DUSP6在肿瘤发生和糖脂代谢中的作用

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摘要 双特异性磷酸酶6(DUSP6)是双特异性磷酸酶(DUSP)家族成员, 其在人体组织中广泛表达, 可特异性地去磷酸化细胞外信号调节激酶1/2(ERK1/2)。由于DUSP6在丝裂原活化蛋白激酶(MAPK)信号通路中的负调控作用, 其在肿瘤增殖、肿瘤对化疗的耐药性、肿瘤诊断、代谢稳态等方面发挥重要作用, 并为药物靶点开发提供新思路。然而, DUSP6对肿瘤和糖脂代谢的影响是多样的, 甚至是部分矛盾的, 这延缓了DUSP6造福人类的进程。该文将总结DUSP6在不同肿瘤和代谢模型中的现有知识, 讨论造成这种矛盾的潜在原因, 并尝试给出一些解决方案。此外, 文章还将总结其分子机制和潜在的转化应用。

Abstract 双特异性磷酸酶6; 细胞外信号调节激酶1/2; 丝裂原活化蛋白激酶; 肿瘤; 糖脂代谢

Dual Specificity Phosphatase 6 in Tumor Development and Glucose and Lipid Metabolism

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Abstract DUSP6 (dual specificity phosphatase 6), which is widely expressed in human tissues, is a member of the DUSP (dual specificity phosphatase) family that dephosphorylates ERK1/2 (extracellular signal-regulated kinase 1/2) specifically. Due to its negative regulation in the MAPK (mitogen-activated protein kinase) signaling pathway, it has been shown to play an essential role in tumor proliferation, tumor resistance or drug sensitivity to chemotherapy, tumor diagnosis, metabolic homeostasis, which provides new ideas for drug target development. However, the effect of DUSP6 on tumors and glucose and lipid metabolism is diverse and partly contradictory. This delays the process of DUSP6 benefiting humanity. The present review will summarize the current knowledge of DUSP6 in different tumor and metabolic models, discuss the potential reasons for this contradiction, and try to give some solutions. This paper will also summarize its underline molecular mechanisms and potential translational applications.

Keywords dual specificity phosphatase 6; extracellular signal-regulated kinase 1/2; mitogen-activated protein kinase; tumor; glucose and lipid metabolism

DUSP (dual specificity phosphatase), a conserved phosphatase family, regulate related physiological activities by dephosphorylating the serine/threonine and tyrosine residues of target substrates [1-3]. As a member of the DUSP family, DUSP6 accedes life activities by dephosphorylating and inactivating ERK1/2 [4]. DUSP6

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表1 典型DUSPs和少数非典型DUSPs的亚细胞定位、底物和相关肿瘤领域

Table 1 Subcellular localization, substrates, and related tumors of typical DUSPs and a few atypical DUSPs

DUSPs/MKPs	种类 Type	亚细胞定位 Subcellular localization	底物 Substrates	相关肿瘤 Related tumors
DUSP1/MKP1	Typical	Nuclear	ERK, JNK, p38	NSCLC (non-small-cell lung cancer) [19]
DUSP2	Typical	Nuclear	ERK, JNK, p38	Bladder cancer [20], colorectal cancer [21]
DUSP4/MKP2	Typical	Nuclear	ERK, JNK, p38	Breast cancer [22], lung adenocarcinoma [23]
DUSP5	Typical	Nuclear	ERK	Human neuroblastoma [24]
DUSP6/MKP3	Typical	Cytoplasmic	ERK	NSCLC [25], pancreatic cancer [26]
DUSP7/MKPX	Typical	Cytoplasmic	ERK	Breast cancer [27]
DUSP8	Typical	Cytoplasmic/nuclear	JNK, p38	Colorectal carcinoma [28]
DUSP9/MKP4	Typical	Cytoplasmic	ERK, p38	Triple-negative breast cancer [29], gastric cancer [30]
DUSP10/MKP5	Typical	Cytoplasmic/nuclear	JNK, p38	Colorectal cancer [31], pancreatic cancer [32]
DUSP14/MKP6	Atypical	Cytoplasmic/nuclear	ERK, JNK, p38	Pancreatic cancer [33]
DUSP16/MKP7	Typical	Cytoplasmic/nuclear	JNK, p38	Burkitt's lymphoma [34], hepatocellular carcinoma [35]
DUSP18	Atypical	Cytoplasmic/nuclear	JNK	Osteosarcoma [36]

