

The Tyrosine Phosphatase SHP2: A Key Molecule Linked both Type 2 Diabetes and Cancers?

Hu Luo, Chunlan Tang, Xuemei Yang and Xiangdong Zhou*

Department of Respiratory Medicine, the First Affiliated Hospital of Third Military Medical University, Chongqing 400038, P.R. China

Abstract

Emerging epidemiological evidence suggests that T2DM may be associated with an increased risk of certain cancers. However, the underlying molecular mechanism linked these two diseases remains largely unknown. SHP2, a non-receptor protein tyrosine phosphatase encoded by pro-oncogene PTPN11, has been reported involved in insulin resistance through PI3K/Akt/mTOR signaling and has also been considered to play a vital role in carcinogenesis via Ras/Erk pathways. Based on our previous studies, we hypothesize that SHP2 may present a key molecule linked both T2DM and cancers through both Ras/Erk and PI3K/AKT/mTOR signaling pathways. We believe that the comprehensive and detailed investigation of SHP2 may provide a new insight into the underlying molecular mechanism linked both T2DM and cancers, thereby facilitating the process to discover novel therapeutic targets to prevent and treat cancers.

Keywords: Type 2 Diabetes Mellitus; Cancer; Breast oncogenesis

Background

Type 2 Diabetes Mellitus (T2DM) is a common disorder, which is characterized by high blood glucose concentration in the context of insulin resistance and/or relative insulin deficiency. Increasing epidemiological evidence suggests that T2DM may be associated with an increased risk of certain cancers including pancreatic [1], hepatic [2], lung [3], colorectal [4], breast [5], bladder [6], gastric [7] and endometrial [8] cancers. These results suggest that the comprehensive investigation of the mechanisms responsible for DM to facilitate occurrence of cancer may provide us new potential therapeutic targets. However, the current studies have been mainly focused on the relationship between DM and cancers, and the molecular mechanism linked these two diseases remains largely unknown.

Abnormal protein tyrosine phosphorylation underlies various diseases of deregulated growth and differentiation, including cancer [9-11]. Src-homology 2 domain-containing phosphatase (SHP2) is a non-receptor protein tyrosine phosphatase encoded by the first identified proto-oncogene PTPN11. Genetic and biochemical studies in recent years have suggested that SHP2 plays a broad role not only in cell proliferation [12], survival [13], and differentiation [14], but also in development [15,16] and tumorigenesis [17-19] of malignancies via Ras/Erk [20], PI3K/Akt [21] and other signaling pathways. In accordance to a recent study [18], our previous studies [22-24] have demonstrated that SHP2 plays a crucial role in breast oncogenesis. Recently, we have also found for the first time that SHP2 is widely expressed by lung cancer cells, and that the high expression of SHP2 may promote the invasion and metastasis of NSCLC through angiogenesis and the lymphatic system [25,26]. As T2DM has also been considered as a risk factor of many kinds of cancers, we begin to speculate whether SHP2 plays a role in the pathogenesis of T2DM? If so, should SHP2 be a potential target linked both T2DM and cancers?

Under this speculation, we have performed a systematic search on the literature data base. It is generally accepted that insulin resistance is due to defective insulin signaling and thus results in the progression of T2DM, but details remain largely unknown. In recent years, several clinical studies [27-30] have declared that metformin, which is considered as a first-line treatment modality for T2DM, reduces incidence of neoplastic diseases in T2DM patients, as compared to other anti-diabetic agents. Studies [31,32] have showed that metformin inhibits the mammalian Target Of Rapamycin Complex 1 (mTORC1), a molecule downstream of PI3K/Akt, resulting in decreased cancer cell

proliferation. These new encouraging experimental data support that the crucial involvement of PI3K/Akt/mTOR signaling pathway in the insulin resistance and progression of diabetes. Besides, Bifulco [33] showed that glucose regulated insulin signaling via the IRS1/MAPK pathway and mitogenesis by modulating the activity and subcellular localization of the SHP2 tyrosine phosphatase. Using a mouse model, Princen found that insulin resistance and impaired glucose uptake existed in SHP2-deficient mice [34]. Further studies [35-39] suggest that SHP2 recruited by Insulin Receptor Substrate-1 (IRS-1), acts as a signal coordinator in pancreatic beta-cells and controlled insulin biosynthesis to maintain glucose homeostasis through Akt and Erk pathways. These abovementioned results strongly suggest that SHP2, recruited by IRS-1, may present a key molecule involved in both T2DM and cancers via both Ras/Erk and PI3K/Akt/mTOR signaling pathways.

