Relationship between PI3K Mutation and Sodium-Iodide Symporter in Anaplastic Thyroid Carcinoma

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Abstract
The sodium-iodide symporter is a transmembrane protein that has important role in radio-iodide therapy in various cancers such as anaplastic thyroid carcinoma. Anaplastic thyroid carcinoma is a rare undifferentiated thyroid tumor, but highly aggressive and lethal malignancy. Usually it is resistant to radio-iodide therapy and a cause of this appearance knows through dysfunction of the sodium-iodide symporter. Some genomic mutations, like PI3K gene mutations, can affect on sodium-iodide symporter functions. This review article explains briefly about PI3K signaling pathway and survey its gene mutations in carcinomas especially in anaplastic thyroid carcinoma and its influence on sodium-iodide symporter and iodide uptake.

Keywords: PI3K Mutation; Sodium-Iodide Symporter; Anaplastic Thyroid Cancer

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Introduction

In mammalian cells, several inositol lipid kinases were discovered. Their functions are phosphorylation of hydroxyls on the inositol head group of phosphatidylinositol. Phosphatidylinositol 3-kinases (PI3Ks) are a family of these enzymes [1]. Various receptor protein tyrosine kinases (PTKs) and non-receptor protein tyrosine kinases (nPTKs) can be activated PI3K, and therefore phosphorylation of D3 hydroxyl of phosphoinositide and production of phosphatidylinositol-3-phosphates can be occur [2, 3]. This review article explains briefly about PI3K signaling pathway and survey its gene mutations in carcinomas especially in anaplastic thyroid carcinoma and its outcomes on sodium-iodide symporter and iodide uptake.

The PI3K signaling pathway

Phosphatidylinositol 3-kinases (PI3Ks) have been arranged into three classes [4, 5]. Information about components of these classes summarized in Table 1.

Table 1 The regulatory and catalytic subunits of the PtdIns 3-kinase family. (Information for this figure was taken from ref: 4, 5, 10).

Function of the class Ia, Ib PtdIns 3-kinases, are phosphorylation of the PtdIns 4,5 P2 and form the PtdIns 3,4,5 P3 as a lipid second messenger. It has an important role in a considerable intracellular signaling network such as: proliferation, growth, survival, embryo implantation and apoptosis [6-8]. Also, it linked to essential cellular processes of tumorigenesis, including cell cycle progression, adhesion, mobility, expansion, angiogenesis, glucose homeostasis, control of cell and organ size[9]. PtdIns 3,4,5 P3 signals which localized to the inner leaflet of the plasma membrane, are highly dynamic and can increase 50-fold above basal levels
within 10 seconds and can be preserved or transient [10].

In 2012, Michael J. Berridge described the PtdIns 3-kinase signaling pathway [5]. In this signaling pathway, the lipid PtdIns 4,5 P2 as a precursor, is phosphorylated on the 3-position by Class IA, IB PtdIns 3-kinases (PtdIns 3-Ks) to produce the lipid second messenger PtdIns 3,4,5 P3 via protein tyrosine kinases (PTKs) receptors (Fig. 1). These enzymes are compel heterodimers for accurate function. Therefore a regulatory subunit firmly bound to a catalytic subunit and form the heterodimeric structure. The regulatory subunits act as typical adaptor proteins and control the subcellular position, combine partners and action of the catalytic subunits (See Table 1). For example, p85 (regulatory subunit) tightly attached to p110 (catalytic subunits), and then add to the phosphorylated tyrosine residues on the cytoplasmic domains of activated growth factor receptors [11].

In another pathway, G protein-coupled receptors (GPCRs) activate the class IB enzymes (p110γ) and translocate to the membrane by binding to the Gβγ subunit (Fig. 2). At the time of transport into the proximity of the membrane, these PtdIns 3-kinases form the 3-phosphorylated lipid messenger PtdIns 3,4,5 P3, to regulate several processes. For example, it binds to other signaling components such as Btk and PLCγ. Also, it stimulates phosphoinositide-dependent kinase 1/2 (PDK1/2) and protein kinase B (PKB), which activate a large number of downstream targets such as: protein synthesis, cell survival, glycosgen metabolism and gene transcription. Also, it stimulates both cytoskeletal rearrangement and superoxide radical (O2−) formation via activation of Rac, Rho and Cdc42 as monomeric G proteins [12, 13].