部分DUSPs的亚细胞定位和主要底物仍存在争议。 例如, DUSP18的亚细胞定位矛盾可能源于物种差异[36]。体内和体外微环境差异造成DUSP14的主要底物不同[17]。 DUSP9 还可以在某些条件下调节JNK[30]。 这些"矛盾"应谨慎对待, 因为它们可能仅限于特定物种、细胞类型、生理状态或微环境。

The subcellular localization and main substrates of the partial DUSPs are still controversial. For instance, the subcellular localization contradiction of DUSP18 may result from species differences [36]. The main substrates of DUSP14 are different, possibly owing to microenvironment differences *in vivo* and *in vitro* [17]. DUSP9 can also regulate JNK under certain conditions [30]. These "contradictions" should be treated with caution because they may be limited to a specific species, cell type, physiological state, or microenvironment.

is well known for its dual regulation of tumors [5]. For example, it is confirmed to inhibit tumorigenesis in ovarian cancer [6], endometrial adenocarcinoma [7], and lung cancer [8]. In contrast, it promotes human glioblastomas [9], thyroid carcinomas [10], and endometrial adenocarcinoma [11] development. Similarly, DUSP6 also has inconsistencies in glucose and lipid metabolism [12]. Furthermore, the potential of DUSP6 in tumor prognosis diagnosis [13], tumor resistance [6,9], and other areas are gradually being tapped. Regardless, under various models and biochemical analyses, we will gradually understand more of the physiological functions and molecular mechanisms of DUSP6.

1 Members of DUSP family

There are 25 members in the DUSP family with the loose enzyme pocket, which contain two types of phosphorylated residues [2]. An intervening cluster of basic amino acids is called the KIM (kinase-interacting motif) in the N-terminal of partial DUSPs, which is important for mediating the enzyme-substrate interaction [1-2]. DUSP has the KIM, is generally classified as a typical one, also known as a MKP (MAP kinase phosphatase), otherwise is called an atypical one, but there are few exceptions [1-2]. DUSPs are widely involved in various life activities, especially tumors. Based on the classification, subcellular localization, substrates, and tumors regulation of DUSPs in mammalian cells, we have summarized the subcellular localization, substrates, and related tumors of some typical DUSPs and a few atypical DUSPs [1-2,5,14-18] (Table 1).

2 The structure-based molecular functions of DUSP6

The human *DUSP6* is located on chromosome 12q21.33 [5], containing three exons and two forms of alternatively spliced transcripts [37]. The C-terminal of DUSP6 mainly depends on the catalytic site (Fig.1) to perform physiological functions [3,5]. Moreover, the NES (nuclear export signal), determines subcellular localization [5]. KIM, which relates to substrate identification [5,38], and Cdc25/rhodanese-homology [3,5], are in the N-terminal of DUSP6 (Fig.1). DUSP6 is activated

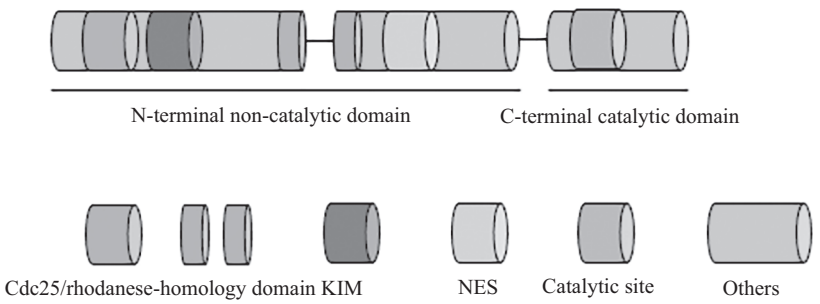


图1 DUSP6部分结构域的简单示意图(根据参考文献[3,5,16]改编)

Fig.1 A simple diagram of some domains of DUSP6 (modified from the references [3,5,16])

by conformational rearrangement after binding to the substrate [5]. The identification of this anchoring may be related to electrostatic effects [39]. Besides, the residues 61–75 of KIM (the core is Arg^{65} which interacts with Asp^{319} in ERK2), residues 161–177, and residues 348–381 of DUSP6 contribute to ERK2 binding for 135-fold, 15-fold, and less than 10-fold, respectively [40]. However, the latter is necessary for ERK2-induced DUSP6 activation [40]. In addition, there are some studies [41-44] discussed the molecular mechanism of DUSP6 in detail.

