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Roles and Signaling Pathways of CITED1 in Tumors: Overview and Novel Insights

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1. Abstract

CBP/p300 interacting trans activator with Glu/Asp-rich car boxy-terminal domain 1 (CITED1) is a transcription activator belongs to a member of the non-DNA-binding transcription co-regulator family. It regulates diverse transcriptions by binding to CBP/p300 co-activators through its conserved trans activating domain CR2, including TGF-β/BMP-SMAD, estrogen, Wnt-β-catenin and androgen-AR signaling pathways. CITED1 not only plays an important role in embryonic development, but also plays a certain regulatory role in the occurrence and development of various tumors. In this article, the biological characteristics, expression regulation, participating signaling pathways, and potential functions of CITED1 in the clinical diagnosis and treatment of tumors were reviewed.

2. Introduction

CITED1 was originally named Melanocyte-Specific Gene 1 (MSG1), as it was believed to be expressed only in melanocytes [1]. Subsequently, extra-melanocytic expression of MSG1 in mammary epithelium, testis, brain, embryonic tissues and some tumors was found and its biological characteristics were also elucidated [1-5]. Therefore, "MSG1" was renamed "CITED1", CBP/p300 interacting transactivator with Glu/Asp-rich carboxy-terminal domain 1.

3. Biological Characteristics of CITED1

CITED1 gene, located on chromosome Xq13.1, is a highly conserved genomic DNA with three exons and two introns, and its 5' end contains TATA Box and potential binding sites for multiple transcription factors (USF, Brn-3, Brn-2, TFE3, Oct-1, AP-2 and Sp1) [6]. The promoter fragment activates transcription of CITED1 gene and eventually encodes a 27kDa nuclear protein. CITED1 shares a highly conserved transcriptional activation region CR2 with other members of the CITED family CITED2 (MRG1 or p35srj), CITED3 and CITED4 [7, 8]. CR2 (amino acids 145–193), a C-terminal acidic domain containing 6 Asp and 6 Glu, enhances the transcriptional activation activity of CITED1 by binding to CBP/p300 co-activators [1, 7]. Hsc70, HIF-1, β-catenin and MITF compete with CITED1 for binding to CBP/p300, thereby repressing related transcription [8-11]. Moreover, phosphorylation of five serine residues of CITED1 in M-phase (Ser16 63 67 71 137) also interferes with the binding of CITED1 to CBP/p300, thus reducing the transcriptional activating activity of CITED1 [12]. Since CITED1 lacks DNA-binding activity, it serves as a mediator to stabilize and augment the interaction

between CBP/p300 and some DNA-binding proteins, then translocate into the nucleus as complexes, where they bind to promoter of target genes and enhance corresponding transcription. Among these include: (1) SMAD4: CITED1 binds to SMAD4 transcription factor through the N-terminal SMAD4 interacting domain (SID, amino acids 30-60), enhancing the TGF-β/BMP induced transcription depending on SMAD hetero-oligomerization [8, 13, 14]; (2) ERα: CITED1 binds to ERα through the N-terminal region of CR2 (amino acids 157-158), which is independent of the interaction region with CBP/p300, coactivating the estrogen-dependent transcription (Figure 1) [15]; (3) TOX3: CITED1 binds to TOX3 HMG box through CR2, significantly enhancing estrogen response element (ERE) dependent transcription and playing an anti-apoptotic role [16]. The subcellular localization of CITED1 is characterized by cellular heterogeneity. In HEK cells and MCF-7 cells, the centralized distribution of CITED1 in the cytoplasm was confirmed to be associated with CRM1-dependent nuclear export signal (NES, 108LMSLVVELGL117) on CR2, while in osteoblasts, PTH-induced nuclear translocation of CITED1 was confirmed to be associated with phosphorylation at Ser79 and activation of PKC [12, 17]. CITED1 is known to be involved in the process of embryonic development, including the development of metanephric mesenchyme, ureter, placenta and brain [4, 5, 14]. The loss of CITED1 often leads to abnormal embryonic development [18]. In addition, CITED1 also plays a certain regulatory role in the occurrence and development of various tumors. In order to provide a valuable theoretical basis for further study of CITED1, this article reviews the research progress of CITED1 in these tumors and its potential function in clinical tumor diagnosis and treatment.

