRODUCTION

GRKs (G-protein-coupled- receptor kinases) are a family of serine/threonine kinases traditionally known for their ability to recognize and phosphorylate agonist-activated G-protein-coupled receptors (GPCRs), leading to their desensitization [1]. In particular, the agonist-dependent conformational change of the receptor renders the latter available for GRK-mediated-phosphorylation, leading to G-protein-uncoupling, to the increase of GPCR affinity for arrestins and clathrin-dependent

receptor internalization [2]. In this manner, GRKs act as crucial negative regulators of a variety of GPCRs, including adrenergic receptors, muscarinic receptors, dopamine, opioid and chemokine receptors [3-6]. Seven subtypes of GRKs (GRK1–7) have been identified to date, subdivided into three groups depending on sequence homology: rhodopsin kinases or visual GRK subfamily (GRK1 and GRK7), the β -adrenergic receptor kinases subfamily (GRK2/GRK3) and the GRK4 subfamily (GRK4, GRK5 and GRK6) [1, 7, 8]. GRKs share a common basic structural architecture [1], characterized by a well-conserved central catalytic domain (~270 aa), a variable-length carboxyl-terminal domain (~105–230 aa) and an N-terminal domain (~185 aa) which includes a Regulator of G protein Signaling Homology (RH) domain [8, 9]. Several studies demonstrate that the expression and activity of GRKs are impaired in many pathological conditions [10-12]. Although GRKs are highly selective for agonist activated GPCRs, others substrates have been identified in the last decade. Indeed, GRKs are able to phosphorylate non-GPCR receptors, such as PDGF-receptor [13], and non-receptor substrates, such as tubulin, synucleins, the β -subunit of the epithelial Na⁺ channel, insulin receptor substrate 1 (IRS-1), NF-kB inhibitor (I κ B α), and others soluble substrates [14-18]. Moreover, GRKs regulate intracellular signaling also in a phosphorylation-independent manner, through the direct interaction with a variety of proteins involved in cellular signaling and trafficking [19-21]. Thus GRKs are multifunctional proteins able to regulate key cellular processes, from receptor activation to nuclear transcription [22], in different cellular compartments [23-25], due to their ability to move within the cell in response to stimuli [25, 26].

II. G-PROTEIN COUPLED RECEPTOR KINASE

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Among GRKs, GRK5 is one of the most studied since it is involved in several pathologic conditions [27-29]. Indeed, GRK5 is up-regulated in failing human myocardium [29-31], and its over-expression in the heart reduced cardiac β -AR responsiveness [32, 33]. Several reports underline the involvement of GRK5 in the regulation of glucose metabolism [30, 34, 35]. Indeed, it has been shown that, the overexpression of GRK5 enhances the internalization of Glucagon Receptor, a GPCR that mediates hyperglycaemic effects of glucagon in Diabetes [36, 37]. Accordingly, GRK5 gene deletion in mice, leads to impaired glucose tolerance and insulin sensitivity [30]. GRK5 attenuates atherosclerosis through multiple cell type-specific mechanisms including desensitization of Tyrosine Kinase receptors, such as macrophage CSF-1R, and the SMC platelet-derived growth factor receptor- β (PDGFR) [28]. Several reports show that GRK5 is also involved in Parkinson disease, due to its ability to phosphorylate the α -synuclein, modulating dopamine-up-take [38, 39].

GRK5 effects on the regulation of intracellular signaling depend on cell type, stimuli, and kinase localization within the cell. GRK5 binds to cellular membranes through C-terminal polybasic domain and an N-terminal phosphatidylinositol-4,5-bisphosphate (PIP2) binding site [40, 41]. While GRK2 and GRK3 are primarily cytoplasmic and are targeted to plasma membrane by binding G $\beta\gamma$ subunits through their C-terminal pleckstrin homology domain, GRK5 constitutively binds phospholipids and displays preferential membrane localization [19]. However, GRK5 is also able to localize into the nucleus, through means of functional nuclear localization sequence (NLS), that allows the kinase to enter the nucleus and bind DNA *in vitro* [24]. Such nuclear localization is regulated by intracellular calcium levels. Indeed, the activation of M3MR increases intracellular calcium levels and activates the calcium sensor protein, CaM, which in turn binds the N-terminal domain of GRK5 promoting its nuclear export [24].

GRK5 shuttles between the cytosol and the nucleus and regulates the activities of transcription factors at different levels. Indeed, GRK5 phosphorylates histone deacetylase 5 (HDAC5), a repressor of myocyte enhancer factor 2 (MEF2), leading to nuclear export of HDAC5 and activation of MEF2 transcription activity, in cardiac hypertrophy [42]. Moreover, in a model of Parkinson disease, the nuclear accumulation of GRK5 inhibits gene

transcription of apoptosis regulator bcl-2, probably increasing HDAC activity [43].

Moreover, GRK5 regulates the activity of the transcription factor NF κ B [44]. Since it binds the inhibitory protein of NF κ B, I κ B α , by means of the RH domain (GRK5-RH) and stabilize the complex I κ B α /NF κ B in the nucleus, thus inhibiting NF κ B transcriptional activity. The intracardiac injection of an adenovirus encoding the N-terminal domain of GRK5, AdGRK5-NT, reduces left ventricular hypertrophy by inhibiting NF κ B-dependent hypertrophic gene expression [45]. Furthermore, Hullmann et al. showed that GRK5, acting in a kinase independent manner, is a facilitator of NFAT activity [46]. All these findings suggest that GRK5, trafficking within the cell, regulates key cellular processes that are involved in the development and progression of several pathological conditions.

GRK5, in addition to the above described roles in the cytoplasm and recently discovered activities in the nucleus, is now also reported herein to be functionally localized to centrosomes [47]. The localization of this kinase within the centrosome suggests another way by which GRKs can affect cellular processes.

III. ROLE OF GRK5 IN CANCER

It's known that the oncogenic phenotype derives from diverse genetic alterations that cause constitutive activation or a loss of function of proteins, such as the loss of allelic heterozygosity [48, 49]. Importantly, chromosome translocation of the 10q24 region has been specifically observed in several tumors, such as thyroid adenoma and glioma [50], suggesting that alteration of some genes in this region could affect the development of tumors. Since GRK5 maps on chromosome 10, at q24 region [51], it is likely that alteration of GRK5 gene, could be involved in certain thyroid or glia tumors. Several reports underline the involvement of GRK5 in the regulation of tumor growth. However, the effects of GRK5 on cancer cell proliferation are controversial depending on its subcellular localization and on the type of cancer. In this review, we discuss these different effects of GRK5 on tumor progression, and the different molecular mechanisms by which GRK5 exerts these effects. Moreover, we will debate about the potential therapeutic strategies for cancer focused on GRK5 as main target.