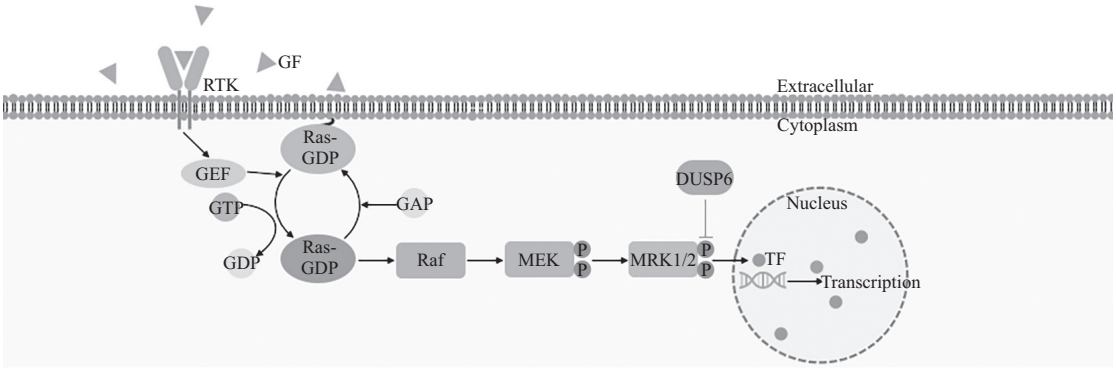
3 The tissue distribution of DUSP6

DUSP6 is widely expressed in most tissues and cells of human beings. Unfortunately, at some tissues in humans, its mRNA and protein levels are not correlated well. For example, DUSP6 is mainly present in the liver and adipose tissue of RNA rather than protein. On the contrary, protein is dominant in pancreas and bronchus [data from The Human Protein Atlas (https://www.proteinatlas.org)]. This character may be due to differences in post-transcriptional and post-translational regulation of DUSP6 [45]. Bioinformatics tools, small molecule inhibitors such as BCI [(*E*)-2-benzylidene-3-(cyclohexylamino)-2,3-dihydro-1*H*-inden-1-one] [46], and tissue-specific *DUSP6* knockout animal models are possible options to study this inconsistency further.

4 DUSP6 in the MAPK signaling pathway

The MAPK signaling pathway transmits signals through a three-stage enzyme-linked reaction, that is, the MAPKKK (MAPKK kinase) (such as Raf-1)-MAPKK (MAPK kinase) (such as MEK1)-MAPK (such as ERK1), thereby controlling cell proliferation, differentiation, apoptosis, metabolism, and immune response [47]. The classic members of the MAPK, namely JNK1/2/3 [c-Jun amino (N)-terminal kinases 1/2/3], ERK1/2, ERK5, and p38 isoforms (α, β, γ, and δ) [47]. Activation of the JNK and p38 MAPK is related to various pathophysiological processes under stress and apoptosis, making them good biological factors that mediate upstream and downstream pathways [47-49]. ERK1/2 participate in specific genes' transcription and expression and be widely applicable regulatory mechanisms in some disease's treatment [50]. ERK5 has so much molecular weight that to control itself transcription by undergoing autophosphorylation of its C-terminal transcriptional activation domain [51-52]. ERK5 also participates in the regulation of tumor resistance and aggressive cancer phenotype, so that it plays an important role in tumorigenesis and metastasis, and as a target for anticancer drug treatment [51].