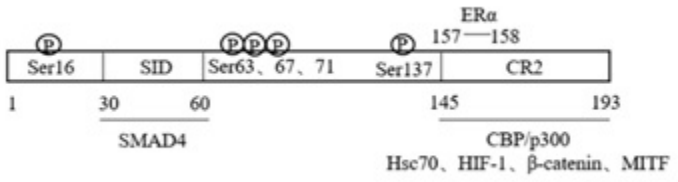

Figure 1: The biological characteristics of CITED1.

4. Expression Regulation of CITED1

Currently, there are few studies on the regulation mechanism of CITED1 expression. Existing studies suggest that some regulatory factors can regulate the expression of CITED1 at the transcriptional or post-transcriptional level. The details are as follows: In melanocytes and melanoma, protein kinase C activators 12-O-tetradecanoyl phorbol-13-acetate (TPA)/Endothelin-1 (ET-1) and activator of receptor tyrosine kinase fibroblast growth factor-2 (FGF-2) regulate the expression of CITED1 at the transcriptional and post-transcriptional levels, respectively [19]. Studies suggest that under UV-B irradiation, epidermal keratinocytes can secrete ET-1 and FGF-2, which act on melanocytes through paracrine, leading to upregulation of CITED1 expression [19].

BRAF activating mutations are also involved in the regulation of CITED1 expression, but they play different roles in different tumor types. BRAF activating mutations are known to be common in melanoma and papillary thyroid carcinoma (PTC). Studies have shown that in melanoma, BRAF activating mutations downregulate CITED1 expression by enhancing the expression and function of transcription factor NR4A1/2 [10]. However, in PTC, BRAF V600E mutation induces high expression of CITED1 mRNA by hypo methylation of CpGs in the CITED1 promoter (especially CpG18 and CpG24) [20]. In addition, non-coding RNA miR-26, Runx1/CBFβ complex and c-Myc were found to be involved in the regulation of CITED1 expression in tumors, but the specific regulatory mechanisms remain to be further explored [21-23].

5. The Main Signaling Pathways and Role of CITED1 in Tumors

5.1. TGF-β/BMP-SMAD Signaling Pathway

TGF-β plays a dual role in tumorigenesis and development. When tumor cells successfully evade the growth inhibition effect of TGF-β, TGF-β-mediated oncogenic functions, such as induction of epithelial-to-mesenchymal transition (EMT), can be utilized to promote tumor cell survival, proliferation, invasion and metastasis. In the process of tumor cell growth and metastasis, various cells in tumor microenvironment often release a large amount of TGF-β, which directly promotes malignant transformation of tumor cells. Studies have found that CITED1 is highly expressed in the invasive fronts of melanoma. CITED1 enhances transcription of TGF-β-SMAD signaling pathway related target genes (JAK1, LIF, IL11, M-RIP and ARHGEF5), promotes the cooperation between Rho-ROCK and JAK1-STAT3 signaling, and provides the high levels of actomyosin contractility for melanoma cells to migrate in the rounded, "amoeboid" mode (Figure 2) [24, 25]. In colorectal cancer (CRC), CITED1 associated with TGF-β-SMAD signaling pathway was also found to be one of the genes leading to the dedifferentiation of CRC invasive front cells, and the metastatic ability of CRC invasive front cells without epithelial phenotype was enhanced [26]. In addition, CITED1 overexpression induces the differentiation of embryonic stem cells (ESCs) into trophoblast cells by activating BMP signaling pathway, leading to the formation of teratoma (Figure 3) [27].