**Figure 1** Activation of the PtdIns 3-kinase signaling pathway via protein tyrosine kinases (PTKs) receptors (reviewed by ref. 5). Abreviatins: PTKRs: Protein Tyrosine kinases Receptors, PDK ½: Phosphoinositide-Dependent kinase 1, PKB: Protein kinase B, Btk: Bruton’s tyrosine kinase, Itk: Inducible T cell kinase, PLCγ: Phospho Lipase Cγ, DAG: Di Acyl Glycerol, S6K1: Ribosomal S6 protein kinase 1, TOR: Target of Rapamycin, GSK3: Glycogen Synthase kinase-3, FOXO: Fork head box O.
Figure 2 Activation of the PtdIns 3-kinase signaling pathway via G protein-coupled receptors (GPCRs) (reviewed by ref.5). Abbreviations: GPCRs: G protein-coupled receptors, PDK ½: Phosphoinositide-Dependent kinase 1, PKB: Protein kinase B, Btk: Bruton’s tyrosine kinase, Itk: Inducible T cell kinase, PLCγ: Phospho Lipase Cγ, DAG: Di Acyl Glycerol, S6K1: Ribosomal S6 protein kinase 1, TOR: Target of Rapamycin, GSK3: Glycogen Synthase kinase-3, FOXO: Fork head box O.

In order to terminate these full activation, three major phosphatases such as: SHIP2, PTEN (broadly expressed) and SHIP (haemopoietic cells expressed) as tumor suppressors, removing a phosphate group from the inositol ring of PIP3 and degrade the PtdIns 3, 4, 5 P3 [14]. In addition, regulation of PI3K can be take place by its intrinsic serine kinase activity [15] or adaptor protein [16]. Altogether, impairing of each these regulators and phosphatases, which are the beginners of many cancers, have been widely investigated [17, 18].

PI3K mutation and carcinomas

For the first time in avian sarcoma virus 16, an oncogenic form of PI3K (v-p3k) was discovered. It can be transformed cells and induce tumors after injecting into chicken [19]. In this manner, V-p3k, can increase the 3’phosphoinositides and transmits the oncogenic and angiogenic signals through its downstream effectors [20], like phosphorylation and activation of the serine-threonine protein kinase AKT and eventually resulting in stimulation of cell growth and survival [21]. It has been reported that PI3K is necessary for the induction of cyclin D1 expression [22], cellular transformation and can be induced by several viral oncoproteins such as Src [23].

Totally, PI3K pathway is an important intracellular mediator in cell proliferation, growth, survival and...
tumorigenesis and frequently activated in cancer cells [24]. For example, lung cancer [25], melanoma [26], ovarian cancer [27], glioblastomas [28], breast cancer [29], large B-cell lymphoma [30], gastro-intestinal cancers [31], prostate cancer [32], colorectal cancer [33], anaplastic thyroid carcinoma [34] and other thyroid carcinomas [35].

As later described, two catalytic and regulatory subunits, including p110α (a 110-kDa) which expressed by PIK3CA gene, and p85α (an 85-kDa) which expressed by PIK3R1 gene, are components of heterodimeric PI3K enzyme, respectively [36]. PIK3CA gene is located on chromosome 3q26.3 and composed of 20 exons. It codes a 124 kDa protein with 1068 amino acids [37]. Related studies have been shown that PI3Ks mutations lead to high frequency of PIK3CA somatic mutations which majority occur between exon 9 (helical domain), exon 20 (kinase domain) and p85 binding domains (exon 1 and 2) that enhancing Akt phosphorylation in human cancers [38] including ovarian cancer [39], lung cancer [40], pituitary tumors [41], cervical cancer [42], non-small cell lung cancer [43], squamous cell carcinomas [44], B-cell lymphoma [45], nasopharyngeal carcinoma [46], gastric carcinoma [47], colorectal cancer [48], breast cancer [49] and thyroid carcinoma [50] especially anaplastic thyroid carcinoma [51].