With classic definition, DUSP6 acts as a phosphatase to regulate ERK1/2 negatively in the MAPK signaling pathway (Fig.2). Specifically, extracellular factors enter the cell through the RTK (receptor tyrosine kinase); then, the GEF (guanine nucleotide exchange factor) promotes the Ras protein to bind to GTP (guanosine triphosphate) to become an activated state. Subsequently, Ras-GTP activates the downstream Raf-MEK-ERK1/2 signaling pathway, and eventually, phosphorylated ERK1/2 enters the nucleus to activate transcription factors [53] (Fig.2). When ERK1/2 hyperactivation is monitored in cells, DUSP6 will dephosphorylate the threonine and tyrosine residues of phos-

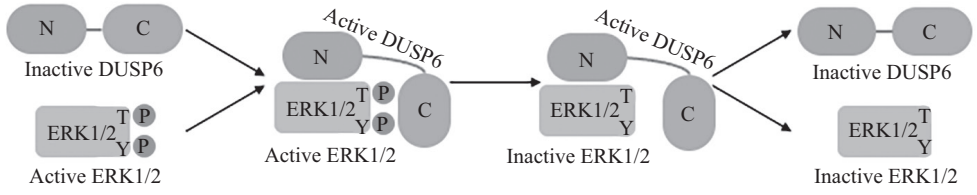


GAP, GTP酶激活蛋白; GDP, 二磷酸鸟苷; GF, 生长因子; P, 磷酸基团; TF, 转录因子。

GAP, GTPase-activation protein; GDP, guanosine diphosphate; GF, growth factor; P, phosphate; TF, transcription factor.

图2 DUSP6在MAPK信号通路中负调控简单示意图

Fig.2 A simple diagram of the negative regulation of DUSP6 in the MAPK signaling pathway



C, C-端; N, N-端; P, 磷酸基团; T, 苏氨酸; Y, 酪氨酸。

C, C-terminal; N, N-terminal; P, phosphate; T, threonine; Y, tyrosine.

图3 DUSP6去磷酸化ERK1/2简单示意图(根据参考文献[3,5]改编)

Fig.3 A simple diagram of DUSP6 dephosphorylates ERK1/2 (modified from the references [3,5])

phorylated ERK1/2 to block the transmission of signals and realize the negative regulation in the MAPK signaling pathway (Fig.3).

5 The tumor and metabolic models of DUSP6

MKPs have crosstalk mechanisms between MAPK signaling pathways and other intracellular signaling modules, which makes MKPs have a broad range of regulatory effects, also making it challenging to explore specific functions [54]. Therefore, a complete tumor model, supplemented by clinical statistics, is necessary to explore DUSP6/MKP3 physiological functions in tumors and metabolic diseases *in vivo* and *in vitro*. Several models have been developed, for instance, DUSP6-deficient or loss-of-function mutants cell line or mice, which shows high ERK1/2 activity owing to DUSP6 depleted; DUSP6-sufficient or gain-of-function mutants cell line or mice, which shows low ERK1/2 activity results from DUSP6 over-abundance. They are the basis for exploring the function of DUSP6 in specific diseases.

6 DUSP6 in tumor development

DUSP6 as a classic tumor suppressor has been broken (Table 2). Its role in tumorigenesis, tumor resistance, and prognostic markers is gradually being explored (Table 2). Additionally, the role of DUSP6 in the different tumors is versatility (Table 2). These may explain many conflicting results foretimes. Although the sample is limited, we could summarize the rules preliminarily: (i) as a tumor suppressor, DUSP6 deficiency becomes an important cause of tumorigenesis; (ii) on the contrary, DUSP6 overabundance guarantees its cancer-promoting ability; (iii) the role of DUSP6 in tumor resistance and prognostic markers is diverse. The possible way to explore this mechanism is structural analysis. Whereas, due to the complexity and dynamic characteristics of the DUSP family structure, the analysis of its fine structure is challenging. Cryogenic cryo-electron microscopy is an effective method for

revealing its high-resolution three-dimensional delicate structure and exploring the compensatory properties of family members from the structure.