A. GRK5 inhibits tumor growth by regulating GPCR signaling

G protein-coupled receptors (GPCRs), the largest family of cell surface proteins involved in signal

transduction, have recently emerged as key regulators of tumor growth and metastasis [52]. Their role in the tumorigenic process depends on the specific tumor type and is due to their direct interaction or cross-talk with others receptors (i.e. EGF receptors) [52-54]. Thus, the pharmacological manipulation of these receptors is becoming an attractive goal for the development of novel strategies to target tumor progression and metastasis. In this context, it is not surprising that GRK5, could be a molecular target of these novel therapeutic strategies. Several studies show that GRK5 may be a negative regulator of cancer cell proliferation, mainly through its ability to desensitize GPCR on plasma membrane. Tsai et al. have shown that in colon cancer cells HCT116, the expression of Tazarotene-induced gene 1 (TIG-1), a putative tumor suppressor, inhibits cell proliferation by inducing GRK5 expression in response to PGE2 [55, 56]. TIG1 suppresses PGE2-stimulated cell proliferation through inhibition of β -catenin pathway, and this effect is mediated by GRK5, since it is ameliorated by GRK5 siRNA. Moreover, the over-expression of GRK5 suppressed PGE2-stimulated β -catenin activation in a dose dependent manner in HCT116 and DLD-1 cells (Fig. 1).

Also in thyroid cancer cells, GRK5 has negative effects on tumor growth, due to its ability to down-regulate GPCRs activity, in particular TSH-receptor activity [57]. The TSH receptor, is a major determinant of thyroid function and most of



Figure 1: TIG-1 inhibits PGE2-dependent cell proliferation through the induction of GRK5 expression

PGE2 binds and stimulates EP2, a GPCR, that activates PI3K; PI3K converts PIP2 in PIP3, that recruits PDK1 and AKT on plasmamembrane. PDK1 phosphorylates and activates AKT, that inhibits GSK3 β , blocking β -catenin degradation and promoting cell proliferation.

TIG-1 induces GRK5 over-expression which on turn inhibits EP2, blocking its signaling transduction with an inhibitory effect on cell proliferation.

the TSH effects on proliferation and differentiation of thyroid cells are mediated by cAMP via an adenylyl- cyclase-activating Gs protein [58]. Indeed, several thyroid cancer types (DTC) have high levels of cAMP compared with normal thyroid tissue (NTT), and it has been demonstrated that this is associated with a reduction of the expression of GRK5 gene and protein levels. The data suggest that GRK5 is involved in the regulation process of TSH-stimulated cAMP response in human DTC. Thus, it is likely to speculate that GRK5 down-regulation of GPCRs could be one of the mechanisms that ensure a proliferative advantage to cancer cell, because the loss of GRK5 activity, allows the cell to escape to a control mechanism of the cellular growth.

GRK5 inhibits cancer cell proliferation in the Kaposi's sarcoma [59]. In tissues of patients with Kaposi's sarcoma, human herpesvirus -8 (KSHV) is consistently present. This gamma-herpesvirus may be involved in the pathogenesis of primary effusion (or body cavity-based) lymphomas [60] and Kaposi's sarcoma (KS) [61], and it contains a gene that encodes a G protein-coupled receptor (KSHV-GPCR) [62]. KSHV-GPCR is constitutively activated and its expression stimulates cell proliferation and causes transformation of mouse fibroblasts [63, 64]. The co-expression of GRK5 inhibits KSHV-GPCR-induced cell proliferation and prevents transformation of rodent fibroblasts.

Altogether, these findings support the proof of concept that GRK5 inhibits tumor growth in different cancer cells, through the phosphorylation of GPCR (Fig. 2) on plasmamembrane.

B. Non-GPCR receptors and tumor growth

Besides GPCRs, other receptor signaling are involved in the development of cancer, such as Thirosine-kinase receptors (TRK) and Frizzled family receptors [65, 66]. It is known that the activation of these receptors is regulated by GRK5

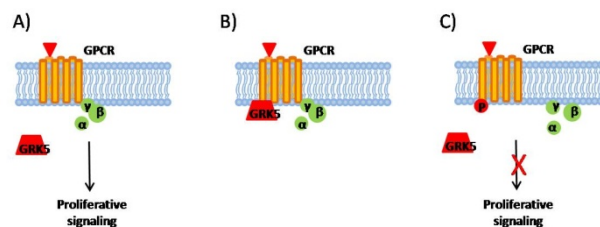


Figure 2 GRK5 inhibits tumor growth through phosphorylation of GPCR A) GPCRs are activated through the interaction with a specific ligand. The activated receptor, through G-protein, stimulates proliferative signaling. B-C) GRK5 interacts (B) and phosphorylates (C) GPCR, promoting un-coupling of G-protein and inhibition of proliferative signaling.

in different cell types [67, 68], although it was never explored in cancer cells. Thus, it is likely that GRK5 could regulate tumor growth also through the regulation of TRK and Frizzled receptors. This could be the inspiration for future studies.

C. GRK5 promotes tumor growth

Besides the above described inhibitory effect of GRK5 on tumor growth when it is located on plasma membrane, in other compartments GRK5 interacts with several intracellular molecules and modulates their stability and activity, thus favoring tumor development and progression. Here we report the effect of GRK5 on some of these molecules.

D. GRK5 regulates p53

An evidence that suggests the ability of GRK5 to promote tumorigenesis, is its ability to inhibit p53, participating to the regulation of genome integrity. p53 is a crucial tumor suppressor that induces cell cycle arrest or apoptosis in response to diverse stresses, and its function is regulated primarily at the level of protein stability through post-translational modifications such as phosphorylation and acetylation [69, 70]. It is well established that the misregulation of p53 level or activity compromises cellular apoptotic response and contributes to tumorigenesis [71, 72]. Chen et al have shown that GRK5 phosphorylates p53 at Thr-55 and promotes its degradation, thus inhibiting p53-mediated apoptosis both in vitro (Fig.3), in cultured human osteosarcoma cells, and in vivo [73]. In particular, GRK5 knockout mice show abnormal p53 levels and enhanced susceptibility in response to irradiation. These findings support an essential role of GRK5 to restrict p53 and protect genomic stability under physiological and pathological conditions. Moreover, this role of GRK5 was confirmed in humans, mice and bovines indicating that, it is conserved across species. How GRK5 coordinates with other p53 regulators in response to various

interaction, which on turn induces poli-ubiquitination and degradation of p53.

genotoxic stresses to maintain genomic stability remains to be further elucidated, but it is clear that GRK5 also acts as stimulator of pro-tumoral effect in the cell, representing a potential target to attenuate resistance to radiation that characterizes some types of cancer.