Anaplastic thyroid carcinoma

Anaplastic thyroid carcinoma (ATC) is a rare undifferentiated thyroid tumor, but highly aggressive and lethal malignancy [52]. In various studies signaling pathways such as: Wnt/beta-catenin [53], cytokine signaling 3 [54], phosphatidylinositol 3- kinase/Akt pathway [55], mitogen-activated protein kinase pathway [56] and also mutations of several genes for example: transcription elongation factor A (SII)-like 4 (TCEAL4) [57], transmembrane protein 34 (TMEM34) [58], Sphingosine 1-phosphate receptor [59], S-phase kinase-associated protein 2 (Skp2) [60], insulin like growth factor-I receptor [61], p53 [62], RET oncogene [63], haemoglobin beta (HBB) gene [64], mismatch repair genes [65], HOX genes [66], miR-17-92 cluster [67], acidic coiled-coil 3 and Aurora-A kinase [68], hepatocyte nuclear factor-1alpha(HNF-1α) [69], major histocompatibility complex class I-related chains A and B (MICA/B) [70] and peroxisomal proliferator-activated receptor-gamma [71] were examined.

With conventional therapies such as surgical resection and radio-iodine treatment can be controlled this carcinoma. However, some patients are resistant to these cure [72]. Findings from several studies have been shown that, expression sodium-iodide symporter gene and proper function of its protein play an important role in thyroid hormone biosynthesis and especially radio-iodine treatment in thyroid carcinomas [73].

Sodium-iodide symporter

The human sodium-iodide symporter (hNIS) gene located on chromosome 19p13.2 [74] and contains 15 exons that are interfering with 14 introns [75]. An open reading frame from nucleotides 348-2276 of the hNIS gene encodes an integral plasma membrane glycoprotein with 643 amino acids (68.7 kDa) and 13 putative transmembrane domains with three N-linked glycosylations (Fig. 3). Glycosylation is necessary, for NIS protein plasma membrane localization, stabilization and folding [76, 77].
Figure 3 Schematic model for NIS protein. An open reading frame from nucleotides 348-2276 of the hNIS gene encodes an integral plasma membrane glycoprotein with 643 amino acids (68.7 kDa) and 13 putative transmembrane domains with three N-linked glycosylation. Glycosylation is necessary for NIS protein plasma membrane localization, stabilization and folding (reviewed by ref. 76, 77).

Sodium-iodide symporter is expressed at the highest level in the thyroid cells [78] and several other tissues like salivary gland [79], gastric mucosa [80], endometrial mucosa [81], placental tissue [82], lactating mammary gland [83,84], stomach [85], intestine [86], colon [87] and ciliary body of the eye [88]. In the thyroid gland, the important function of NIS protein as the molecular basis of iodide accumulation, is actively uptakes of iodide with an electrogenic stoichiometry of two Na$^+$ per one I$^-$, from the bloodstream for incorporation into thyroid hormones (Fig. 4). However it can be transports other anions like: I$^-$ ≥ SeCN$^-$ > SCN$^-$ > ClO$_3^-$ > NO$_3^-$, with proportionate ostensible affinities, respectively [89].

Figure 4 Schematic model for iodide accumulation. In the thyroid gland, the important function of NIS protein as the molecular basis of iodide accumulation, is actively uptakes of iodide with an electrogenic stoichiometry of two Na$^+$ per one I$^-$, from the bloodstream for incorporation into thyroid hormones (reviewed by ref. 107).
Several transcription factors such as: AP2 and Sp1 have an important role in regulation of NIS expression [90]. Maturation and cell-surface trafficking of NIS protein can be influenced by various mutations like: G543E mutation [91], a δ-amino group at position 124 (R124H) mutation [92], angiotensin I converting enzyme (Gln1069Arg) mutation [93], V59E missense mutation [94], G395R mutation [95] and Q267E mutation [96].