The factors, include the tumor's microenvironment, specificity, adaptability to regulation, and differences in experimental controls, make DUSP6 a versatile tumor regulator. Simultaneously, there are some more specific factors: (i) DUSP6 provides different signal crosstalk. For instance, the murine *dusp6* promoter contains a β-catenin-binding site (not in humans), making *dusp6* a downstream target of the β-catenin signaling to regulate ERK. Therefore, in mouse hepatoma cells, dusp6 provides signal crosstalk between Wnt/β-catenin and Ras/MAPK [69]. This also reminds us that we should consider species differences when exploring the physiological functions of DUSP6; (ii) the expression of DUSP6 is regulated by many factors. For example, in pancreatic cancer [67] and esophageal

表2 DUSP6 在人类肿瘤发展中的各种作用

Table 2 Various roles of DUSP6 in human tumor development

DUSP6角色 Role of DUSP6	肿瘤类型 Tumor type	DUSP6表达 DUSP6 expression	结果 Results
Potential tumor prognostic marker	Gastric cancer	High (R & P) [55]	High expression of DUSP6 protein predicts poor overall and progression-free survival [55]
	Hepatocellular carcinoma	High (P) [13]	High expression of DUSP6 protein in tumor tissue when compared with the peritumor tissue is significantly associated with the recurrence of tumor [13]
	NSCLC	Low (R) [56-57]	Low expression of DUSP6 mRNA reveals poor prognosis [56] and has a significantly lower overall survival rate than other patients with lung adenocarcinomas [57]
Regulating tumor resistance	Cervical adenocarcinoma	-	DUSP6 deficiency reduces the tumor cells viability and increases drug sensitivity [58]
	Human glioblastomas	High (R & P) [9]	DUSP6 overexpression increases tumor resistance to cisplatin-mediated cell death [9]
	Ovarian cancer	Low (P) [6]	DUSP6 insufficient results in increased resistance to cisplatin in ovarian cancer cells [6]
Tumor promotion	Acute myeloid leukemia	High (P) [59]	DUSP6 knocking down makes tumor cells grow slowly [59]
	Breast cancer	-	DUSP6 as a scaffolding protein to promote cancer growth [60]; DUSP6 depleted suppresses cells proliferation, migration, invasion, and arrests cells at G_0/G_1 phase [61]
	Human glioblastomas	High (R) [9]	DUSP6 upregulation exacerbates the malignant phenotype [9]
	Thyroid carcinoma	High (R [10,62] & P [62])	DUSP6 knocking down reduces neoplastic properties [10,62]
Tumor suppression	Esophageal squamous cell carcinoma	Low (R & P) [63]	DUSP6 overexpressing promotes tumor cells apoptosis [63]
	Lung cancer	Low (R & P) [8]	DUSP6 overabundance inhibits tumor cells growth [8]
	Ovarian cancer	Low (P) [6]	DUSP6 restoration inhibits cell proliferation, anchorage-independent growth ability, and tumor development [6]
	Pancreatic cancer	Low (R & P) [64-67]	DUSP6 acts as a tumor suppressor in pancreatic cancer [64-67]
	Prostate cancer	Low (R & P) [68]	Forced expression of DUSP6 suppresses the invasion and growth of tumor cells [68]
Tumor suppression/promotion	Endometrial adenocarcinoma	Low (P) [7]/ High (P) [11]	DUSP6 overexpression significantly attenuates tumor cell growth, invasion, migration abilities [7]; DUSP6 overexpression enhances tumor cell growth [11]

R, mRNA; P, protein。现阶段, DUSP6表达水平的研究聚焦于mRNA或蛋白, 但其mRNA水平与蛋白水平有时并不很匹配, 这表明DUSP6可能存在转录后调控[6]。此外, 几乎没有研究报道DUSP6酶活性与肿瘤的关联性, 这可能因为酶活性变化相较于mRNA和蛋白质更为迅速, 且其受温度等外界因素影响大, 因而相关研究难度高。

R, mRNA; P, protein. At present, the research on the expression level of DUSP6 focuses on mRNA or protein, but its mRNA level and protein level sometimes do not match very well, which indicates that DUSP6 may have post-transcriptional regulation [6]. In addition, few studies have reported the relationship between DUSP6 enzyme activity and tumors, which may be difficult to study because the enzyme activity changes more rapidly than mRNA and protein, and it is greatly affected by external factors such as temperature.

squamous cell carcinoma [63], promoter hypermethylation leads to loss of DUSP6 expression. While in ovarian cancer [6], DUSP6 protein deficiency is due to the ubiquitination/proteasome degradation mediated by high intracellular ROS (reactive oxygen species) accumulation; (iii) DUSP6 has other functions besides ERK1/2 negative regulator. For instance, in NSCLC [56], DUSP6 depletion shows increased phosphorylation of ERK5 instead of ERK1/2 and expression of SMAD2/3, thereby destroying the cellular tubulin network and actin-stress fibers and ultimately affecting the interaction cadherin-catenin complexes at the adherent junctions. Meanwhile, in breast cancer [60], DUSP6 binds with progesterone receptors-B's common docking domain to bridge PR-B and casein kinase II to act as a scaffold protein to promote tumor growth. In summary, DUSP6 is so fascinating and elusive in terms of tumor regulation.