E. GRK5 phosphorylates moesin

Cancer metastasis involves the cell local invasion and migration so that detached cells from the primary tumor mass can colonize distant organs. Among the molecular mediators of cancer cell migration and invasion, moesin is part of ERM complex (Ezrin-Radixin-Moesin) that links membrane components to actin cytoskeleton, regulating cytoskeleton remodeling and cell adhesions [74, 75]. Altered expression or intracellular distribution of ERMs has been linked to tumor metastasis. In particular, ERM proteins interact with membrane through an N-terminal FERM domain, and with actin through C-terminal domain. The intra-molecular interaction between these two domains masks several binding sites leading to inactivation of ERM proteins [74]. The phosphorylation of ERM proteins by different kinases interrupts this intra-molecular interaction and activates the ERM-complex [74]. Chakraborty et al demonstrated that GRK5 colocalizes with moesin on the plasma membrane, catalyzes its phosphorylation at T66 residue, and regulates cellular distribution of moesin promoting actin remodeling and, then, invasion and metastasis of PC3 cells (Fig.4)[76]. Moreover, in a xenograft model of human prostate cancer, GRK5 silencing reduced tumor growth, invasion and metastasis [76]. Taken together, these results propose GRK5 as a key contributor to the growth and metastasis of prostate cancer.

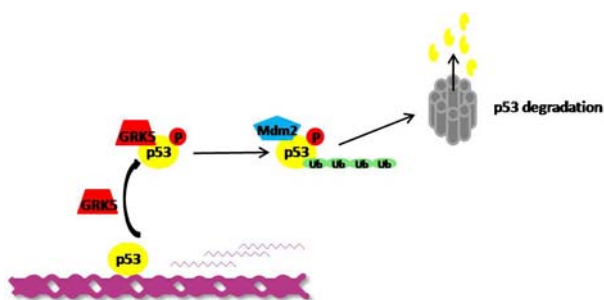


Figure 3 GRK5 promotes p53 degradation GRK5 interacts with and phosphorylates p53 leading to an increase of p53-MDM2

F. GRK5 phosphorylates nucleophosmin, NPM1

Cancer cells are able to escape from normal mechanisms of cell cycle control; indeed, many “*oncosuppressors*” are genes that act as cell cycle – checkpoint, such as Rb and p53. These genes, determine a cell cycle arrest when the cellular genome has accumulated irreversible damages, or when the extracellular environment is not conducive to cell replications (i.e. without

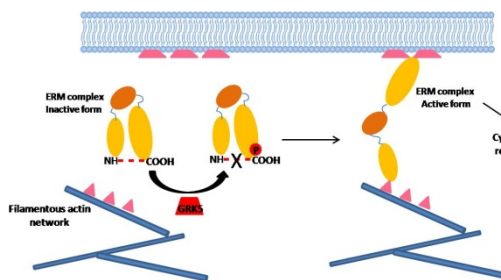


Figure 4 GRK5 promotes cytoskeleton remodeling inducing cancer cell migration and invasion. In the inactive form of ERM-complex, the COOH and NH domains interact, determining a close conformation of the complex. GRK5 phosphorylates an ERM-component (Moesin), interrupting this intra-molecular interaction and activating ERM-complex. In the activated form of the ERM-complex, the COOH domain interacts with cytoskeleton while the NH domain interacts with plasma membrane, inducing cytoskeleton remodeling and, consequently, cell migration and invasion.

growth factors). Genetic alterations that determine loss of function of these genes are typical of cancer cell [77]. Among the regulator of cell cycle progression in cancer, GRK5 could represent a candidate molecule, given its nuclear localization and the identification of new nuclear substrates of this kinase. Indeed, it has been demonstrated that in the nucleus GRK5 interacts with and phosphorylates nucleophosmin (NPM1)[78], a multifunctional protein involved in the regulation of cell cycle, centrosomal duplication and apoptosis, that is overexpressed in several cancer types [79]. NPM1 function is regulated primarily through phosphorylation by PLK1, that leads to the protection from cell death [80]; Indeed, the inhibitor of PLK1, that induces apoptosis, is used in the treatment of several cancers, including esophageal cancer [81], neuroblastomas [82], and others [83]. GRK5 phosphorylates NPM1 at Ser-4, a site shared with PLK1, suggesting the possibility of an interplay between GRK5 and PLK1, in the regulation of NPM1. In particular GRK5-depleted cells were more sensitive to apoptosis induced by PLK1 inhibition, while cells with high GRK5 levels exhibited reduced sensitivity to PLK1 inhibition [78]. GRK5-dependent regulation of cell sensitivity to PLK1 inhibitors is an important finding with potential implications in combined therapies with these

inhibitors. Indeed, it is likely to speculate that in subjects with higher levels of GRK5, the administration of PLK1 inhibitor could be ineffective and that therapeutic approach based on both PLK1 and GRK5 inhibition, could be more effective than PLK1 inhibition alone, in certain cancer types characterized by hyperactivation of PLK1- signaling.

Several other reports support the association between GRK5 activity and cell cycle regulation. In particular in Hela cells, breast cancer cells and also in non-transformed cells, GRK5 localizes in centrosomes during interphase and promotes G2/M transition thus affecting cell cycle progression [47]. The knock down of GRK5 leads to G2/M arrest, even if the mechanism through which GRK5 exerts this effect is not clear yet.

IV. TARGETING GRK5 AS POTENTIAL THERAPEUTIC STRATEGY FOR CANCER

The regulation of the expression and activity of GRKs has yielded promising results in the treatment of multiple diseases, from heart failure and diabetes to cancer and inflammatory diseases, in several animal models and cell culture systems [17, 25, 84, 85]. Given these findings, a selective inhibitor of GRK2 has been synthesized and tested both in cardiovascular diseases and tumors [18, 86-88]. On the opposite, whereas its inhibition strongly correlates with cardiac protection or regression of some tumors, to date no available specific inhibitors have been designed and synthesized for GRK5. To date, only one inhibitor of GRK5 has been recently reported [89], the amlexanox, that directly binds the active site of the kinase in a manner that mimics the adenine ring of ATP, and significantly inhibits MEF2 transcriptional activity, in association with the inhibition of GRK5 in cells. However, this inhibitor is not strictly selective for GRK5, and it has not been tested in cancer yet. It could be useful to synthesize specific inhibitor of GRK5 for the treatment of those tumors characterized, for instance, by low levels of the pro-apoptotic protein p53, to promote cell cycle arrest and apoptosis. On the opposite, given the anti-tumoral effect of GRK5 acting on GPCRs, the induction of GRK5 levels could be the effective strategy for the treatment of GPCR-dependent tumors. Several compounds are available that induce CREB activity [90], a transcription factor that regulate the expression of several genes, including GRK5 gene. Thus the use of these compounds could be effective to induce GRK5 expression in cancer. Little is known about the nuclear effects of GRK5 in cancer. It is likely that GRK5 could enter the

nucleus and regulate the activity of transcription factors which in turn induce the expression of pro- and anti-apoptotic genes. It has been shown that GRK5 inhibits HDAC5 in the nucleus, promoting MEF2 expression in cardiac myocytes [22, 42]. Given the main role of these enzymes in cancer progression and the use of HDAC inhibitors as anti-cancer drugs [91, 92], it could be interesting to evaluate such phenomenon also in tumor cells.

