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Lipid Signaling in Tumorigenesis

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Abstract

Lipids are important cellular building blocks and components of signaling cascades. Deregulation of lipid metabolism or signaling is frequently linked to a variety of human diseases such as diabetes, cardiovascular diseases, and cancer. It is widely believed that lipid molecules or their metabolic products are involved in tumorigenic inflammation and thus, lipids are implicated as significant contributors or even primary triggers of tumorigenesis. Lipids are believed to directly or indirectly activate growth promoting signals such as those involving LPA, insulin, IGF-1 and EGF to promote cancer cell growth. Cellular levels of certain lipids, including sphingosine-1-phosphate and ceramide, maintain a delicate balance between cell death and survival and alterations in their levels lead to unfavorable consequences including tumorigenesis. This article provides an overview of current knowledge that implicates lipids in tumorigenesis and explores the potential mechanisms that support a positive link between obesity and cancer.

Keywords

Cancer; Ceramide; Lipid metabolism; Monoglyceride lipase; Obesity; Sphingosine-1-phosphate

Introduction

Obesity is commonly defined as an imbalance in energy storage and expenditure in the human body that leads to an excessive accumulation of lipids. Obesity is consistently implicated as a contributing factor in the development of cancer. Epidemiological evidence demonstrates that increased body mass index (BMI) is associated with an increased incidence of multiple human malignancies including cancers of the esophagus, colon, kidney, endometrium and gallbladder (1). Because excessive accumulation of lipid in the adipose tissue leads to obesity that contributes to increased BMI, which may explain the existence of a correlation between obesity and cancer. The molecular details of this correlation, however, remain unclear.

Lipids play important roles in multiple cellular processes such as metabolism, proliferation, apoptosis as well as cell migration. A variety of enzymes are responsible for their activities

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in important signaling pathways. Normally lipids and lipid-modifying enzymes maintain the balance of lipid metabolism and lipid signaling, the disruption of which is involved in a large variety of human diseases (2). Since cell growth and metabolism are usually deranged in cancer cells, the regulation of these processes by lipids implicates potentially vital roles of lipids in cancer development. This review outlines principal mechanisms by which lipids are involved in tumorigenesis.

Inflammation links lipids to cancer

Inflammation is increasingly considered a potent promoter of tumorigenesis. Interestingly, obesity contributes to a subacute inflammatory state (3,4). Adipose tissue secretes numerous cytokines that in turn can stimulate the activity of tissue-resident macrophages as well as other inflammatory cells and thus promote the development of cancer (5). Initially identified as a glycoprotein that caused necrosis of tumors and later as an important inflammatory cytokine (6), tumor necrosis factor-α (TNFα), has been shown to be overexpressed in adipose tissue and is related to insulin resistance observed in both rodent models of obesity and humans (7,8). Contrary to the function as its name implies, TNFα together with IL-17 is able to stimulate glycolysis and growth factor production in multiple colorectal cancer cell lines and are postulated to promote inflammation-mediated colorectal tumorigenesis (9). Furthermore, TNFα exhibited a tumor-promoting role in both mouse cancer models and human cancers (10–14). Inhibitors of TNFα including etanercept and infliximab have shown antitumor activities in patients with advanced cancers (15–17). Other inflammatory cytokines such as interleukin-6 (IL-6) and plasminogen activator inhibitor 1 (PAI1) produced in adipose tissues also contribute to an increased risk of cancer in obese patients (5). However, direct evidence is still needed to link cytokines secretion in adipose tissue to tumor formation in obese patients.

