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Metabolical Activities of Phosphoinositide 3-Kinase Pathway and its Connection to Non-Classical Actions of Thyroid Hormones

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Abstract

Mutations in biochemical pathways mediators are often found in cancer, and it is observed that via phosphoinositide 3-kinase (PI3K) is associated with tumor development and progression. This pathway is involved in several metabolic processes, including regulation of gene expression by non-classical actions of thyroid hormone. The objective of this paper is to provide a brief literature review of progress in information obtained on the PI3K on the last fifteen years. It was used the PubMed database, with the assistance of MeSh (Medical Subject Headings) and as descriptor "Phosphoinositide 3-Kinase" AND "Thyroid Hormones" to the selection of base articles, and later were included references found in those to complement the review. It stands between the information obtained from them that PI3Ks are lipid kinases that phosphorylate the 3-OH group of moderatory inositol molecules of cellular functions regulatory proteins. The PI3K pathway is involved in a wide variety of cellular processes, including intracellular traffic, cytoskeletal organization, apoptosis prevention, cell growth and transformation and it is important for various cell lineages differentiation. This pathway inhibitors promoted multiple possibilities of experiments, which led to the discovery of a relationship between PI3K pathway and other proteins such as protein kinase B (also known as AKT), mammalian target of rapamycin (mTOR) and oncoprotein RAS. The via was also associated with the expression of cancer related genes and hormones, including thyroid hormone. Thyroid hormones (TH) can work by other mechanisms besides the classical pathway, which occurs through receptors and responsive elements. The alternative to it is the non-classical or non-genomic pathway, in which TH activates PI3K, either by binding to TRβ or to αvβ3 integrin. This activation results in the transcription of specific genes, such as hypoxia inducing factor (HIF-1α) glucose transporter 1 (GLUT1), calcineurin inhibitor (ZAKI4α), among others.

Keywords: Cancer; Phosphoinositide 3-kinase; Protein kinase B; Non-genomic pathways

Introduction

Cancer is the number of over than 100 different types of diseases characterized by uncontrolled growth of abnormal cells with invasive potential. It is entailed by various conditions and has several factors that can either start it or promote it [1]. It is the leading cause of death in economically developed countries and the second leading cause in developing countries [2].

Its high incidence in the world is due to the urbanization and technological advancement process that drove the adoption of thrusters cancer habits and increased risk factors (such as smoking), also enabled the aging population that changed the world mortality profile. Formerly deaths were caused mainly by infectious diseases and currently there is a higher occurrence of chronic diseases [2-1].

According to estimatives, there were 14.1 million new cancer cases and a total of 8.2 million deaths from cancer worldwide in 2012 [1]. Cancer is currently the second leading cause of death in the United States, and is expected to surpass heart diseases as the leading cause of death. The overall estimate of 1,658,370 new cases is the equivalent of more than 4,500 new cancer diagnoses each day. In addition, about 60,290 cases of female breast carcinoma were expected to be diagnosed in 2015 [3].

Cancer detected in an early stage, has a more favorable condition for treatment and, consequently, its cure [1]. Gene mutations in biochemical pathways mediators are often found in cases of cancer, these changes generally involve receptors, G proteins, nuclear transcription factors and signaling kinases, including the phosphoinositide 3 -kinase (PI3K), whose biochemical pathway has been associated to tumor development and progression [4].

Materials and methods

PubMed database was utilized, with MeSh (Medical Subject Headings) tool, to select articles with two descriptors: Phosphoinositide 3-Kinase AND Thyroid Hormones.

Articles were added to the initial search to agregate ideas between different studies. The cutoff applied was to use articles published after the year 2000. To analyze those articles, data were separated into subsections and emphasized those articles with higher citation frequency.

Characterization and PI3K protein action

PI3K comprises a family of lipid kinases that phosphorylate a 3-OH group of inositol molecules acting as moderators of proteins that regulates many cell functions [5]. They are heterodimeric enzymes composed of a 110-kDa catalytic subunit and a 85-kDa catalytic subunit [6].

The pathway activated with PI3K enzymes can be initiated or inactivated by mutations. Most common examples of mutational activation occur in cancer [5]. The PI3K pathway is involved in a wide variety of cellular processes including intracellular modifications, cytoskeletal organization, apoptosis prevention, growth and cell differentiation; furthermore, they play a relevant role in differentiating several cell lines [7]. Other functions could be related to immunity, cardiac function and metabolism [5].