An innovative strategy has been proposed that is specific for cancer and is based on a competitive interaction with GRK5 cytosolic substrates rather than inhibition of its activity, the TAT-RH peptide [93]. TAT-RH binds I κ B α , the inhibitory protein of NF κ B, thus stabilizing I κ B α -NF κ B complex and blocking NF κ B transcriptional activity. In cultured tumor cells, different dosages of TAT-RH reduced cell survival and increased apoptosis. In BALB/c mice, the anti-proliferative effects of TAT-RH appear to be dose-dependent and highest dose completely inhibits tumor growth. Thus, TAT-RH is a promising compound for the treatment of those tumors which are NF κ B dependent [94].

V. CONCLUSIONS AND FUTURE PROSPECTIVE

GRK5 is a multifunctional protein that is able to move within the cell in response to various stimuli to regulate key intracellular signaling from receptor activation, on plasmamembrane, to gene transcription, in the nucleus. Thus, GRK5 is involved in the development and progression of several pathological conditions such as cardiac hypertrophy and failure, diabetes and cancer.

The proof of concept that GRK5 is involved in the regulation of cancer progression derives from the discovery that GRK5 was part of a subset of gene targets required for mitotic progression in human cancer cells. However, its role in tumor growth is still complex and ambiguous, since GRK5 exerts opposite effects, depending on tumor cell type and kinase localization within the cell. Indeed, when the kinase is localized at plasma membrane, it often exerts an anti-tumoral effect, attenuating growth-associated pathway through its ability to desensitize GPCR and non GPCR-receptors (TSH, PGE2R, PDGFR). On the contrary, when GRK5 moves to others compartments, such as cytosol and nucleus, it promotes tumor growth acting on non receptor-substrates, such as p53, AUKA and NPM1.

Given these different effects of GRK5 on tumor growth, targeting GRK5 could be an useful anti-cancer strategy, for specific tumor types. In this context, further studies will be needed to better define the nuclear effects of GRK5 and the

possibility to regulate its subcellular localization in order to regulate its functions within the tumor cell as necessary.

REFERENCES

- [1] J. A. Pitcher, N. J. Freedman, and R. J. Lefkowitz, "G protein-coupled receptor kinases," *Annu Rev Biochem*, vol. 67, pp. 653-92, 1998.
- [2] E. Reiter and R. J. Lefkowitz, "GRKs and beta-arrestins: roles in receptor silencing, trafficking and signaling," *Trends Endocrinol Metab*, vol. 17, pp. 159-65, May-Jun 2006.
- [3] M. Tiberi, S. R. Nash, L. Bertrand, R. J. Lefkowitz, and M. G. Caron, "Differential regulation of dopamine D1A receptor responsiveness by various G protein-coupled receptor kinases," *J Biol Chem*, vol. 271, pp. 3771-8, Feb 16 1996.
- [4] R. R. Gainetdinov, L. M. Bohn, J. K. Walker, S. A. Laporte, A. D. Macrae, M. G. Caron, R. J. Lefkowitz, and R. T. Premont, "Muscarinic supersensitivity and impaired receptor desensitization in G protein-coupled receptor kinase 5-deficient mice," *Neuron*, vol. 24, pp. 1029-36, Dec 1999.
- [5] I. Aramori, S. S. Ferguson, P. D. Bieniasz, J. Zhang, B. Cullen, and M. G. Cullen, "Molecular mechanism of desensitization of the chemokine receptor CCR-5: receptor signaling and internalization are dissociable from its role as an HIV-1 co-receptor," *EMBO J*, vol. 16, pp. 4606-16, Aug 1 1997.
- [6] C. Doll, F. Poll, K. Peuker, A. Loktev, L. Gluck, and S. Schulz, "Deciphering micro-opioid receptor phosphorylation and dephosphorylation in HEK293 cells," *Br J Pharmacol*, vol. 167, pp. 1259-70, Nov 2012.
- [7] M. Oppermann, M. Diverse-Pierluissi, M. H. Drazner, S. L. Dyer, N. J. Freedman, K. C. Peppel, and R. J. Lefkowitz, "Monoclonal antibodies reveal receptor specificity among G-protein-coupled receptor kinases," *Proc Natl Acad Sci U S A*, vol. 93, pp. 7649-54, Jul 23 1996.
- [8] J. M. Willets, R. A. Challiss, and S. R. Nahorski, "Non-visual GRKs: are we seeing the whole picture?," *Trends Pharmacol Sci*, vol. 24, pp. 626-33, Dec 2003.
- [9] R. B. Penn, A. N. Pronin, and J. L. Benovic, "Regulation of G protein-coupled receptor kinases," *Trends Cardiovasc Med*, vol. 10, pp. 81-9, Feb 2000.
- [10] R. Gros, J. L. Benovic, C. M. Tan, and R. D. Feldman, "G-protein-coupled receptor kinase activity is increased in hypertension," *J Clin Invest*, vol. 99, pp. 2087-93, May 1 1997.
- [11] M. Ungerer, M. Bohm, J. S. Elce, E. Erdmann, and M. J. Lohse, "Altered expression of beta-adrenergic receptor kinase and beta 1-adrenergic receptors in the failing human heart," *Circulation*, vol. 87, pp. 454-63, Feb 1993.
- [12] M. S. Lombardi, A. Kavelaars, P. M. Cobelens, R. E. Schmidt, M. Schedlowski, and C. J. Heijnen, "Adjuvant arthritis induces down-regulation of G protein-coupled receptor kinases in the immune system," *J Immunol*, vol. 166, pp. 1635-40, Feb 1 2001.