7 DUSP6 in metabolism

7.1 DUSP6 in glucose and lipid metabolism

DUSP6 is not only limited to tumor regulation, but also plays an important role in glucose and lipid metabolism (Fig.4). DUSP6 deficiency affects systemic glucose tolerance in mice [12]. *dusp6* and *dusp8* double knockout mice increase energy expenditure in mice to protect them from obesity induced by a high-fat diet, reduce their serum triglyceride, lipid content in the liver, and visceral adipose tissues and improve their glucose tolerance [70]. This resistance to high-fat diet-induced obesity by increasing energy expenditure in mice is further confirmed in dusp6 deficiency mice, which reveals the mechanism is that the dusp6-insufficient leads to improvement of the gut microbiota

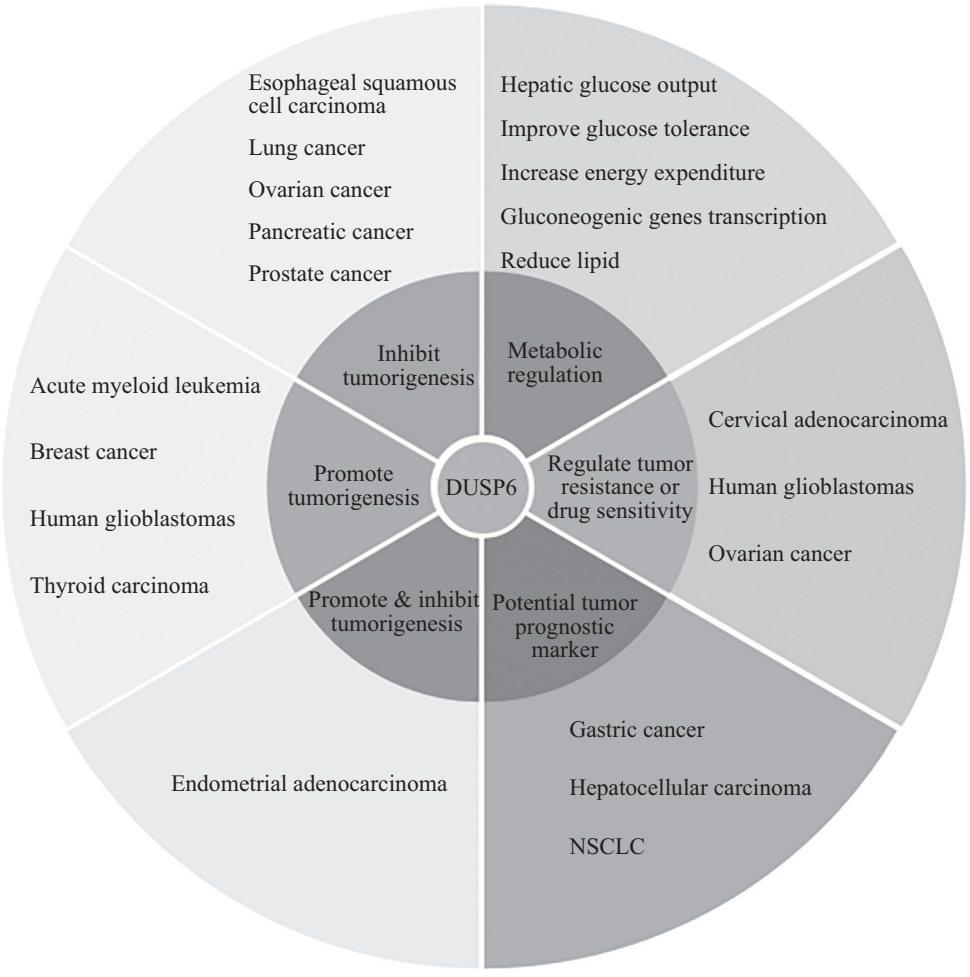


图4 DUSP6在肿瘤发展和糖脂代谢中作用简单示意图

Fig.4 A simple diagram of DUSP6 in tumor development and glucose and lipid metabolism