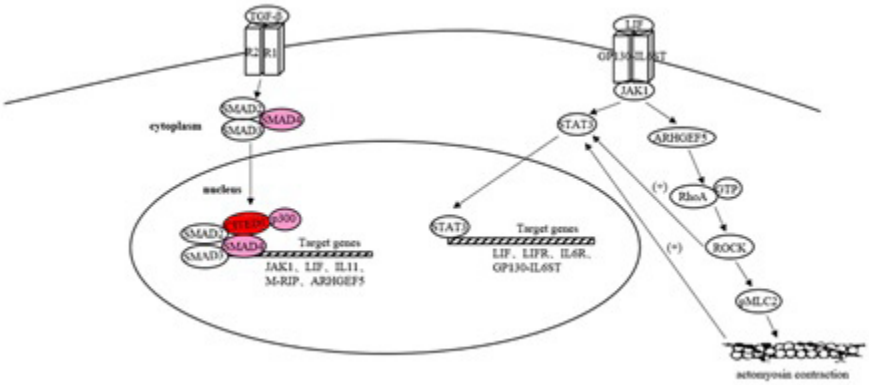

Figure 2: CITED1 promotes amoeboid melanoma migration.

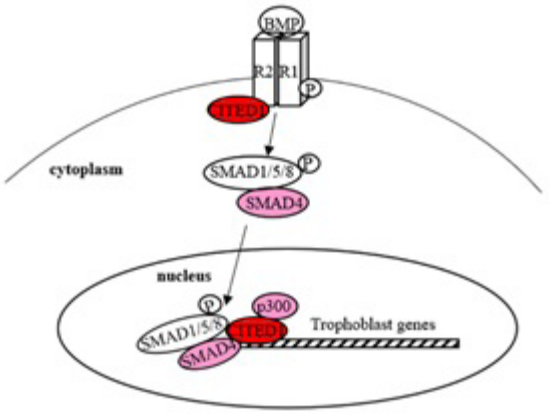

Figure 3: CITED1 induces teratoma formation by activating BMP-SMAD signaling pathway.

5.2. Estrogen Signaling Pathway

CITED1 is known to activate the transcription of Stanniocalcin 2 (STC2) and Amphiregulin (AREG) via estrogen signaling pathway during adolescent breast development, thus promoting the growth of mammary epithelium and formation of mammary ducts [2, 28]. And the continuous activation of this signaling pathway in breast cancer patients is a good prognosis marker, possibly due to the maintenance of the histological similarity between breast cancer tissue and normal breast tissue [28]. But CITED1 also can selectively coactivate estrogen-dependent ER-mediated transcription of TGF-α, promoting the growth of MCF-7 breast cancer cells in an autocrine manner. And this effect is more apparent when the estrogen concentration is low, because CITED1 enhances the sensitivity of ER positive MCF-7 breast cancer cells to estrogen [15]. In addition, the EGR2/CITED1 transcription factor complex can bind to the erbB2 promoter and improve the expression of HER2 [29]. And that the overexpression of HER2 is known to be related to the occurrence and poor prognosis of breast cancer, so the mechanism and clinical role of CITED1 in breast cancer still need to be further studied (Figure 4).

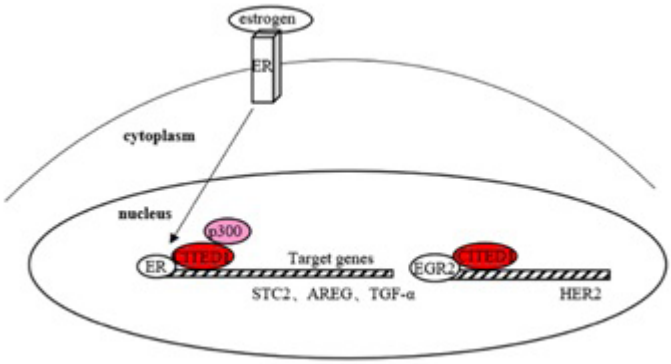

Figure 4: The role of CITED1 in breast cancer.