- [13] K. L. Hildreth, J. H. Wu, L. S. Barak, S. T. Exum, L. K. Kim, K. Peppel, and N. J. Freedman, "Phosphorylation of the platelet-derived growth factor receptor-beta by G protein-coupled receptor kinase-2 reduces receptor signaling and interaction with the Na(+)/H(+) exchanger regulatory factor," *J Biol Chem*, vol. 279, pp. 41775-82, Oct 1 2004.
- [14] C. V. Carman, T. Som, C. M. Kim, and J. L. Benovic, "Binding and phosphorylation of tubulin by G protein-coupled receptor kinases," *J Biol Chem*, vol. 273, pp. 20308-16, Aug 7 1998.
- [15] A. N. Pronin, A. J. Morris, A. Surguchov, and J. L. Benovic, "Synucleins are a novel class of substrates for G protein-coupled receptor kinases," *J Biol Chem*, vol. 275, pp. 26515-22, Aug 25 2000.
- [16] I. H. Lee, S. H. Song, C. R. Campbell, S. Kumar, D. I. Cook, and A. Dinudom, "Regulation of the epithelial Na⁺ channel by the RH domain of G protein-coupled receptor kinase, GRK2, and Galphaq/11," *J Biol Chem*, vol. 286, pp. 19259-69, Jun 3 2011.
- [17] M. Ciccarelli, J. K. Chuprun, G. Rengo, E. Gao, Z. Wei, R. J. Peroutka, J. I. Gold, A. Gumpert, M. Chen, N. J. Otis, G. W. Dorn, 2nd, B. Trimarco, G. Iaccarino, and W. J. Koch, "G protein-coupled receptor kinase 2 activity impairs cardiac glucose uptake and promotes insulin resistance after myocardial ischemia," *Circulation*, vol. 123, pp. 1953-62, May 10 2011.
- [18] D. Sorriento, G. Santulli, A. Franco, E. Cipolletta, L. Napolitano, J. Gambardella, I. Gomez-Monterrey, P. Campiglia, B. Trimarco, G. Iaccarino, and M. Ciccarelli, "Integrating GRK2 and NFkappaB in the Pathophysiology of Cardiac Hypertrophy," *J Cardiovasc Transl Res*, Jul 30 2015.
- [19] P. Penela, C. Ribas, and F. Mayor, Jr., "Mechanisms of regulation of the expression and function of G protein-coupled receptor kinases," *Cell Signal*, vol. 15, pp. 973-81, Nov 2003.
- [20] K. Lorenz, M. J. Lohse, and U. Quitterer, "Protein kinase C switches the Raf kinase inhibitor from Raf-1 to GRK-2," *Nature*, vol. 426, pp. 574-9, Dec 4 2003.
- [21] S. Liu, R. T. Premont, C. D. Kontos, S. Zhu, and D. C. Rokey, "A crucial role for GRK2 in regulation of endothelial cell nitric oxide synthase function in portal hypertension," *Nat Med*, vol. 11, pp. 952-8, Sep 2005.
- [22] Y. Zhang, S. J. Matkovich, X. Duan, J. I. Gold, W. J. Koch, and G. W. Dorn, 2nd, "Nuclear effects of G-protein receptor kinase 5 on histone deacetylase 5-regulated gene transcription in heart failure," *Circ Heart Fail*, vol. 4, pp. 659-68, Sep 2011.
- [23] A. Fusco, G. Santulli, D. Sorriento, E. Cipolletta, C. Garbi, G. W. Dorn, 2nd, B. Trimarco, A. Feliciello, and G. Iaccarino, "Mitochondrial localization unveils a novel role for GRK2 in organelle biogenesis," *Cell Signal*, vol. 24, pp. 468-75, Feb 2012.
- [24] L. R. Johnson, M. G. Scott, and J. A. Pitcher, "G protein-coupled receptor kinase 5 contains a DNA-binding nuclear localization sequence," *Mol Cell Biol*, vol. 24, pp. 10169-79, Dec 2004.
- [25] D. Sorriento, A. Fusco, M. Ciccarelli, A. Rungi, A. Anastasio, A. Carillo, G. W. Dorn, 2nd, B. Trimarco, and G. Iaccarino, "Mitochondrial G protein coupled receptor kinase 2 regulates proinflammatory responses in macrophages," *FEBS Lett*, vol. 587, pp. 3487-94, Nov 1 2013.
- [26] J. I. Gold, J. S. Martini, J. Hullmann, E. Gao, J. K. Chuprun, L. Lee, D. G. Tilley, J. E. Rabinowitz, J. Bossuyt, D. M. Bers, and W. J. Koch, "Nuclear translocation of cardiac G protein-Coupled Receptor kinase 5 downstream of select Gq-activating hypertrophic ligands is a calmodulin-dependent process," *PLoS One*, vol. 8, p. e57324, 2013.
- [27] Z. Suo, A. A. Cox, N. Bartelli, I. Rasul, B. W. Festoff, R. T. Premont, and G. W. Arendash, "GRK5 deficiency leads to early Alzheimer-like pathology and working memory impairment," *Neurobiol Aging*, vol. 28, pp. 1873-88, Dec 2007.
- [28] J. H. Wu, L. Zhang, A. C. Fanaroff, X. Cai, K. C. Sharma, L. Brian, S. T. Exum, S. K. Shenoy, K. Peppel, and N. J. Freedman, "G protein-coupled receptor kinase-5 attenuates atherosclerosis by regulating receptor tyrosine kinases and 7-transmembrane receptors," *Arterioscler Thromb Vasc Biol*, vol. 32, pp. 308-16, Feb 2012.
- [29] N. Dzimir, C. Basco, A. Moorji, B. Afrane, and Z. Al-Halees, "Characterization of lymphocyte beta 2-adrenoceptor signalling in patients with left ventricular volume overload disease," *Clin Exp Pharmacol Physiol*, vol. 29, pp. 181-8, Mar 2002.
- [30] L. Wang, M. Shen, F. Wang, and L. Ma, "GRK5 ablation contributes to insulin resistance," *Biochem Biophys Res Commun*, vol. 429, pp. 99-104, Dec 7 2012.
- [31] Z. M. Huang, J. I. Gold, and W. J. Koch, "G protein-coupled receptor kinases in normal and failing myocardium," *Front Biosci (Landmark Ed)*, vol. 16, pp. 3047-60, 2011.
- [32] E. P. Chen, H. B. Bittner, S. A. Akhter, W. J. Koch, and R. D. Davis, "Myocardial function in hearts with transgenic overexpression of the G protein-coupled receptor kinase 5," *Ann Thorac Surg*, vol. 71, pp. 1320-4, Apr 2001.
- [33] H. A. Rockman, D. J. Choi, N. U. Rahman, S. A. Akhter, R. J. Lefkowitz, and W. J. Koch, "Receptor-specific in vivo desensitization by the G protein-coupled receptor kinase-5 in transgenic mice," *Proc Natl Acad Sci U S A*, vol. 93, pp. 9954-9, Sep 3 1996.
- [34] Z. Xia, T. Yang, Z. Wang, J. Dong, and C. Liang, "GRK5 intronic (CA)_n polymorphisms associated with type 2 diabetes in Chinese Hainan Island," *PLoS One*, vol. 9, p. e90597, 2014.
- [35] H. Li, W. Gan, L. Lu, X. Dong, X. Han, C. Hu, Z. Yang, L. Sun, W. Bao, P. Li, M. He, L. Sun, Y. Wang, J. Zhu, Q. Ning, Y. Tang, R. Zhang, J. Wen, D. Wang, X. Zhu, K. Guo, X. Zuo, X. Guo, H. Yang, X. Zhou, D. Consortium, A.-T. D. Consortium, X. Zhang, L. Qi, R. J. Loos, F. B. Hu, T. Wu, Y. Liu, L. Liu, Z. Yang, R. Hu, W. Jia, L. Ji, Y. Li, and X. Lin, "A genome-wide association study identifies GRK5 and RASGRP1 as type 2 diabetes loci in Chinese Hans," *Diabetes*, vol. 62, pp. 291-8, Jan 2013.
- [36] L. Krilov, A. Nguyen, T. Miyazaki, C. G. Unson, R. Williams, N. H. Lee, S. Ceryak, and B. Bouscarel, "Dual mode of glucagon receptor internalization: role of