In addition to the inflammatory cytokines released by adipose tissue, numerous mediators of inflammation have been identified to be metabolic products of lipids. Eicosanoids, a series of metabolic products from arachidonic acid (AA) that is usually released from phospholipids through the actions of phospholipase A2 (PLA2) as well as other lipases, are potent pro-inflammatory mediators involved in inflammatory diseases (18). One of the enzymes in the biosynthetic pathway of eicosanoids (Fig. 1), cyclooxygenase 2 (COX-2), has been shown to be intimately related to colorectal tumorigenesis. COX-2 is overexpressed in most colorectal carcinomas and its up-regulation is also demonstrated in pre-malignant adenomas (10–22). Earlier studies of familial adenomatous polyposis (FAP), a predisposing pathological condition of colorectal cancer, identified germ line loss-of-function mutations of APC gene (23,24), based on which several models of colorectal cancer have been generated. In an Apc delta716 knockout mouse, an animal model for human FAP, both COX-2 gene knockout and a COX-2 inhibitor significantly decreased the number and size of the intestinal polyps (25). Aspirin, another inhibitor of COX-2, is also found to be associated with reduced risk of fatal colon cancer, and regular and prolonged use of aspirin is also linked to reduced deaths due to cancers of the colon and rectum (26). COX-2 inhibitors such as the highly selective COX-2 inhibitor celecoxib are even administered as adjunctive therapy for patients with familial polyposis and are currently being studied to extend its use in other cancers (27).

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The role of COX-2 in colorectal tumorigenesis is mainly attributed to its mediation of the generation of PGE2, one of the products from AA that promotes cancer-induced angiogenesis and growth of tumor cells (28,29). Studies have shown that COX-2 levels were increased in obesity-associated inflammatory foci in the human breast tissues (30). Studies have also shown that overexpression of COX2 and resulting increased production of PGE2 are associated with elevated levels of aromatase expression (30). Increased levels of aromatase presumably could contribute to the development of hormone-dependent breast cancer in obese women. Overall, increasing amount of evidence suggests a role of obesity-related inflammation in cancer development.

Hyperinsulinemia mediates obesity-induced malignancies

A compensatory response to obesity in obese individuals is the development of insulin resistance and ensuing hyperinsulinemia (5,31), which is a common finding in type-2 diabetes. In type-2 diabetes, it is thought that insulin resistance is limited to some tissues such as adipose tissue and skeletal muscles (31), other tissues may still maintain their sensitivity to insulin. It has been shown that insulin has growth-stimulatory effect both *in vitro* and *in vivo* (32). Obesity-induced hyperinsulinemia could therefore in part, contribute to cellular transformation in cells of insulin-sensitive tissues. There is evidence in support of this hypothesis, for example, the incidence of cancer occurrence in different organs, such as breast, liver and colon, has been shown to positively correlate with the prevalence of type-2 diabetes (33–35).

Insulin exerts its effects mainly through insulin receptors (IRs). Different isoforms of IRs are involved in distinct signaling pathways, by either activating the phosphoinositide 3-kinase (PI3K) pathway (Fig. 2) or the Ras-Raf-MEK-MAPK signaling pathway to promote cell growth and cell survival (36). Insulin has been shown to act as a tumor promoter of colon cancer in rats (37), and it is also demonstrated that insulin plays a positive role in macromolecular synthesis and cancer cell growth *in* breast cancer cells (38). The downstream mediator of insulin signaling, insulin receptor substrate1 (IRS1), which binds to several oncogenic proteins, is also shown to be linked to tumorigenesis. For example, overexpression of IRS1 has been shown to promote cell proliferation and reduce autophagy-dependent cell death in NIH/3T3 fibroblasts (39). In addition, insulin receptor-2 (IRS2), is shown to be involved in breast cancer metastasis (40). Furthermore, hyperinsulinaemia condition may also promote the generation of insulin-like growth factor-I (IGF1) in the liver (41). Currently, a number of anticancer drugs targeting IGF1 are in clinical trials (42). Results show that inhibiting the activity of various components in insulin signaling pathway leads to reduction of cancer cell growth or improvement of anticancer drug efficacy (43–46).