5.3. Wnt-β-Catenin Signaling Pathway

Wnt-β-catenin signaling pathway is involved in maintaining the balance between proliferation and differentiation in a variety of tumors, and this role is related to transcription coactivator CBP/p300 [30-32]. Specifically, the binding of CBP to β-catenin activates transcription of cell proliferation-related genes, while the binding of p300 to β-catenin mediates transcription of cell differentiation-related genes [33]. CBP/ P300 is known to be the main protein interacting with CITED1. Thus, CITED1 may act as a coregulator regulating the balance between CBP/β-catenin-mediated transcription (maintaining stem/progenitor cell proliferation) and p300/β-catenin-mediated transcription (initiating cell differentiation). During vertebrate development, CITED1 is highly expressed in the progenitor cells of embryonic tissues, but downregulated and ultimately not expressed when they differentiate into mature tissues. And due to the persistent presence of undifferentiated components, embryonic tumors usually have high expression of CITED1 [34]. CITED1 is expressed in both cytoplasm and nucleus of Wilms' tumor (WT) blastema. CITED1 in the cytoplasm confers cancer cells stemness by inhibiting the Wnt-β-catenin signaling pathway, while CITED1 in the nucleus is more tumorigenic [35, 36]. In hepatoblastoma, CITED1 induces cell proliferation by upregulating inhibitors Kringle containing transmembrane protein 1 (KREMEN1) and CXXC Finger protein 4 (CXXC4) of Wnt signaling pathway [37]. It was found that CITED1 was highly expressed in adenomatous polyposis coli (APC)-deficient CRC mouse models and human tissue samples, and knocking down CITED1 extended the lifespan of APC-deficient CRC mice. As a member of β-catenin degradation complex, APC is known to negatively regulate β-catenin. Loss of APC can induce activation of Wnt-β-catenin signaling pathway and enhance c-Myc-dependent CITED1 transcription, while negative feedback of upregulation of CITED1 expression inhibits hyperactivation of Wnt signaling pathway and maintains the activity of Wnt signaling pathway at the level of promoting tumor development (Figure 5) [23]. In addition, CITED1 has also been found to promote tumor cell proliferation by inhibiting Wnt/β-catenin signaling pathway in PTC [38].

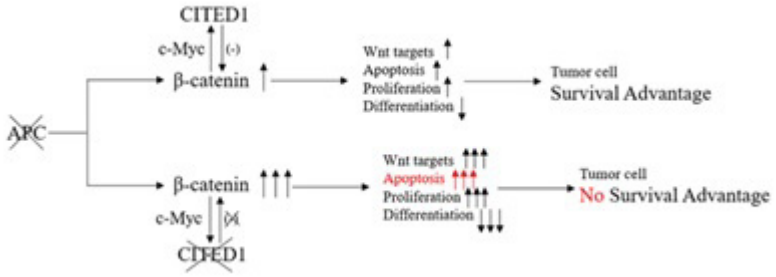

Figure 5: The mechanism of CITED1 on colorectal tumorgenesis in the absence of APC.

5.4. Androgen/Androgen Receptor Signaling Pathway

The androgen/androgen receptor (AR) signaling pathway plays an important role in all stages of prostate cancer occurrence and development. CITED1 is known to enhance the transcriptional activity of AR [15]. Study has found that the expression of CITED1 is not increased in human prostate cancer tissue samples, but it is highly expressed in PIN-like tissue samples (a precursor to prostate cancer) of AR-E231G mutation mice, and knocking down CITED1 can reduce the viability and proliferation of LNCaP prostate cancer cell line [39]. Thus, it is speculated that CITED1 plays a role in promoting the survival of premalignant cells during prostate cancer initiation, but its sustained overexpression is not necessary for tumor progression.