- PKC α , GRKs and beta-arrestins," *Exp Cell Res*, vol. 317, pp. 2981-94, Dec 10 2011.
- [37] P. Shah, A. Vella, A. Basu, R. Basu, W. F. Schwenk, and R. A. Rizza, "Lack of suppression of glucagon contributes to postprandial hyperglycemia in subjects with type 2 diabetes mellitus," *J Clin Endocrinol Metab*, vol. 85, pp. 4053-9, Nov 2000.
- [38] P. Tarantino, E. V. De Marco, G. Annesi, F. E. Rocca, F. Annesi, D. Civitelli, G. Provenzano, V. Scornaienchi, V. Greco, C. Colica, G. Nicoletti, and A. Quattrone, "Lack of association between G-protein coupled receptor kinase 5 gene and Parkinson's disease," *Am J Med Genet B Neuropsychiatr Genet*, vol. 156B, pp. 104-7, Jan 2011.
- [39] S. Hara, S. Arawaka, H. Sato, Y. Machiya, C. Cui, A. Sasaki, S. Koyama, and T. Kato, "Serine 129 phosphorylation of membrane-associated alpha-synuclein modulates dopamine transporter function in a G protein-coupled receptor kinase-dependent manner," *Mol Biol Cell*, vol. 24, pp. 1649-60, S1-3, Jun 2013.
- [40] M. M. Thiyagarajan, R. P. Stracquatano, A. N. Pronin, D. S. Evanko, J. L. Benovic, and P. B. Wedegaertner, "A predicted amphipathic helix mediates plasma membrane localization of GRK5," *J Biol Chem*, vol. 279, pp. 17989-95, Apr 23 2004.
- [41] J. A. Pitcher, Z. L. Fredericks, W. C. Stone, R. T. Premont, R. H. Stoffel, W. J. Koch, and R. J. Lefkowitz, "Phosphatidylinositol 4,5-bisphosphate (PIP₂)-enhanced G protein-coupled receptor kinase (GRK) activity. Location, structure, and regulation of the PIP₂ binding site distinguishes the GRK subfamilies," *J Biol Chem*, vol. 271, pp. 24907-13, Oct 4 1996.
- [42] J. S. Martini, P. Raake, L. E. Vinge, B. R. DeGeorge, Jr., J. K. Chuprun, D. M. Harris, E. Gao, A. D. Eckhart, J. A. Pitcher, and W. J. Koch, "Uncovering G protein-coupled receptor kinase-5 as a histone deacetylase kinase in the nucleus of cardiomyocytes," *Proc Natl Acad Sci U S A*, vol. 105, pp. 12457-62, Aug 26 2008.
- [43] P. Liu, X. Wang, N. Gao, H. Zhu, X. Dai, Y. Xu, C. Ma, L. Huang, Y. Liu, and C. Qin, "G protein-coupled receptor kinase 5, overexpressed in the alpha-synuclein up-regulation model of Parkinson's disease, regulates bcl-2 expression," *Brain Res*, vol. 1307, pp. 134-41, Jan 11 2010.
- [44] D. Sorriento, M. Ciccarelli, G. Santulli, A. Campanile, G. G. Altobelli, V. Cimmini, G. Galasso, D. Astone, F. Piscione, L. Pastore, B. Trimarco, and G. Iaccarino, "The G-protein-coupled receptor kinase 5 inhibits NF κ B transcriptional activity by inducing nuclear accumulation of IkappaB alpha," *Proc Natl Acad Sci U S A*, vol. 105, pp. 17818-23, Nov 18 2008.
- [45] D. Sorriento, G. Santulli, A. Fusco, A. Anastasio, B. Trimarco, and G. Iaccarino, "Intracardiac injection of AdGRK5-NT reduces left ventricular hypertrophy by inhibiting NF-kappaB-dependent hypertrophic gene expression," *Hypertension*, vol. 56, pp. 696-704, Oct 2010.
- [46] J. E. Hullmann, L. A. Grisanti, C. A. Makarewich, E. Gao, J. I. Gold, J. K. Chuprun, D. G. Tilley, S. R. Houser, and W. J. Koch, "GRK5-mediated exacerbation of pathological cardiac hypertrophy involves facilitation of nuclear NFAT activity," *Circ Res*, vol. 115, pp. 976-85, Dec 5 2014.
- [47] A. M. Michal, C. H. So, N. Beeharry, H. Shankar, R. Mashayekhi, T. J. Yen, and J. L. Benovic, "G Protein-coupled receptor kinase 5 is localized to centrosomes and regulates cell cycle progression," *J Biol Chem*, vol. 287, pp. 6928-40, Feb 24 2012.
- [48] C. Iobagiu, C. Lambert, M. Raica, S. Lima, A. Khaddage, M. Peoc'h, and C. Genin, "Loss of heterozygosity in tumor tissue in hormonal receptor genes is associated with poor prognostic criteria in breast cancer," *Cancer Genet*, vol. 208, pp. 135-42, Apr 2015.
- [49] S. Thiagalingam, S. Laken, J. K. Willson, S. D. Markowitz, K. W. Kinzler, B. Vogelstein, and C. Lengauer, "Mechanisms underlying losses of heterozygosity in human colorectal cancers," *Proc Natl Acad Sci U S A*, vol. 98, pp. 2698-702, Feb 27 2001.
- [50] S. van Zelderen-Bhola, R. Vink, J. Smit, H. Wessels, and H. Morreau, "Translocations (X;10)(p22;q24) and (1;10)(q21;q11) in a follicular adenoma of the thyroid without apparent involvement of the RET protooncogene," *Cancer Genet Cytogenet*, vol. 112, pp. 178-80, Jul 15 1999.
- [51] R. T. Premont, A. D. Macrae, S. A. Aparicio, H. E. Kendall, J. E. Welch, and R. J. Lefkowitz, "The GRK4 subfamily of G protein-coupled receptor kinases. Alternative splicing, gene organization, and sequence conservation," *J Biol Chem*, vol. 274, pp. 29381-9, Oct 8 1999.
- [52] R. T. Dorsam and J. S. Gutkind, "G-protein-coupled receptors and cancer," *Nat Rev Cancer*, vol. 7, pp. 79-94, Feb 2007.
- [53] T. W. Moody, B. Nuche-Berenguer, T. Nakamura, and R. T. Jensen, "EGFR Transactivation by Peptide G Protein-Coupled Receptors in Cancer," *Curr Drug Targets*, Jan 7 2015.
- [54] Y. Audigier, F. X. Picault, C. Chaves-Almagro, and B. Masri, "G Protein-Coupled Receptors in cancer: biochemical interactions and drug design," *Prog Mol Biol Transl Sci*, vol. 115, pp. 143-73, 2013.
- [55] C. C. Wu, F. M. Tsai, R. Y. Shyu, Y. M. Tsai, C. H. Wang, and S. Y. Jiang, "G protein-coupled receptor kinase 5 mediates Tazarotene-induced gene 1-induced growth suppression of human colon cancer cells," *BMC Cancer*, vol. 11, p. 175, 2011.
- [56] F. M. Tsai, C. C. Wu, R. Y. Shyu, C. H. Wang, and S. Y. Jiang, "Tazarotene-induced gene 1 inhibits prostaglandin E2-stimulated HCT116 colon cancer cell growth," *J Biomed Sci*, vol. 18, p. 88, 2011.
- [57] T. Metaye, E. Menet, J. Guilhot, and J. L. Kraimps, "Expression and activity of g protein-coupled receptor kinases in differentiated thyroid carcinoma," *J Clin Endocrinol Metab*, vol. 87, pp. 3279-86, Jul 2002.
- [58] G. Vassart and J. E. Dumont, "The thyrotropin receptor and the regulation of thyrocyte function and growth," *Endocr Rev*, vol. 13, pp. 596-611, Aug 1992.
- [59] E. Geras-Raaka, L. Arvanitakis, C. Bais, E. Cesarman, E. A. Mesri, and M. C. Gershengorn, "Inhibition of constitutive signaling of Kaposi's sarcoma-associated herpesvirus G protein-coupled receptor by

