PGC-1α在肿瘤中的作用最新研究进展

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摘要 过氧化物酶体增殖物激活受体γ辅助活化因子1α(PGC-1α)是一种重要的调节多种代谢途径的蛋白, 如氧化代谢和能量代谢。它还参与调控线粒体的合成及功能。鉴于肿瘤细胞代谢的改变和适应性强的特点, 研究PGC-1α在肿瘤中的作用至关重要。尽管PGC-1α在癌症中的表达及临床研究很多, 但PGC-1α在癌症中的作用仍存在许多争议。该文将回顾PGC-1α在癌症中的一些最新研究数据, 为进一步了解PGC-1α与肿瘤之间的关系提供更多的参考。

关键词 PGC-1α; 抗肿瘤; 促肿瘤

Advances in Research on Effect of PGC-1α in Tumors

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Abstract The peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α)is an important regulator of diverse metabolic pathways, such as oxidative metabolism and energy homeostasis. It is also involved in regulating mitochondrial biogenesis and function. Given the altered and highly adaptable metabolism of tumor cells, it is very important to study the role of PGC-1α in tumor. Although the expression and clinical research of PGC-1α in cancer are many, there are still many controversies about the role of PGC-1α in cancer. This article will review the latest research data of PGC-1α in cancer, and provide more reference for further understanding the relationship between PGC-1α and cancer.

Keywords PGC-1α; anti-tumor; tumor promotion

代谢的重编程是癌细胞的重要特征, 它给予癌细胞在缺乏营养的微环境下生长和生存的能力[1], 而过氧化物酶体增殖物激活受体γ辅助激因子1α(peroxisome proliferator-activated receptor γ co-activator 1α, PGC-1α)对于细胞快速适应能量缺失的环境至关重要。PGC-1α是线粒体生物合成和功能的主要调节因子, 还包括对氧化磷酸化、脂肪酸/脂质代谢和活性氧(ROS)水平的调节[2]。鉴于肿瘤细胞代谢的改变和高度适应性, 研究PGC-1α在肿瘤中的作用是很有意义的。许多研究显示, PGC-1α的高表达和低表达都与肿瘤及预后不良有关。因此, PGC-1α作为肿瘤的促进剂还是抑癌剂仍存在争议。

1 PGC-1α简介

*PGC-1α*基因定于染色体4p15.2, 由编码91 kDa蛋白的13个外显子组成。PGC-1α蛋白质的N-端区域能与组蛋白乙酰转移酶蛋白(如p300或SRC-1)相互作用, 促进转录复合物对DNA的连接, N-端半部

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有3个LXXLL序列能与多种转录因子结合。在C末端有一个富含精/丝氨酸的模体结构和一个RNA加工域, 在mRNA剪接中起着重要的作用[3]。

PGC-1α蛋白能与PPARγ、核呼吸因子1/2(Nrf1-2)、叉头盒O3(FOXO 3a)、环-AMP(cAMP)反应元件结合蛋白(cAMP-response element binding protein, CREB)和雌激素相关受体-α(ERRα)等20种核受体因子结合[2,4]。PPARγ以其在脂肪生成、热生成和线粒体合成过程中的作用而闻名, 而Nrf1/2、ERRα和FoxO3a对线粒体生成、抗氧化防御和代谢应激的快速反应具有重要意义(图1); 更重要的是, 它们既是PGC-1α的靶标, 也是PGC-1α的合作伙伴[5-6]。

作为代谢适应的关键调节因子, PGC-1α的活性在转录后水平也得到了精细的调节。例如, 组蛋白乙酰转移酶GCN5的抑制作用和SIRT1(sirtuin 1)去乙酰化酶的激活作用是应对代谢变化的主要调节循环, 这些酶分别对乙酰辅酶A和NAD^+的水平作出应答[7]。此外, AMP依赖的蛋白激酶(AMPK)和p38能促进PGC-1α的活性, 而磷酸化的AKT能抑制其活性[2-3](图1)。