response to diet-mediated stress [71]. As a downstream component of the Dex (dexamethasone) signal, dusp6 regulates gluconeogenic genes transcription, hepatic glucose output, and lipid metabolism with the FOXO1 (forkhead box protein O1) participation [72-74]. Moreover, DUSP6 mediates TCR (T cell receptor)-engaged glycolysis by TCR–JNK/p38–IL-21 pathway instead of the classic ERK1/2 pathway [75]. dusp6 increases the resistance of murine podocytes to inflammation and apoptosis induced by high glucose [76].

The above research mainly focuses on the active role of DUSP6 in glucose and lipid metabolism. However, DUSP6 is also regulated by other factors. Under the stimulation of serum growth factors, DUSP6 degradation and phosphorylation are mediated by MEK/ERK and PI3K (phosphoinositide 3-kinase)/mTOR (mammalian target of rapamycin) signaling pathways, with the core are Ser159 & Ser197 and Ser159 of DUSP6 N-terminal domain, respectively [77-78]. This once again proves that DUSP6 has a signal crosstalk mechanism. Additionally, DUSP6 affects cell glucose outputting, and its degradation is regulated by the insulin mediated MEK/ERK pathway in the liver [79]. All of these may mean that DUSP6 may be in the middle position in the glucose and lipid metabolism and together constitute a complete feedback loop. For a more intuitive display, there is a simple table to show the regulation of DUSP6 in some regions (Table 3). However, the first problem we need to solve is that DUSP6 also has inconsistencies in glucose and lipid metabolism [12]. This may be due to the genetic background of the mice, the selected high-fat feeding standards, and the different measurement methods. Therefore, it may be a solution to formulate the gold standard for mouse experiments in the field of glucose and lipid metabolism as soon as possible.

7.2 DUSP6 in other metabolism pathways

Currently, the capabilities of DUSP6 in other metabolism fields are gradually being valued. A rapid positive feed-forward and a later negative feed-back loop regulation of DUSP6 controls PDGF (platelet-derived growth factor)-induced ERK activation [80]. After acute exercise, skeletal muscle but not adipose tissue DUSP6 is reduced by 43% and remains below pre-exercise level after two hours recovery with unknown mechanism [81]. Another study confirms that DUSP6 plays a role in skeletal muscle [82], with the mechanism is that Six1 regulates ERK1/2 pathway during regeneration by control DUSP6 transcription directly. In hippocam-

表3 调控DUSP6的因子、因素或通路

Table 3 Regulators, factors or pathways regulating DUSP6

调控因子/因素/通路 Regulators/factors/pathways	结果 Results	相关领域 Related regions
Acute exercise	Acute exercise reduces DUSP6 mRNA levels, which may be related to Dex	Other metabolisms [81]
DUSP6 promoter hypermethylation	Loss of *DUSP6* mRNA expression	Esophageal squamous cell carcinoma [63], pancreatic cancer [67]
Fms-like tyrosine kinase 3 with internal tandem duplication, FLT3 ITD	FLT3 ITD sustains high DUSP6 protein expression	Acute myeloid leukemia [59]
Growth factor signaling pathway	DUSP6 is phosphorylated and degraded upon growth factor stimulation by MEK/ERK-dependent manner [78] and PI3K/mTOR [77]	Glucose and lipid metabolism [77-78]
Hypoxia	Hypoxia increases *DUSP6* mRNA endogenous level in a HIF-1-dependent manner	Malignant melanoma and colon adenocarcinoma cells [45]
Insulin	MEK/ERK pathway mediates insulin-promoted degradation of DUSP6 protein	Glucose and lipid metabolism [79]
ROS accumulation	Loss of DUSP6 protein expression is mediated by ubiquitination degradation mediated by high intracellular ROS accumulation	Ovarian cancer [6]
Wnt/β-catenin signaling pathway	dusp6, which as a downstream target of β-catenin, provides signal crosstalk between Wnt/β-catenin and Ras/MAPK	Mouse hepatoma cells [69]