Lipid anabolism and cancer

The rapid proliferation of cancer cells demands a sufficient supply of lipids for synthesis of critical cellular structures such plasma membranes or membranes of cellular organelles. In tumor cells, Fatty Acid Synthase (FASN) is responsible for the synthesis of most of the fatty acids to meet the increased rate of proliferation (47). It has been observed that obesity is correlated with poor outcomes in prostate cancer patients, the rationale for which is still

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under investigation. Interestingly, overexpression of FASN has been found in both primary and metastatic prostate tumors and is related to poor prognosis in prostate cancer patients (48,49). Attenuation of the activity of FASN either by RNA interference-mediated silencing or by inhibitors decreases cell growth and causes cell death in prostate cancer (50,51). FASN is therefore considered to be a candidate oncogene in prostate cancer (52), portending an important role of excessive lipid synthesis in tumor cell growth.

In a previous study, we showed that expression of monoglyceride lipase (MGL), an enzyme that is important in the lipid metabolic pathway, is reduced or absent in several types of human cancers (53). Exogenous expression of MGL in tumor cells lacking MGL suppresses tumor cell growth while its depletion via RNAi knockdown increases Akt phosphorylation (53). It remains to be determined whether this observed MGL-mediated cell growth suppression associates with the action of lipase activity. Nevertheless, reduction in MGL expression is expected to alter the MGL-mediated lipid metabolism in different stages of tumor formation.

Current studies of cancer metabolism have led to a reassessment of the function of lipid droplets. Lipid droplets are intracellular organelles containing abundant neutral lipids such as triacylglycerides and cholesterylesters (54). It is shown that lipid droplets are important for various cellular functions including cell signaling and metabolism (54). Cancer cells usually harbor a large number of lipid droplets that may be critical for the increased energy consumption and cell survival under stress conditions such as hypoxia (55). This increase in lipid droplets may also be an accompanying consequence of upregulated lipid synthesis in cancer cells. Increased lipid synthesis therefore seems to be one of the important features of cancer cell metabolism, and obesity, with lipid surplus, may fuel this process.

Lipid signaling pathways in cancer cells

In addition to the impacts of altered lipid metabolism on cancer as shown above, over the years, it has been found that a number of lipids are virtually components of tumor-modulating signaling pathways. One such lipid is lysophosphatidic acid (LPA), which normally is a bioactive phospholipid that plays important roles in cell proliferation and survival through its binding to G-protein-coupled receptors. Through these receptors, deregulated LPA signaling is involved in inflammation and tumorigenesis (56). LPA can be generated from phosphatidic acid by the action of PLA_2; and can also be produced from hydrolysis of lysophosphatidyl-choline by autotaxin (ATX or NPP2), a major LPA-producing phospholipase (56). The ATX-LPA receptor axis, together with other oncogenic events, promotes tumor progression (57).

One of the most important pathways involved in the development of colon cancer, the β-catenin pathway, mediates LPA-induced proliferation in colon cancer cells (58). A recent study also showed that LPA was associated with lipogenic pathways and lipid synthesis in ovarian cancer cells, which was critical for LPA-induced cell proliferation (59). ATX expression is upregulated with obesity and this characteristic of ATX production is specific to the visceral fat depot, a prominent feature frequently observed in obese patients (60). Interestingly, these findings suggest that LPA may be a mediator of both obesity-induced

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inflammation and obesity-triggered lipid synthesis in cells, which could be potential contributing factors of tumor progression.

Sphingolipids, which constitute a vital part of the structural components of cell membranes, are also shown to be associated with tumor development. One of its central members, ceramide, plays important roles in multiple cellular signaling pathways; and ceramide dysregulation has been observed in cancer pathogenesis (61,62). Different subtypes of ceramide have distinct roles in the controlling of tumor progression. C16-ceramide is an important second messenger in various stress responses and promotes tumor cell growth whereas C18-ceramide has been shown to induce autophagy or apoptosis in tumor cells (62). In a study of human head and neck squamous cell carcinoma (HNSCC), it was shown that C16-ceramide was present at higher levels in the majority of tumor tissues than in corresponding normal tissues while C18-ceramide showed an opposite pattern. Defects in C18-ceramide production are associated with increased aggressiveness of HNSCC (63). And C18-ceramide is considered as an important mediator of chemotherapy-induced cell death in various cancer cells (62).