2 肿瘤中PGC- 1α的调控机制

PGC-1α的表达上升主要通过如下两种通路: 一是AMPK介导的PGC-1α的磷酸化, 这是PGC-1α启动子自诱导表达所必需的[8]。另一种是PGC-1α/ERRα自激活系统[9]。其他的诱导因子还包括p53和黑色素瘤谱系基因*MITF*[2]。相比之下, 有许多机制能下调PGC-1α蛋白水平。首先, *PPARGC1A*基因容易发生甲基化, 这在其他疾病, 特别是代谢综合征的研究中得到了证明[10-11]。在糖尿病患者中甲基化可能是由于DNA甲基转移酶DNMT3b所致, 它通常参与胚胎发生过程中的DNA甲基化, 并被发现在乳腺癌、结肠癌和前列腺癌中上调[12]。*PPARGC1A*甲基化在癌症中的作用还尚未报道。

其次, PGC-1α可以通过泛素–蛋白酶体途径调节。PGC-1α蛋白被GSK3β磷酸化后被降解[13]。在神经元和癌细胞中, 核蛋白Necdin能抑制PGC-1α的泛素化, 从而有助于维持OXPHOS的完整性[14]。有趣的是, Necdin还能抑制乳腺癌的转移[15], 并且在其他肿瘤中表现出抑癌特性[16]。此外, TGF-β在肺癌细胞中能抑制PGC-1α的表达[17], 其他已知的能影响肿瘤发生的炎症细胞因子, 如TNFα、IL-6及TWEAK, 也可能抑制PGC-1α表达[18-20]。当然, 需要更多的研究来探讨所有这些和类似的因子在调控PGC-1α和癌细胞代谢中的作用。自噬有助于清除功能失调的线粒体, 这是由E3连接酶Parkin介导的。而Parkin活性的丧失会导致其下游靶标PARIS(ZNF746)的积累, PARIS是PGC-1α的转录抑制因子[21]。许多报告均显示, Parkin在癌症中的缺失或失活突变[22], 因此, 研究PARIS和PGC-1α下调在这些癌症中是很有意义的。

研究发现, 有大约20多个microRNAs能下调PGC-1α的表达, 大多在正常组织中进行, 主要是骨骼肌和肝细胞。例如, 在肥胖患者中发现miR-130b水平较高, 并且它在肌肉组织中能直接下调PGC-1α的表达[23]。在肿瘤方面, miRNAs 485、485-3p和-5p能直接抑制PGC-1α的表达, 约30例乳腺癌患者中发现PGC-1α被下调, 在肿瘤转移的患者中表

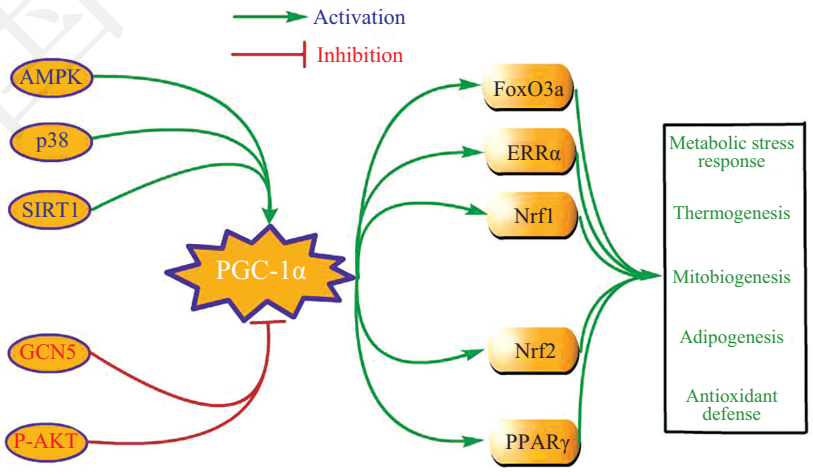

图1 PGC-1α信号通路

Fig.1 Signal path of PGC-1α

现得更明显[24]。同样在小鼠肝癌模型和人肝癌细胞株中, PGC-1α直接被miR-23a下调, 而IL6信号转导因子和转录激活因子3(STAT3)信号转导通路则使其表达上调[25]。许多研究报道了miR-23a在癌症中的作用, 但并没有对PGC-1α进行研究; 有趣的是, miR-23a在肿瘤中经常被下调[26]。相似地, miR-217可以抑制细胞增殖和诱导细胞凋亡, 研究发现, 在乳腺癌细胞中它能结合*PGC-1α*的mRNA并下调其表达[27]。另外, 降低表达水平并不是癌细胞阻止PGC-1α活性的唯一途径, 因为PGC-1α活性也可以被乙酰化所抑制, 特别是被GCN5所抑制。这种乙酰转移酶在造血系统恶性肿瘤和结肠癌等多种类型的癌组织中都有高表达, 而在结肠癌中, Myc可促进GCN5的表达, 从而加强了Myc与PGC-1α之间的反向关系[28]。