pal neuronal cell lines and immature cortical neuronal cultures, dusp6 sufficiency blocks the over-activation of ERK and thus protects these cells from oxidative toxicity [83]. Additionally, dusp6 deficiency significantly reduces AMPA receptor-induced oligodendrocyte death by enhancing ERK1/2 phosphorylation [84]. DUSP6 is widely expressed in tissues and organs but has been studied in limited areas. More data need to be provided on DUSP6 in specific organizations to completely describe the blueprint of DUSP6's mechanism of action.

8 The relationship between glucose and lipid metabolism and tumor development

Glucose and lipid metabolism and tumors are not separated but affect each other. On the one hand, the occurrence of cancer is often accompanied by abnormal lipid levels, which may be due to the high energy requirements for tumor cell proliferation and metastasis [85]. For example, the levels of TC (total cholesterol) and LDL-C (low-density lipoprotein cholesterol) in breast cancer patients are significantly higher, but HDL-C (high-density lipoprotein cholesterol) is lower than those in healthy people [86]. Patients (41.3%) with colorectal cancer have significantly higher levels of LDL-C but not HDL-C [87]. Half of the patients with ALL (acute lymphoblastic leukemia) show dyslipidemia, which is manifested by increased serum TG (triglyceride) and LDL-C, and decreased HDL-C, meantime, all of them exhibit lower plasma Apo A-I (apolipoprotein A-I) and higher Apo B-100 and C-II levels [88]. High expression of Apo E is detected in gastric cancer [89]. On the other hand, abnormal glucose and lipid metabolism may induce and promote tumors. For instance, the accumulation of linoleic acid promotes breast cancer cell metastasis [90]. The cholesterol metabolite 27-hydroxycholesterol stimulates prostate cancer cell proliferation [91]. Apo E is related to the metastasis of lung adenocarcinoma [92]. Glycogen accumulation accelerates the occurrence of liver tumors in a dose-dependent manner; meanwhile, eliminating it abrogates liver growth and cancer incidence [93]. Although the causal relationship is still unclear, it can be confirmed that the two often threaten human nutrition and health at the same time. From another perspective, the development of drug targets for the glucose and lipid metabolism pathway is a new idea for treating tumors.

9 Summary and prospects

Tumors and metabolic diseases seriously affect human health and well-being. Some tumor regulators are presented in family form, such as the DUSPs. DUSPs have many members, with high structural consistency, wide distribution, and diverse functions. They play a vital role in cell signal transduction, epigenetic regulation, transcription factors secretion, and stem cell proliferation. Analogously, these also imply that other members of the DUSPs family with highly conserved structures may also have the characteristic of diversity. In addition, through the crosstalk mechanisms of the signaling pathways, a subset restrains and compensates for each other. However, they are rare family factors working peacefully and gently.

DUSP6 regulates ERK1/2 negatively in the MAPK signaling pathway to be a dual regulator in tumor and metabolism is a classic definition. In particular, when the monitor detects that ERK1/2 is hyperactivation, DUSP6 dephosphorylates and inactivates them, thereby stabilizing cell growth and glucose and lipid metabolism in a suitable range. Besides, DUSP6 is extremely widespread in mammalian tissues and cells. Interestingly, the mRNA and protein levels of DUSP6 are not correlated very well in human tissue. Furthermore, DUSP6 is widely involved in treating some tumors and is a very promising tumor prognostic biomarker in certain tumors. Unfortunately, the definition of the causality of DUSP6 on tumor and metabolism regulation is very vague, which has caused us trouble to explore its role further. The expression of DUSP6 in tumors and glucose and lipid metabolism is a dynamic equilibrium process, which is greatly affected by the internal environment; therefore, the dynamic expression level of DUSP6 may be a breakthrough in the future exploration of the causal relationship between DUSP6 and tu-

morigenesis and glucose and lipid metabolism. Nevertheless, existing evidence breaks the classic definition of DUSP6 and expands it. In conclusion, the extensive exploration and rational use of DUSP6 will benefit all humanity in the future.

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