Another member of the Sphingolipid family, sphingosine-1-phosphate (S1P), is a biologically active lipid signaling molecule associated with various physiological or pathological conditions of almost all organs of the human body. It plays a role in regulation of different cellular processes in cancer cells such as growth, survival and metastasis. It also controls the recruitment of inflammatory cells and the production of cytokines that are important for inflammation and tumorigenesis. Interestingly, S1P can inhibit the pro-apoptotic ceramide, which is a precursor of S1P (64). For the production of S1P, ceramide is first converted to sphingosine by ceramidase and sphingosine is then converted to S1P through the action of sphingosine kinase (SphK). A ceramide–sphingosine–S1P rheostat model is proposed, in which ceramide and sphingosine work as pro-apoptotic mediators while S1P behaves as an anti-apoptotic factor; the imbalance of these lipids could lead to uncontrolled cell growth (65). Obesity is correlated with an elevated level of plasma S1P in both human and rodent models (66), which may tip the ceramide–sphingosine–S1P rheostat into an oncogenic state.

Phosphoinositides and cancer

Phosphoinositides (PtdIns) are a class of phospholipids that play important roles in a wide variety of cellular processes. Lipid phosphatidylinositol (PtdIns) embedded in cell membranes can be phosphorylated on the hydroxyl groups at the 3, 4 and 5 positions of the inositol ring to generate various phosphoinositides (67). Phosphoinositide kinases and phosphoinositide phosphatases elaborately control the level of specific phosphoinositide species, as well as their localization and functions (67). Alterations in genes that encode phosphoinositide-modifying enzymes are related to many human diseases including cancer (68). The regulatory roles of phosphoinositides in specific cellular responses including formation of signaling scaffolds, membrane traffic, cytoskeleton dynamics, nuclear activities and the transportation across the membrane are achieved primarily through their interactions with other proteins (69,70).

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Regarding the phosphoinositides relevant to cancer, one well-established example is the involvement of PtdIns(4,5)P_2 in the PI3K-Akt signaling pathway (Fig. 2) that is commonly activated in human cancers (71). Phosphatidyl-inositide 3-kinases (PI3Ks) are a family of enzymes involved in many cellular processes including cell survival, proliferation and differentiation (71). The members of the mammalian PI3K family are generally classified into three classes (class I, II, and III). Class I PI3Ks are heterodimeric enzymes composed of a regulatory subunit and a catalytic subunit that can phosphorylate PtdIns(4,5)P_2 to generate PtdIns(3,4,5)P_3 (67). To date two subtypes of Class I PI3Ks, class IA and class IB, have been identified and their actions are controlled by largely distinct upstream signals. There are abundant genetic and laboratory studies supporting a role of class IA PI3K in cancer (72,73).

Class IA PI3K works downstream of receptor tyrosine kinases (RTKs) and upon insulin or growth factor binding, RTKs are activated (Fig. 2). PI3K is then recruited to cell membrane through the interaction of its p85 regulatory subunit with tyrosine phosphate motifs on RTKs or to adaptor proteins associated with the receptors, leading to activation of the catalytic subunit of PI3K, p110. The activated p110 catalyzes the conversion of PtdIns(4,5)P_2 into PtdIns(3,4,5)P_3, which then signals to downstream effectors such as the Serine/Threonine kinase Akt. Activated Akt phosphorylates a number of substrates that are important for cell proliferation and cell survival (Fig. 2) (72–74). The PI3K-Akt signaling, like many other cell signaling pathways, is tightly controlled in normal cells. One important regulator of the pathway is phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase, PTEN, that functions to dephosphorylate PtdIns(3,4,5)P_3 and convert it back into PtdIns(4,5)P_2 and thus blocks its downstream signals. The wrestling in balance of PI3K and PTEN activity through the production of PtdIns(3,4,5)P_3 modulates normal cell growth and survival (72,73).