6. Potential Function of CITED1 in Clinical Tumor Diagnosis and Treatment

The expression of CITED1 in melanoma, PTC, WT and CRC is higher than that in normal tissues, and its expression level is closely related to tumor stage, metastasis and prognosis. In melanoma, high expression of CITED1 is considered as a biomarker to distinguish melanoma from benign nevus [40]. BRAF V600E mutational load is known to be negatively correlated with melanoma progression [41]. Therefore, the low mutational load of BRAF V600E (<5%) combined with the synergistic high expression of CITED1 can be used as an indicator of poor prognosis of melanoma. In addition, CITED1, as a negative regulator of MITF, is expected to enhance the expression of MITF by targeting CITED1, thereby activating tyrosinase and inducing CDKN1A/p21 and CDKN1C/p57-dependent cell growth arrest to increase the sensitivity of melanoma to chemotherapy drugs [11]. In the diagnosis and treatment of thyroid cancer, the accuracy of CITED1 in differentiating PTC from benign thyroid nodules and other types of thyroid cancer by immunohistochemical technology is 93% and 89% respectively [42]. The reason for the limitation of this accuracy is that CITED1 is also expressed in a small amount in follicular adenoma and follicular thyroid cancer [43]. Therefore, it is recommended to use CITED1 in combination with HBME-1 and Galectin-3 for differential diagnosis [44]. In addition, high expression of CITED1 has been confirmed to be associated with clinical stage (P=0.003) and lymph node metastasis (P=0.006) of PTC [45], and can be used as an indicator of PTC diagnosis and poor prognosis.

The expression level of CITED1 in WT blastema has also been confirmed to be positively correlated with tumor stage [34]. CITED1 is expected to be a prognostic indicator of WT and can inhibit tumor cell proliferation or promote terminal differentiation by targeting CITED1. Other scholars have proposed that dual staining of CITED1 and epithelial cell markers (such as cytokeratin) by immuno-

fluorescence can improve the recognition ability of blestemal WT in histologically high-risk groups and thus guide treatment [46]. In the diagnosis and treatment of CRC, with the improvement of endoscopic equipment and techniques, the detection rate of early CRC has increased greatly, and the presence of lymph node metastasis has become a major concern to determine the treatment strategy. In T1 CRC, the high expression of CITED1 is an independent risk factor for lymph node metastasis (P=0.010) [47]. Therefore, CITED1 can be used as a potential marker to predict CRC metastasis and prognosis and to guide treatment. Of course, the mechanism of CITED1 in the above tumors is still unknown and needs to be further explored. Meanwhile, whether CITED1 plays a role in other tumors and has potential diagnostic and therapeutic functions needs to be further confirmed. For example, high-throughput sequencing of cancer associated fibroblasts (CAF) induced EMT model of lung cancer cells showed that CITED1 expression was upregulated in the early EMT stage of A549 cells (3-24h) [48]. And Kaplan Meier-plotter database analysis showed that CITED1 expression level was negatively correlated with lung cancer patients PFS (HR=1.54, p=6E-05) and OS (HR=1.17, p=0.024). We believe that with the further study of CITED1, its tumor promoting effect will become clearer.

7. CITED1 with Beige Fat

Beige fat is produced by white fat in response to certain inducible factors, a process called fat beige [49, 50]. Like brown fat, beige fat is a thermogenic adipose tissue. But unlike brown fat, which degrades and disappears with age, beige fat persists in the dorsal spine region of the neck, above the clavicle and around the aorta in adults, and can be metabolized and produce heat after stimulation such as cold, which has therapeutic effects on obesity and type 2 diabetes [51]. CITED1 as a newfound marker of beige fat, the focus of research has shifted to the regulation of beige fat production, obesity and type 2 diabetes in recent years. Cyanidin-3-glucoside (Cy3G), interleukin-4 (IL-4) and peroxisome proliferator-activated receptor γ (PPARγ) et al. are known to upregulate CITED1 expression to induce fat beige, which is related to tumor energy metabolism and immune regulation [52-54]. In the future, it remains to be seen whether CITED1 can establish a relationship with tumor development through fat beige.