PI3K enzymes catalyze modifications of phosphatidylinositol 4,5-biphosphate (PIP2) to phosphatidylinositol 3,4,5-triphosphate (PIP3). PIP3 initiates a phosphorylation cascade of proteins and G-protein activation, thus attracting several effectors to the membrane. In most tissues, PI3K is regulated primary by tyrosine kinase receptors and integrin receptors [8].

The PI3K family consists of fifteen proteins sharing a sequence in their kinase domains but have different specificities and actions. They are divided into three important classes according to their structures and biochemical characteristics. There are four class I PI3K enzymes that synthetize PIP3 and are the best characterized class because they are responsible for a large majority part of the known functions of PI3K, and link the activity of this pathway with tyrosine kinase receptors and G-protein couple receptors [9,5].

The class II PI3Ks (C-terminal C2 domain, PI3K-C2) and class III kinases are associated with vacuolar protein sorting 34 (Vps34) specific to phosphatidylinositol. The protein activity of these two classes still remains unknown [9]. In mammals, there are eight PI3K isoforms, four of class I, three of class II and one of Class III. In plants and yeasts there is only one PI3K protein of class III while in model species such as Caenorhabditis elegans and Drosophila melanogaster there is only one isoform of each of these three classes [5].

PI3K chemical inhibitors

In the years 1993 and 1994 it was discovered that Wortmannin, a sterol-like fungal metabolite with anti-inflammatory action described for the first time at 1974, is an inhibitor of PI3K pathways, besides being permeable at a phospholipid membrane [5]. The action mechanism of Wortmannin involves a covalent attack of Lys833 at an ATP binding site of PI3K, at an electrolytic site of non-mutated shape [9].

At the same time, the first synthetic inhibitor of PI3K pathway, LY294002, was produced by Eli Lilly company researchers and distributed among the scientific community. Then, it was confirmed that LY294002, as well as Wortmannin, binds to the ATP ligand site. Both present some limitations, Wortmannin being a reactive electrolyte and LY294002 having micromole affinity [5,9].

These findings played an essential role in recent elucidation of PI3K pathways and promoted multiple experimental possibilities, by creating availability and reliability for a great number of researchers. The sum of scientific results culminated in the association of various cellular responses to the PI3K signaling pathway, including mitogenesis, glucose uptake, chemotaxis, actin rearrangement and membrane ruffling. These findings elucidated the role of PI3K pathways in many biological processes [5]. Otherwise, the low selectivity of LY294002 and Wortmannin between PI3K isoforms hampers the synthesis of selective inhibitors for all PI3K pathways [9].

The first selective inhibitor for the public domain was IC87114, made available in 2003. It is as inhibitor for competition with the ATP ligand site selective for the isoform p110δ. This finding was followed by development of inhibitors to isoforms p110γ, and p110β. In 2005, a PI3K inhibitor was administered for the first time in humans, denominated TG100-115 [5,9].

PI3K and Cancer

Several studies try to elucidate the way that biochemical PI3K pathway associates with cancer. In the year 1994 it was verified that oncoprotein RAS is an activator of PI3K pathway associated with some growth factors that lead to growth and cell proliferation [5]. The P110α isoform of PI3K is frequently mutated in solid tumors, and some analyses suggest that P110α is a kinase most commonly altered in the human genome, considering that mutations in its sequence occur in a cumulative frequency of 15% in all cancer cases [9].

In 1995 it was demonstrated that PI3K regulates apoptosis. Indeed it was related to the pleckstrin homology (PH) domain, a strongly conserved moderator, based in 120 amino acids, commonly found at class I PI3K effector, leading to identification of similar proteins by correspondence to this domain [5].

Another important moderator is a phosphatase and tensin homolog (PTEN), a tumor suppressor gene with loos of function or just mutated in many varieties of cancer, including prostate cancer [6]. In 1998 PTEN was found as a negative PI3K regulator with inhibitory function due to its phosphoinositol-3-phosphatase activity that effectively stops PI3K cascade by dephosphorilation of second messengers PIP3 and PIP2 [10].

Since PTEN acts to diminish PI3K effects, a loss of function leads to a hyperactivity of the PI3K cascade, thus promoting abnormalities in metabolic cell activities such as migration, survival and cell growth [10].

Indeed, the PI3K pathway was related to an increase of vascular epidermal growth factor (*VEGF*) gene expression, with higher levels found in urine of patients with prostate cancer, suggesting that VEGF has a role in prostate cancer in a manner that indirectly associated with PI3K [6].

Other proteins involved in the PI3K via

Protein kinase B (PKB), also named AKT, participates in signal transduction of PI3K to regulate cell survival and intermediate metabolism. Many proto-oncogenes product moderate PI3K activation and, as a consequence, PI3K was identified in many altered cell functions in carcinomas [11].