As PtdIns(3,4,5)P_3 is an important component of the growth/survival regulatory pathways, and enhanced PtdIns(3,4,5)P_3 signaling leads to uncontrolled cell growth and cancer development. Studies thus far indicate that PI3K pathway is one of the most frequently altered pathways in human cancer (75). PIK3CA, which encodes the p110α catalytic subunit of PI3K, is mutated in a wide range of malignancies including glioblastomas, and cancers of the stomach, breast and lung (76). It is found that p110α is frequently mutated at residue 1047 (H1047R) that is associated with increased lipid kinase activity (76). In addition, studies have shown that mutation occurring in the inter-Src homology-2 (iSH2) domain of p85α, a regulatory subunit of PI3K, abrogates its p110-inhibitory activity while maintaining its p110-stabilizing activity (77). Such changes are found to be associated with increased cell survival, growth and transformation (77).

Germline mutations in PTEN have been identified in autosomal dominant hamartomatous and cancer-predisposing syndromes such as Cowden's disease and Bannayan-Zonana syndrome. Inactivation of PTEN is observed in a wide range of sporadic human cancers including glioblastoma, melanoma and cancers of the kidney, lung, endometrium and breast. Furhtermore, heterozygous PTEN deletion is known to increase tumor susceptibility in mice (78,79). Since PTEN is a negative regulator of PI3K signaling, loss of function of PTEN causes cellular PtdIns(3,4,5)P_3 accumulation and increased activity of its downstream effectors, and therefore facilitates cancer development (80,81). Taken together, current

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findings on the PI3K signaling pathways all point to a significant role of phosphoinositides in cancer.

In addition to PTEN, other phosphatases including SHIP1/2 (SH2 domain-containing inositol 5-phosphatase 1/2) can also hydrolyze PtdIns(3,4,5)P_3 and convert it into PtdIns(3,4)P_2. (68), and alteration of these enzymes may play a role in tumorigenesis. Indeed, aberrations in SHIP1 signaling are shown to be involved in the development several types of cancer (68). SHIP1 expression is largely restricted to hemopoietic cells; and it controls various cellular processes, including cell survival, proliferation, differentiation, and cell migration, through its negative regulation of the PI3K pathway. Specifically, SHIP1 is able to attenuate cytokine signal transduction in myeloid cells to suppress cell survival and proliferation. Many studies demonstrate that SHIP1 may exert a tumor suppressive effect during the development of leukemia and lymphoma (82). Consistent with a tumor-suppressive role of SHIP1, SHIP1$^{-/-}$ mice develop myeloproliferative-like phenotypes that are usually associated with chronic myelogenous leukemia (CML), and myeloid progenitors from SHIP1$^{-/-}$ mice are significantly more responsive to low levels of cytokines and growth factors than their wild-type counterparts (83). Primary cells from patients with CML show a substantial reduction in SHIP1 expression and expression of BCR–ABL1 oncogene, the main cause of CML, also inhibits SHIP1 expression. This may suggest that suppression of SHIP1 would contribute to CML development (84). Interestingly, studies have also shown that reexpression of exogenous SHIP1 in Jurkat leukemia cells lacking SHIP1 expression causes a significant reduction of PtdIns(3,4,5)P_3 and decreased PI3K-Akt signaling (85). These findings indicate that SHIP1 may exhibit a tumor-suppressive activity resembling that of PTEN by reducing the levels of PtdIns(3,4,5)P_3.