Various diseases, for instance congenital hypothyroidism, is due to different mutations, missense and disturbance of NIS function [97, 98]. In addition, iodide transport in thyrocytes was mediated by distinctive substances such as thyrotropin [99], cyclic AMP [100] and insulin growth factor 1[101]. Also sodium-iodide symporter can be inhibited by TNFα, ceramide, TGFβ1, aging [102], iodide [103,104] and natural competitive inhibitor such as: perchlorate (ClO4⁻) and thiocyanate (SCN⁻) [105,106]. In the best of our knowledge about functional characterization, topology, biochemical characterization, family, mechanism and medical impact, post-translational regulation of NIS and its expression and radio-iodide uptake in extra thyroidal tumors have been described in several review articles [76, 77,107,108]. In a comprehensive manner, focus on NIS gene and its protein regulation [109] or its gene transfer [110] can be a good plan of action for access to some cancer treatments; for example: breast cancer [111], prostate cancer [112], pulmonary tumors [113], glioma [114], lung cancer [115], liver cancer [116] and thyroid cancer [117].

**PI3K mutation and Sodium-iodide symporter**

In previous studies, involvement of PI3K signal transduction pathway in sodium-iodide symporter (NIS) were reported [118]. The PI3K signaling pathway can be regulated NIS glycosylation and plasma membrane localization [119]. In other word, upregulation of PI3K can be spoiled glycosylation of sodium-iodide symporter protein. Therfore increases the non-glycosylated NIS protein and resulted in lacking cell surface trafficking, which necessary for iodide uptake ability [120]. In several studies, re-expression of NIS gene and induction of iodide transport with some elements were examined. For example, all-trans retinoic acid mediates sodium-iodide symporter induction and iodide transport in MCF-7 breast cancer cells [121] and human thyroid cancer cell lines [122] or LY294002 as a phosphoinositide-3-kinase reversible inhibitor can be an increase NIS expression and function in thyrocytes [123] and can be sensitize tumor cells to radiation[124]. Also LY294002 made of lead compound for developing more impressive and endurable reagents for cancer treatment [125]. In addition, it can induce expression of the cyclin-dependent kinase inhibitor p27KIP1 and arrest the cells in G1 phase [126]. However, effect of other substances on sodium-iodide symporter function, such as histone acetylation [127], MEK signaling [128] and a PARP inhibitor [129] were investigated .

**Conclusion**

Always, management, treatment and eradication of the diseases, especially cancers are great wishes of man. Hence, in order to receive to this major goal, he/she thinks, investigate and examine. Perhaps knowing answer of this question, what is cause of cancer onset? is difficult. But severe endeavor of investigators and scientists to arrival ansewer of this question, constantly are benefit. Signaling pathway study like PI3K pathway, and increase knowledge of its components are consequence of these efforts. Proliferation, growth, survival, apoptosis, cell cycle progression, adhesion, mobility, expansion, angiogenesis and glucose homeostasis are some examples of PI3K pathway’s role in the considerable intracellular signaling network. Review of related studies shown that mutation or dysfunction of each component of this pathway can be cause of cancer type’s onset similar to thyroid cancers particularly anaplastic thyroid carcinoma. Although, this malignancy is rare but it is aggressive and resistant to conventional chemo and radio-iodide therapy. Usage target therapy and inhibitors including PI3K inhibitor, or gene transfer specifically NIS gene transfer in a gene therapy manner, can be helpful for these
patients and do hope to increase survival time.

References


80. Altorjay A, Dohán O, Szilágyi A, Paroder M, Wapnir IL, Carrasco N. Expression of the Na\(^{+}\)/I symporter (NIS) is markedly decreased or absent in gastric cancer and intestinal metaplastic mucosa of Barrett esophagus. *BMC Cancer*. 2007, 7:5-14