8. Conclusion and Prospect

In summary, CITED1, as a transcriptional activator, exerts transcriptional regulation through multiple signaling pathways including TGF-β/BMP-SMAD, estrogen, Wnt-β-catenin and androgen-AR. Current studies on CITED1 in tumors mainly focus on melanoma, PTC, breast cancer, WT and CRC, and it is expected to become a potential tumor marker and therapeutic target in the future.

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References

1. Shioda T, Fenner MH, Isselbacher KJ. msg1, a novel melanocyte-specific gene, encodes a nuclear protein and is associated with pigmentation. Proc Natl Acad Sci U S A. 1996; 93(22): 12298-12303.
2. Howlin J, McBryan J, Napoletano S. CITED1 homozygous null mice display aberrant pubertal mammary ductal morphogenesis. Oncogene. 2006; 25(10): 1532-1542.
3. Del Valle I, Buonocore F, Duncan AJ. A genomic atlas of human adrenal and gonad development. Wellcome Open Res. 2017; 2: 25.
4. Gerstner JR, Landry CF. Expression of the transcriptional coactivator CITED1 in the adult and developing murine brain. Dev Neurosci. 2007; 29(3): 203-212.
5. Rodriguez TA, Sparrow DB, Scott AN. Cited1 is required in trophoblasts for placental development and for embryo growth and survival. Mol Cell Biol. 2004; 24(1): 228-244.
6. Fenner MH, Parrish JE, Boyd Y. MSG1 (melanocyte-specific gene 1): mapping to chromosome Xq13.1, genomic organization, and promoter analysis. Genomics. 1998; 51(3): 401-407.
7. Fernandes MT, Calado SM, Mendes-Silva L. CITED2 and the modulation of the hypoxic response in cancer. World J Clin Oncol. 2020; 11(5): 260-274.
8. Yahata T, de Caestecker MP, Lechleider RJ. The MSG1 non-DNA-binding transactivator binds to the p300/CBP coactivators, enhancing their functional link to the Smad transcription factors. J Biol Chem. 2000; 275(12): 8825-8834.
9. Ng PK, Yu RM, Kwong TF. Transcriptional regulation and functional implication of the grass carp CITED1 (gcCITED1) in the negative regulation of HIF-1. Int J Biochem Cell Biol. 2010; 42(9): 1544-1552.
10. Smith AG, Lim W, Pearen M. Regulation of NR4A nuclear receptor expression by oncogenic BRAF in melanoma cells. Pigment Cell Melanoma Res. 2011; 24(3): 551-563.
11. Howlin J, Cirenajwis H, Lettiero B. Loss of CITED1, an MITF regulator, drives a phenotype switch in vitro and can predict clinical outcome in primary melanoma tumours. PeerJ. 2015; 3: e788.
12. Shi G, Boyle SC, Sparrow DB. The transcriptional activity of CITED1 is regulated by phosphorylation in a cell cycle-dependent manner. J Biol Chem. 2006; 281(37): 27426-27435.
13. Shioda T, Lechleider RJ, Dunwoodie SL. Transcriptional activating activity of Smad4: roles of SMAD hetero-oligomerization and enhancement by an associating transactivator. Proc Natl Acad Sci U S A. 1998; 95(17): 9785-9790.
14. Brown AC, Muthukrishnan SD, Guay JA. Role for compartmentalization in nephron progenitor differentiation. Proc Natl Acad Sci U S A. 2013; 110(12): 4640-4645.
15. Yahata T, Shao W, Endoh H. Selective coactivation of estrogen-dependent transcription by CITED1 CBP/p300-binding protein. Genes Dev 2001; 15(19): 2598-2612.
16. Dittmer S, Kovacs Z, Yuan SH. TOX3 is a neuronal survival factor that induces transcription depending on the presence of CITED1 or phosphorylated CREB in the transcriptionally active complex. J Cell

Sci. 2011; 124(Pt 2): 252-260.