In light of these findings, small-molecule activators of SHIP1 have been developed as therapeutics for the treatment of hematopoietic cancers and show promising results by either inhibiting the cell growth and survival signals mediated by PI3K or enhancing the cytotoxic effects of other therapeutics (86,87). In contrast to those described for SHIP1, SHIP2 has not been identified as a tumor suppressor. Several reports suggest a positive role of SHIP2 in tumorigenesis. For example, increased expression of SHIP2 has been observed in multiple breast cancer cell lines and SHIP2 knockdown reduces EGF-mediated Akt activation and EGFR levels, whereas reexpression of exogenous SHIP2 increases EGFR protein levels (88,89). Furthermore, SHIP2 depletion inhibits cell proliferation in cultured cells and SHIP knockdown inhibits tumor growth and metastasis in animals (88). Examination of patient tissues shows that SHIP2 expression is upregulated in the majority of breast cancer tissues when compared with normal breast tissues (88,89). SHIP2 also plays a role in actin cytoskeleton remodeling, cell adhesion and lamellipodia formation during cell spreading on type I collagen, implicating its involvement in cancer metastasis. This function of SHIP2 is postulated to depend on its coordination with PI3K in maintaining a certain gradient of phosphoinositides (90,91). Thus far, there is no clear evidence linking the oncogenic activity of SHIP2 with its phosphatase activity on PtdIns(3,4,5)P_3. Future studies are needed to further investigate the mechanisms of action of SHIP2 in tumoregenesis.

Unlike the abovementioned PtdIns-regulatory enzymes that mainly modulate phosphorylation status of the inositol ring, Phosphoinositide-specific phospholipase C (PLC)

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are enzymes that hydrolyze PtdIns(4,5)P_2 on the glycerol side of the phosphodiester bond (92). This action converts PtdIns(4,5)P_2 into two second messengers, diacylglycerol (DAG) and inositol-1,4,5-trisphosphate (Ins(1,4,5)P_3), which in turn regulate their downstream effectors to control diverse cellular processes (92). Six isoforms have been identified for the mammalian phospholipase C, including PLC (β, γ, δ, ε, ζ, η) (93). It is speculated that the role of PLC enzymes in tumorigenesis is achieved through its modulation of local PtdIns(4,5)P_2 concentrations, by the action of the aforementioned second messengers or even by their scaffolding interactions (68).

A study of carcinoma cell directionality upon EGF stimulation demonstrates that PLCγ could be involved in triggering the early phases of cell migration (94). It is shown that PLCγ promotes the formation of cell protrusions for adhesion and determines the direction of cancer cell migration upon EGF stimulation in a cofilin-dependent manner (94). Cofilin is an actin-binding protein involved in actin polymerization and increases the number of barbed ends, which are important for initiation of cell migration (95). The action of cofilin is delicately regulated in normal cells; and one of the aspects of its regulation involves the phosphorylation and binding of PtdIns(4,5)P_2 and subsequent inactivation of cofilin. Activity of the cofilin plays a critical role in tumor progression as it determines the invasiveness of tumor cells (96). PLCγ is also shown to act upstream of cofilin in controlling cancer cell motility in ErbB2-stimulated cell migration (97). Together, these studies demonstrate that lipid molecules, such as PtdIns, are important in regulation of cell growth, survival, proliferation and cell migration, and dysregulation of these molecules may contribute to cancer development.

Conclusions and perspectives

Growing body of evidence suggests that dysregulation in cellular metabolism appears to play an important role in cancer development. It is clear that tumor cells tend to reprogram the cellular metabolism to provide sufficient energy and nutrition to fuel their excessive growth. More and more evidence indicate that alterations in lipid metabolism play important roles in oncogenic process. In this context, various metabolic enzymes involved in the aberrant lipid metabolism of cancer cells could be considered as targets for anticancer treatment. Our current understandings of aberrant metabolic changes occurring in cancer cells are still inadequate and further investigation in this area is needed for future development of interventional strategies for the prevention and treatment of cancer.