The PKB activation encompasses many related complex events in other proteins. First, the PIP3 and PIP2 second messengers, generated by PI3K, attract PKB to the plasm membrane by affinity to the PH domain. Once close to the membrane, at least two PKB products are rapidly phosphorylated: Threonine 308 (Thr308) and Serine 473 (Ser473). The Thr308 phosphorylation promotes change in its conformation that allows access to substrates that bind to T-loop. In the case of PKB, this reaction is catalyzed by phosphoinositide-dependent kinase 1 (PDK1) [11]. When PKB is activated it transmits signs of growth factor survival and inactivates apoptotic pathways [6].

The name of the protein mammalian target of rapamycin (mTOR) originates from its interfering in immunosuppressing rapamycin. It controls protein synthesis and cell growth through integration with some nutrients and by growth factors signaling [9,10].

This protein is a related member of the phosphatidylinositol 3-kinase family, that includes in addition to mTOR, kinases important to the control of genomic integrity such as ataxia telangiectasia mutated (ATM), ATM and Rad3 (ATR) related kinases, and DNA-dependent protein kinase (DNA-PK) [9].

The catalytic domain of mTOR is similar to PI3K enzymes. The greatest degree of equivalence is in the C-terminal domain that is highly homologous to PI3K phosphotransferase domain [12]. The presence of catalytic domains related to PI3K corroborates the hypothesis that target proteins of rapamycin act as lipids or kinases in vivo. Research studies demonstrate mTOR is involved in PI3K and PKB pathways in cells stimulated by growth factors [10].

Non-classic thyroid hormone pathway

Thyroid hormone (TH) stimulates lipolysis and lipogenesis, besides being involved in regulation of lipids and carbohydrates in liver, skeletal muscle and cardiac tissues [7]. Thyroxin (T4), the predominant TH, and 3,5,3-Triiodothyronine (T3), the most potent TH, regulate growth, metabolism, development [13] and maturation of many organs and tissues during the neonatal and fetal stages [14].

Thyroid hormone receptors (THR) are proteins that originate from thyroid hormone receptor alpha (THRA) and beta (THRB). These receptors act in some genes according to sequences denominated hormone response elements (HRE) located in the promoter region of target genes [7].

On the other hand, TH may act through alternative mechanisms besides this classic pathway, also named non-classic or non-genomic pathway, because it initiates on a plasma membrane or in cytoplasm where TH can activate PI3K, either by binding to thyroid hormone receptor beta or integrin αvβ3, or even by signaling of a mitogen-activated protein kinase (MAPK) cascade through integrin αvβ3 [15].

The cytoplasmic activation of PI3K pathway by TH results in gene-specific transcription, such as Hypoxia-Inducible Factor 1 (HIF-1α), glucose transporter 1 (GLUT1) and calcineurin inhibitor (ZAKI-4α) [16].

Oliveira et al. demonstrate that T3 increases leptin gene expression with a short period of time, and suppresses by PI3K inhibitor LY294002 with no toxicity, indicating a non-genomic action of TH by PI3K pathway.

T3 is also capable of activating the PI3K pathway with a phosphorylation cascade of AKT, mTOR and p70S6K. This signaling effect stimulates *Na/K-ATPase* and *KCNH2* gene activity, which can be diminished by the use of LY294002 and Wortmannin [17,18].

The PI3K activation by TRβ/T3 and subsequent phosphorylation of other kinases such as AKT and P70S6K lead to gene induction and transcriptional regulation. It was found that an induction of this non-classical pathway provokes more intense cell responses, possibly by TH signaling with amplification of a kinase-to-kinase mechanism, before reaching the genomic level [19].

Conclusion

PI3K comprises a family of lipid kinases that phosphorylate a 3-OH group of inositol molecules acting as moderators of proteins that regulates many cell functions. The PI3K pathway is involved in a wide variety of cellular processes.

Inhibitors of this pathway promoted multiple experimental possibilities, that played an essential role in the elucidation of PI3K relation to other proteins cascades, like PKB (also known as AKT), mTOR (mammalian target of rapamycin) and oncoprotein RAS. The pathway was also associated to cancer-related gene expression and hormones, among them thyroid hormones.

Thyroid hormones can work by other mechanisms besides the classical pathway, which occurs through receptors and responsive elements. The alternative to it is the non-classical or non-genomic pathway, in which the hormone activates PI3K, either by binding to TRβ or to αvβ3 integrin.

Within cancer researches the PI3K pathway is extremely important por being related to most of malignant neoplasms. It is primordial to elucidate completely the biochemical pathway in order to develop mechanisms of cancer control.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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