17. Lin Z, Feng R, Li J. Nuclear translocation of CBP/p300-interacting protein CITED1 induced by parathyroid hormone requires serine phosphorylation at position 79 in its 63-84 domain. Cell Signal. 2014; 26(11): 2436-2445.
18. Novitskaya T, Baserga M, de Caestecker MP. Organ-specific defects in insulin-like growth factor and insulin receptor signaling in late gestational asymmetric intrauterine growth restriction in Cited1 mutant mice. Endocrinology. 2011; 152(6): 2503-2516.
19. Li H, Ahmed NU, Fenner MH. Regulation of expression of MSG1 melanocyte-specific nuclear protein in human melanocytes and melanoma cells. Exp Cell Res. 1998; 242(2): 478-486.
20. Sassa M, Hayashi Y, Watanabe R. Aberrant promoter methylation in overexpression of CITED1 in papillary thyroid cancer. Thyroid. 2011; 21(5): 511-517.
21. Lu JC, Zhang YP. E2F, HSF2, and miR-26 in thyroid carcinoma: bioinformatic analysis of RNA-sequencing data. Genet Mol Res. 2016; 15(1): 15017576.
22. van Bragt MP, Hu X, Xie Y. RUNX1, a transcription factor mutated in breast cancer, controls the fate of ER-positive mammary luminal cells. Elife. 2014; 3: e03881.
23. Méniel V, Song F, Phesse T. Cited1 deficiency suppresses intestinal tumorigenesis. PLoS Genet. 2013; 9(8): e1003638.
24. Cantelli G, Orgaz JL, Rodriguez-Hernandez I. TGF-β-Induced Transcription Sustains Amoeboid Melanoma Migration and Dissemination. Curr Biol. 2015; 25(22): 2899-2914.
25. Sanz-Moreno V, Gaggioli C, Yeo M. ROCK and JAK1 signaling cooperate to control actomyosin contractility in tumor cells and stroma. Cancer Cell. 2011; 20(2): 229-245.
26. Oku Y, Shimoji T, Takifuji K. Identification of the molecular mechanisms for dedifferentiation at the invasion front of colorectal cancer by a gene expression analysis. Clin Cancer Res. 2008; 14(22): 7215-7222.
27. Xu Y, Luo X, Fang Z. Transcription coactivator Cited1 acts as an inducer of trophoblast-like state from mouse embryonic stem cells through the activation of BMP signaling. Cell Death Dis. 2018; 9(9): 924.
28. McBryan J, Howlin J, Kenny PA. ERalpha-CITED1 co-regulated genes expressed during pubertal mammary gland development: implications for breast cancer prognosis. Oncogene. 2007; 26(44): 6406-6419.
29. Dillon RL, Brown ST, Ling C. An EGR2/CITED1 transcription factor complex and the 14-3-3sigma tumor suppressor are involved in regulating ErbB2 expression in a transgenic-mouse model of human breast cancer. Mol Cell Biol. 2007; 27(24): 8648-8657.
30. Zhan T, Rindtorff N, Boutros M. Wnt signaling in cancer. Oncogene. 2017; 36(11): 1461-1473.
31. Anastas JN, Moon RT. WNT signalling pathways as therapeutic targets in cancer. Nat Rev Cancer. 2013; 13(1): 11-26.
32. Clevers H, Nusse R. Wnt/β-catenin signaling and disease. Cell. 2012; 149(6): 1192-1205.
33. Bordonaro M, Lazarova DL. Determination of the Role of CBP- and p300-Mediated Wnt Signaling on Colonic Cells. JMIR Res Protoc. 2016; 5(2): e66.
34. Murphy AJ, Pierce J, de Caestecker C. SIX2 and CITED1, markers of nephronic progenitor self-renewal, remain active in primitive elements of Wilms' tumor. J Pediatr Surg. 2012; 47(6): 1239-1249.
35. Fukuzawa R, Anaka MR, Morison IM. The developmental programme for genesis of the entire kidney is recapitulated in Wilms tumour. PLoS One. 2017; 12(10): e0186333.