The Hypothesis

Epidemiological evidence suggests that T2DM is a risk factor of lung cancer. Studies focused on the common signal pathway shared by both T2DM and cancers may provide us new potential therapeutic targets. SHP2 plays a vital role in both insulin resistance and cancers through PI3K/Akt/mTOR and Ras/Erk pathways respectively. We speculate that SHP2 may present a key target linked both T2DM and cancers: on one hand, the high expression or activation of SHP2 results in excessive tyrosine dephosphorylation on IRS-1/2, which is a key part of insulin resistance. On the other hand, overactivation of SHP2 can sequentially activate PI3K/Akt/mTOR and Ras/Erk pathways, while both pathways are generally accepted to be closely associated with tumorigenesis and progression of cancers. The role of SHP2 involved in T2DM and cancers are schematically described in Figure 1. Further investigation of SHP2 may provide a new insight into the underlying molecular mechanism linked both T2DM and cancers, thus help

*Corresponding author: Zhou Xiangdong, Department of Respiratory Medicine, The First Affiliated Hospital of Third Military Medical University, No.30 in Gao Tanyan Street, Sha Pingba District, Chongqing, P.R. China, Tel: +86-023-687-556-79; E-mail: xiangdongzhou@126.com

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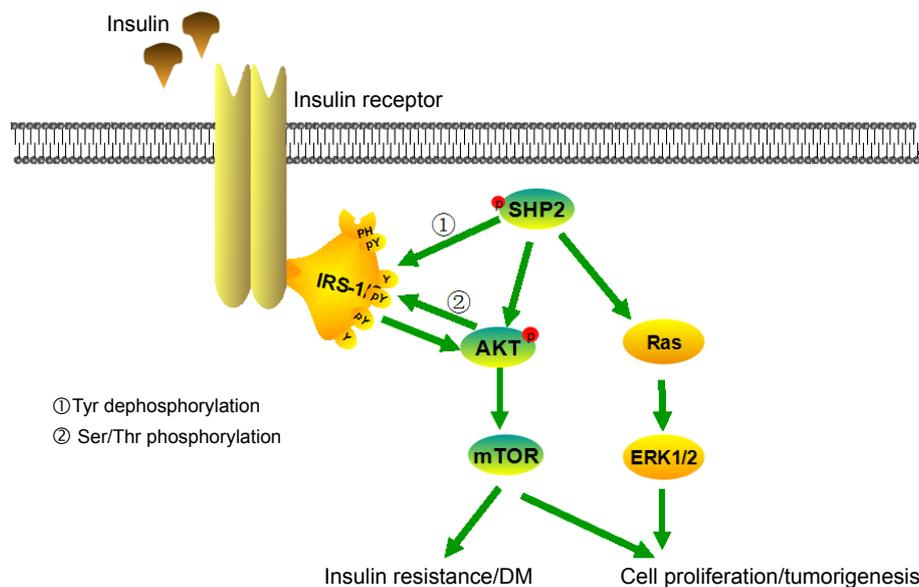


Figure 1: The role of SHP2 involved in T2DM and cancers are schematically.

to discover new potential therapeutic targets in the prevention and treatment of cancers.

Evaluation of the Hypothesis

The role of PI3K/Akt/mTOR signaling pathway in T2DM

It has been generally accepted that the understanding of insulin resistance is the key to the prevention and treatment of T2DM. However, the mechanism underlying insulin resistance is not entirely clear. Large number of studies in recent years has established the central role of PI3K/Akt/mTOR signaling in numerous cellular processes including metabolism, growth, survival, and motility. As a ser/thr protein kinase, Akt could enhance the phosphorylation of IRS-1/2 and hamper the insulin-induced signal transduction. Um et al. [40] reported that mTOR-raptor complex, also called mammalian Target of Rapamycin Complex 1 (mTORC1), and its downstream target S6 Kinase 1 (S6K1) mediate nutrient-induced insulin resistance by down regulating insulin receptor substrate proteins with subsequent reduction in Akt phosphorylation. Fraenke et al. [41] and Xie et al. [42] also demonstrated that mTOR played a critical role in beta-cell adaptation to hyperglycemia. Chronic inhibition of mTOR with rapamycin augments insulin resistance, beta cell dysfunction, and death. These data strongly suggest that aberrant activation PI3K/AKT/mTOR pathway plays a vital role in pathogenesis and progression of T2DM [43,44].