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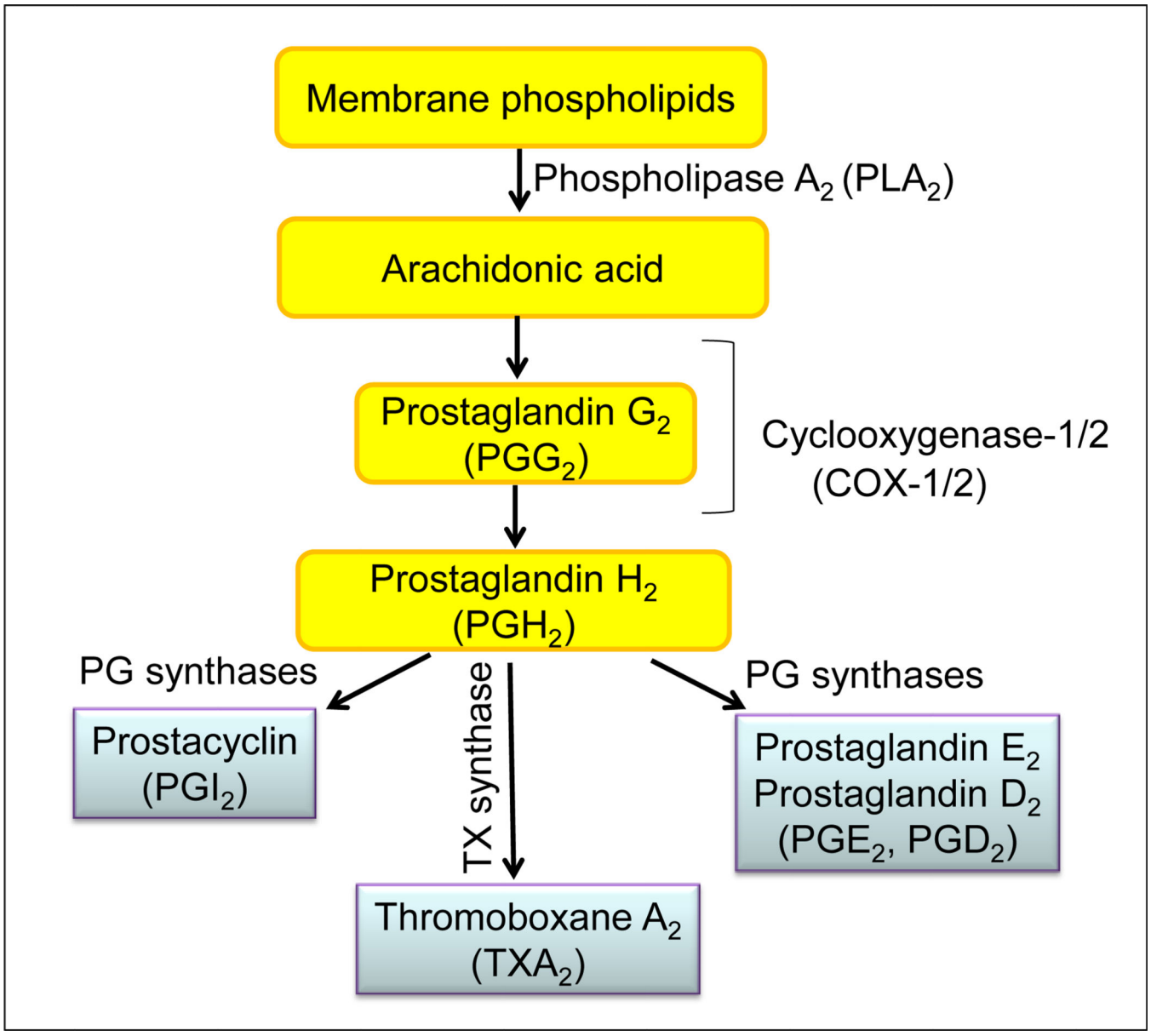


Figure 1.
Schematic of arachidonic acid metabolic cascade including enzymes and metabolic products involved in this signaling cascade.