36. Murphy AJ, Pierce J, de Caestecker C. CITED1 confers stemness to Wilms tumor and enhances tumorigenic responses when enriched in the nucleus. Oncotarget. 2014; 5(2): 386-402.
37. Murphy AJ, de Caestecker C, Pierce J. CITED1 expression in liver development and hepatoblastoma. Neoplasia. 2012; 14(12): 1153-1163.
38. Wang Y, Huang H, Hu F. CITED1 contributes to the progression of papillary thyroid carcinoma via the Wnt/β-catenin signaling pathway. Onco Targets Ther. 2019; 12: 6769-6777.
39. Thompson VC, Day TK, Bianco-Miotto T. A gene signature identified using a mouse model of androgen receptor-dependent prostate cancer predicts biochemical relapse in human disease. Int J Cancer. 2012; 131(3): 662-672.
40. Huang C, Sheng Y, Jia J. Identification of melanoma biomarkers based on network modules by integrating the human signaling network with microarrays. J Cancer Res Ther. 2014; 10 Suppl: C114-24.
41. Sevilla A, Morales MC, Ezkurra PA. BRAF V600E mutational load as a prognosis biomarker in malignant melanoma. PLoS One. 2020; 15(3): e0230136.
42. Baloch Z, Mete O, Asa SL. Immunohistochemical Biomarkers in Thyroid Pathology. Endocr Pathol. 2018; 29(2): 91-112.
43. Pfeifer A, Wojtas B, Oczko-Wojciechowska M. Molecular differential diagnosis of follicular thyroid carcinoma and adenoma based on gene expression profiling by using formalin-fixed paraffin-embedded tissues. BMC Med Genomics. 2013; 6: 38.
44. Xin Y, Guan D, Meng K. Diagnostic accuracy of CK-19, Galectin-3 and HBME-1 on papillary thyroid carcinoma: a meta-analysis. Int J Clin Exp Pathol. 2017; 10(8): 8130-8140.
45. Xia E, Wang Y, Bhandari A. CITED1 gene promotes proliferation, migration and invasion in papillary thyroid cancer. Oncol Lett. 2018; 16(1): 105-112.
46. Sehic D, Ciornei CD, Gisselsson D. Evaluation of CITED1, SIX1, and CD56 protein expression for identification of blastemal elements in Wilms tumor. Am J Clin Pathol. 2014; 141(6): 828-833.
47. Nasu T, Oku Y, Takifuji K. Predicting lymph node metastasis in early colorectal cancer using the CITED1 expression. J Surg Res. 2013; 185(1): 136-142.
48. Song J, Wang W, Wang Y. Epithelial-mesenchymal transition markers screened in a cell-based model and validated in lung adenocarcinoma. BMC Cancer. 2019; 19(1): 680.
49. Wu J, Boström P, Sparks LM. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. Cell. 2012; 150(2): 366-376.
50. Wu J, Cohen P, Spiegelman BM. Adaptive thermogenesis in adipocytes: is beige the new brown? Genes Dev. 2013; 27(3): 234-250.
51. Cohen P, Spiegelman BM. Brown and Beige Fat: Molecular Parts of a Thermogenic Machine. Diabetes. 2015; 64(7): 2346-2351.

52. Matsukawa T, Villareal MO, Motojima H. Increasing cAMP levels of preadipocytes by cyanidin-3-glucoside treatment induces the formation of beige phenotypes in 3T3-L1 adipocytes. J Nutr Biochem. 2017; 40: 77-85.

53. Lizcano F, Vargas D, Gómez Á. Human ADMC-Derived Adipocyte Thermogenic Capacity Is Regulated by IL-4 Receptor. Stem Cells Int. 2017; 2017: 2767916.

54. Vargas D, Rosales W, Lizcano F. Modifications of Human Subcutaneous ADMSC after PPARγ Activation and Cold Exposition. Stem Cells Int. 2015; 2015: 196348.