The role of Ras/Erk signaling pathway in cancers

The Ras family of GTPases (HRas, NRas and KRas) comprises of proteins that are highly conserved across species and play key roles in numerous basic cellular functions, including control of proliferation, differentiation, and apoptosis. Under normal physiological conditions, Ras/Erk activation is transient. However, excessive or sustained activation of Ras/Erk signaling pathway has been found in patients with a wide variety of cancers [45-47], suggesting the significant role of the Ras/Erk signaling pathway in cancer initiation and promotion. So far, several different mechanisms have been explored to account for the abnormal activation of Ras signaling pathways in tumorigenesis, including mutations in Ras, loss of GAP proteins, overexpression of

RTKs (such as EGFR), and also abnormal phosphorylation of tyrosine phosphatase upstream of Ras/Erk [48]. Besides, there is a cross-talk and complex feedback loop between Ras/Erk and PI3K/Akt/mTOR pathways [49,50], thus combined inhibition of these two pathways has been suggested as a therapeutic strategy in treatment of cancers [51,52].

Shp2 is upstream of Ras and PI3K pathways and plays a important role in both insulin resistance and carcinogenesis

SHP2, a ubiquitous tyrosine phosphatase, is thought to be inactive by forming intramolecular folding without stimulations, whereas it becomes active when the N-terminal SH2 domains bind to phosphorylated molecules, including Grb2-associated binder (Gab), IRS-1 and etc., by forming an open conformation. Shp2 was reported to be a modulator that prolongs the activation of Erk [18,20,22], which suggests its role in carcinogenesis and development of several kinds of malignancies. Furthermore, Lima et al. [36] reported that insulin-induced IRS-1/SHP2 complex was associated with insulin resistance and played a role in the control of AKT phosphorylation in an animal model. Princen et al. [34] demonstrated that SHP2 deficiency led to up regulation of PI3K/Akt pathways and insulin resistance in cardiomyocytes. Zhang et al. [39] also reported that SHP2 acted as a signal coordinator in beta-cells, orchestrating multiple pathways including PI3K/Akt and Ras/Erk to control insulin biosynthesis to maintain glucose homeostasis. Besides, a recent review focusing on insulin resistance also highlighted the role and therapeutic potential of SHP2 in the control of insulin action and glucose metabolism [53].

Taken together, these abovementioned results strongly prompt us to consider that: on one hand, SHP2 is involved in carcinogenesis and development of cancers mainly through Ras/Erk pathway. On the other hand, SHP2 also plays a significant role in insulin resistance of T2DM via PI3K/Akt/mTOR pathway. Importantly, Ras/Erk pathway can have a cross-talk with PI3K/Akt/mTOR one. Based on these findings, we conclude that SHP2 might present a key molecule linked both T2DM and cancers.

To verify our hypothesis, the following issues will be carefully and comprehensively addressed for some certain cancer such as lung cancer:

- 1) Animal model (mouse) for T2DM should be firstly established.
- 2) Inhibition of SHP2 to test the activation of PI3K/AKT/mTOR and Ras/Erk between T2DM and T2DM-SHP2^{low} groups.
- 3) Xenograft tumor experiments to compare the tumor formation between T2DM and T2DM-SHP2^{low} groups (non-small cell lung cancer A549 cell line will used) in order to examine the involvement of the activation of PI3K/AKT/mTOR and Ras/Erk.
- 4) Large-scale prospective study should be performed to test the expression of SHP2 in T2DM patients and the relationship between SHP2 expression and incidence of lung cancer. According to our speculation, these T2DM patients who have higher expression of SHP2 may also be suffered from higher risk of lung cancer.

Consequences of the Hypothesis and Discussion

Although a growing number of epidemiological studies suggest that T2DM may be associated with an increased risk of certain cancers, no paper up to date, to our knowledge, has elucidated the underlying mechanism linked both T2DM and cancers. In the present paper, we assume that SHP2 may present a key molecule linked both T2DM and cancers via regulating Ras/Erk and PI3K/AKT/mTOR signaling pathway. Further and comprehensive investigation of SHP2 may provide a new insight into the molecular mechanism linked both T2DM and cancers, thus help us to discover new potential therapeutic targets in the prevention and treatment of cancers. Although some questions have not been explained completely, there are still enough evidence for us to hypothesize that SHP2 may be a key target linked T2DM and cancers and a potential target for the intervention and potential therapy for cancers.

Conflict of Interest

All authors declare no conflicts of interest.

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