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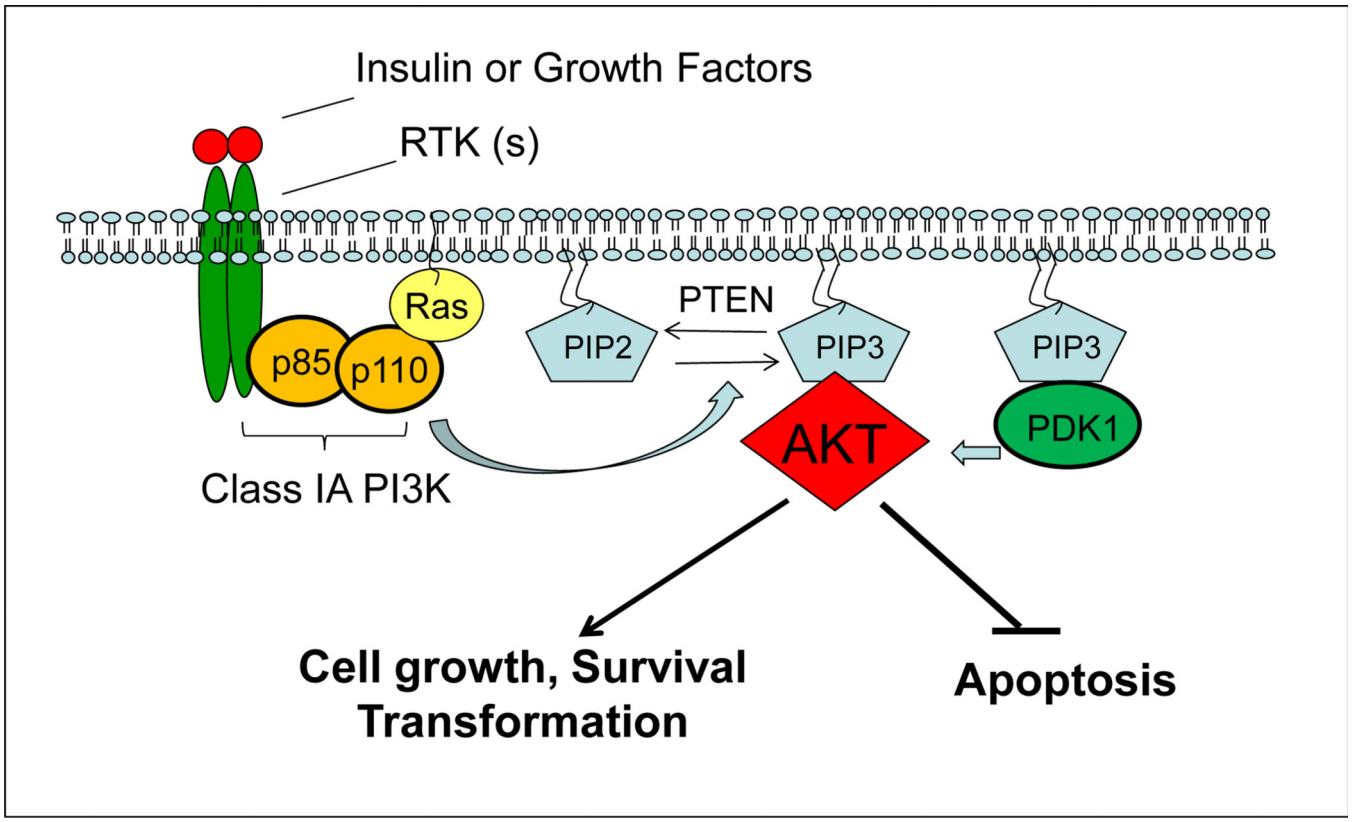


Figure 2.
Schematic of PI3-K-AKT signaling pathway.