protein kinases in mammalian cells in culture," *J Exp Med*, vol. 187, pp. 801-6, Mar 2 1998.

[60] R. G. Nador, E. Cesarman, A. Chadburn, D. B. Dawson, M. Q. Ansari, J. Sald, and D. M. Knowles, "Primary effusion lymphoma: a distinct clinicopathologic entity associated with the Kaposi's sarcoma-associated herpes virus," *Blood*, vol. 88, pp. 645-56, Jul 15 1996.

[61] M. K. Offermann, "Kaposi's sarcoma and HHV-8," *Trends Microbiol*, vol. 4, p. 419, Nov 1996.

[62] E. Cesarman, R. G. Nador, F. Bai, R. A. Bohenzky, J. J. Russo, P. S. Moore, Y. Chang, and D. M. Knowles, "Kaposi's sarcoma-associated herpesvirus contains G protein-coupled receptor and cyclin D homologs which are expressed in Kaposi's sarcoma and malignant lymphoma," *J Virol*, vol. 70, pp. 8218-23, Nov 1996.

[63] L. Arvanitakis, E. Geras-Raaka, A. Varma, M. C. Gershengorn, and E. Cesarman, "Human herpesvirus KSHV encodes a constitutively active G-protein-coupled receptor linked to cell proliferation," *Nature*, vol. 385, pp. 347-50, Jan 23 1997.

[64] C. Bais, B. Santomaso, O. Coso, L. Arvanitakis, E. G. Raaka, J. S. Gutkind, A. S. Asch, E. Cesarman, M. C. Gershengorn, and E. A. Mesri, "G-protein-coupled receptor of Kaposi's sarcoma-associated herpesvirus is a viral oncogene and angiogenesis activator," *Nature*, vol. 391, pp. 86-9, Jan 1 1998.

[65] M. K. Paul and A. K. Mukhopadhyay, "Tyrosine kinase - Role and significance in Cancer," *Int J Med Sci*, vol. 1, pp. 101-115, 2004.

[66] P. Polakis, "Wnt signaling and cancer," *Genes Dev*, vol. 14, pp. 1837-51, Aug 1 2000.

[67] J. H. Wu, R. Goswami, X. Cai, S. T. Exum, X. Huang, L. Zhang, L. Brian, R. T. Premont, K. Peppel, and N. J. Freedman, "Regulation of the platelet-derived growth factor receptor-beta by G protein-coupled receptor kinase-5 in vascular smooth muscle cells involves the phosphatase Shp2," *J Biol Chem*, vol. 281, pp. 37758-72, Dec 8 2006.

[68] M. Chen, M. Philipp, J. Wang, R. T. Premont, T. R. Garrison, M. G. Caron, R. J. Lefkowitz, and W. Chen, "G Protein-coupled receptor kinases phosphorylate LRP6 in the Wnt pathway," *J Biol Chem*, vol. 284, pp. 35040-8, Dec 11 2009.

[69] A. J. Levine, "p53, the cellular gatekeeper for growth and division," *Cell*, vol. 88, pp. 323-31, Feb 7 1997.

[70] A. M. Bode and Z. Dong, "Post-translational modification of p53 in tumorigenesis," *Nat Rev Cancer*, vol. 4, pp. 793-805, Oct 2004.

[71] F. Toledo and G. M. Wahl, "Regulating the p53 pathway: in vitro hypotheses, in vivo veritas," *Nat Rev Cancer*, vol. 6, pp. 909-23, Dec 2006.

[72] D. Sorriento, C. Del Giudice, A. Bertamino, M. Ciccarelli, I. Gomez-Monterrey, P. Campiglia, E. Novellino, M. Illario, B. Trimarco, N. De Luca, and G. Iaccarino, "New small molecules, ISA27 and SM13, inhibit tumour growth inducing mitochondrial effects of p53," *Br J Cancer*, vol. 112, pp. 77-85, Jan 6 2015.

[73] X. Chen, H. Zhu, M. Yuan, J. Fu, Y. Zhou, and L. Ma, "G-protein-coupled receptor kinase 5

phosphorylates p53 and inhibits DNA damage-induced apoptosis," *J Biol Chem*, vol. 285, pp. 12823-30, Apr 23 2010.

[74] M. Arpin, D. Chirivino, A. Naba, and I. Zwaenepoel, "Emerging role for ERM proteins in cell adhesion and migration," *Cell Adh Migr*, vol. 5, pp. 199-206, Mar-Apr 2011.

[75] D. J. Mackay, F. Esch, H. Furthmayr, and A. Hall, "Rho- and rac-dependent assembly of focal adhesion complexes and actin filaments in permeabilized fibroblasts: an essential role for ezrin/radixin/moesin proteins," *J Cell Biol*, vol. 138, pp. 927-38, Aug 25 1997.

[76] P. K. Chakraborty, Y. Zhang, A. S. Coomes, W. J. Kim, R. Stupay, L. D. Lynch, T. Atkinson, J. I. Kim, Z. Nie, and Y. Daaka, "G protein-coupled receptor kinase GRK5 phosphorylates moesin and regulates metastasis in prostate cancer," *Cancer Res*, vol. 74, pp. 3489-500, Jul 1 2014.

[77] G. Della Porta, P. Radice, and M. A. Pierotti, "Onco-suppressor genes in human cancer," *Tumori*, vol. 75, pp. 329-36, Aug 31 1989.

[78] C. H. So, A. M. Michal, R. Mashayekhi, and J. L. Benovic, "G protein-coupled receptor kinase 5 phosphorylates nucleophosmin and regulates cell sensitivity to polo-like kinase 1 inhibition," *J Biol Chem*, vol. 287, pp. 17088-99, May 18 2012.

[79] S. Grisendi, C. Mecucci, B. Falini, and P. P. Pandolfi, "Nucleophosmin and cancer," *Nat Rev Cancer*, vol. 6, pp. 493-505, Jul 2006.

[80] X. Liu and R. L. Erikson, "Polo-like kinase (Plk)1 depletion induces apoptosis in cancer cells," *Proc Natl Acad Sci U S A*, vol. 100, pp. 5789-94, May 13 2003.

[81] T. Ito, F. Sato, T. Kan, Y. Cheng, S. David, R. Agarwal, B. C. Paun, Z. Jin, A. V. Olaru, J. P. Hamilton, F. M. Selaru, J. Yang, N. Matsumura, K. Shimizu, J. M. Abraham, Y. Shimada, Y. Mori, and S. J. Meltzer, "Polo-like kinase 1 regulates cell proliferation and is targeted by miR-593* in esophageal cancer," *Int J Cancer*, vol. 129, pp. 2134-46, Nov 1 2011.

[82] S. Ackermann, F. Goeser, J. H. Schulte, A. Schramm, V. Ehemann, B. Hero, A. Eggert, F. Berthold, and M. Fischer, "Polo-like kinase 1 is a therapeutic target in high-risk neuroblastoma," *Clin Cancer Res*, vol. 17, pp. 731-41, Feb 15 2011.

[83] M. Steegmaier, M. Hoffmann, A. Baum, P. Lenart, M. Petronczki, M. Krssak, U. Gurtler, P. Garin-Chesa, S. Lieb, J. Quant, M. Grauert, G. R. Adolf, N. Kraut, J. M. Peters, and W. J. Rettig, "BI 2536, a potent and selective inhibitor of polo-like kinase 1, inhibits tumor growth in vivo," *Curr Biol*, vol. 17, pp. 316-22, Feb 20 2007.

[84] H. A. Rockman, W. J. Koch, and R. J. Lefkowitz, "Seven-transmembrane-spanning receptors and heart function," *Nature*, vol. 415, pp. 206-12, Jan 10 2002.

[85] S. L. Belmonte and B. C. Blaxall, "G protein coupled receptor kinases as therapeutic targets in cardiovascular disease," *Circ Res*, vol. 109, pp. 309-19, Jul 22 2011.

[86] X. Fu, S. Koller, J. Abd Alla, and U. Qwitterer, "Inhibition of G-protein-coupled receptor kinase 2

(GRK2) triggers the growth-promoting mitogen-activated protein kinase (MAPK) pathway," *J Biol Chem*, vol. 288, pp. 7738-55, Mar 15 2013.

[87] I. Gomez-Monterrey, A. Carotenuto, E. Cipolletta, M. Sala, E. Vernieri, A. Limatola, A. Bertamino, S. Musella, P. Grieco, B. Trimarco, E. Novellino, G. Iaccarino, and P. Campiglia, "SAR study and conformational analysis of a series of novel peptide G protein-coupled receptor kinase 2 inhibitors," *Biopolymers*, vol. 101, pp. 121-8, Jan 2014.

[88] A. Carotenuto, E. Cipolletta, I. Gomez-Monterrey, M. Sala, E. Vernieri, A. Limatola, A. Bertamino, S. Musella, D. Sorriento, P. Grieco, B. Trimarco, E. Novellino, G. Iaccarino, and P. Campiglia, "Design, synthesis and efficacy of novel G protein-coupled receptor kinase 2 inhibitors," *Eur J Med Chem*, vol. 69, pp. 384-92, Nov 2013.

[89] K. T. Homan, E. Wu, A. Cannavo, W. J. Koch, and J. J. Tesmer, "Identification and characterization of amlexanox as a G protein-coupled receptor kinase 5 inhibitor," *Molecules*, vol. 19, pp. 16937-49, 2014.

[90] M. Xia, R. Huang, V. Guo, N. Southall, M. H. Cho, J. Inglese, C. P. Austin, and M. Nirenberg,

"Identification of compounds that potentiate CREB signaling as possible enhancers of long-term memory," *Proc Natl Acad Sci U S A*, vol. 106, pp. 2412-7, Feb 17 2009.

[91] S. Ropero and M. Esteller, "The role of histone deacetylases (HDACs) in human cancer," *Mol Oncol*, vol. 1, pp. 19-25, Jun 2007.

[92] R. W. Johnstone, "Histone-deacetylase inhibitors: novel drugs for the treatment of cancer," *Nat Rev Drug Discov*, vol. 1, pp. 287-99, Apr 2002.

[93] D. Sorriento, A. Campanile, G. Santulli, E. Leggiero, L. Pastore, B. Trimarco, and G. Iaccarino, "A new synthetic protein, TAT-RH, inhibits tumor growth through the regulation of NFkappaB activity," *Mol Cancer*, vol. 8, p. 97, 2009.

[94] D. Sorriento, M. Illario, R. Finelli, and G. Iaccarino, "To NFkappaB or not to NFkappaB: The Dilemma on How to Inhibit a Cancer Cell Fate Regulator," *Transl Med UniSa*, vol. 4, pp. 73-85, Sep 2012.