在上文中, 我们描述了PGC-1α在肿瘤中的调控机制, 但PGC-1α在肿瘤中的具体作用还不得而知, 有许多研究者通过观察PGC-1α在癌症中的表达水平, 并利用siRNA基因敲除或过表达的方法, 来研究PGC-1α在癌症中的作用。一些研究表明, PGC-1α在癌症中的表达降低, 如结肠癌[29]、乳腺癌[30]和卵巢癌[31], 而在部分其他研究中PGC-1α在癌症中的表达上升[32]。尽管已经发表了许多研究报告, 但PGC-1α在癌症中的作用仍然存在争议。因此, 下文将阐述PGC-1α在癌症中的作用及作用机制(表1)。

3 PGC-1α的促肿瘤作用

Shiota等[32]发现, PGC-1α能够在前列腺癌细胞中通过激活雄激素受体促进细胞生长, 而当*PGC-1α*基因被敲除后, 癌细胞的生长受到抑制。此外, PGC-1α在砷诱导的皮肤癌患者的肿瘤组织中水平显著上升, 这可能与其细胞增殖速度加快和线粒体的合成增强相关[33]。Bhalla等[34]也发现, 在PGC-1α转基因小鼠中, PGC-1α可以诱导乙酰辅酶A羧化酶和脂肪酸合成酶产生来促进肿瘤的生成和生长, 该研究还显示, 在小鼠中敲除PGC-1α后, 能够减少化学致癌物诱导的肝癌以及结肠癌的产生。这提示我们PGC-1α或许具有促进肿瘤发生的作用。相似地, Shin[35]首次证明了, PGC-1α的过表达可以通过上调Sp1和乙酰辅酶A结合蛋白促进细胞增殖以及肿瘤生成, 并且PGC-1α过表达还会导致抗氧化酶(如过氧化氢酶、超氧化物歧化酶等)的增加和ROS诱导的凋亡作用减弱。同样, *PGC-1α*基因的敲除可显著降低PGC-1α阳性黑色素瘤细胞系的细胞数量并诱导其凋亡, 提示PGC-1α对PGC-1α阳性黑色素瘤细胞的存活至关重要[36]。此外, 在PGC-1α缺失的黑色素瘤细胞中, 超氧化物歧化酶2(SOD2)的水平降低。而在黑素瘤细胞中过表达PGC-1α后, 其ROS解毒酶基因表达显著上升, 这些数据说明, PGC-1α促进抗氧化酶基因的表达, 在维持黑色素瘤细胞存活中起着至关重要的作用[36]。Vazquez等[36]也证明了PGC-1α缺失的细胞, 肿瘤体积明显缩小, 提示PGC-1α可能在肿瘤的生长中也起着重要的作用。脂肪合成代谢重编程是肿瘤细胞具有的一种特征。葡萄糖和谷氨酰胺通过为脂肪生成酶提供细胞质柠檬酸来帮助脂肪酸合成[37]。而同时谷氨酰胺也可以作为线粒体燃料, 这似乎对肿瘤的生存很重要[38]。在ErbB2阳性的乳腺癌细胞中, PGC-1α/ERRα复合物能够直接调控谷氨酰胺合成酶的表达, 为脂肪酸合成的重编程提供充足的谷氨酰胺[39]。而PGC-1α的过表达或ERRα的激活, 赋予了乳腺癌细胞即使在有限的营养条件也具有生长优势, 相关临床资料显示, PGC-1α的高表达伴随着不良预后, 这可能与其下游靶基因谷氨酰胺通路被激活有关[39]。PGC-1α的表达受到多种转录通路的影响。比如在黑色素瘤中, 黑色素细胞谱系转录主调节因子MITF就能够激活PGC-1α的表达[40]。而在PGC-1α缺失的黑色素瘤细胞中, 线粒体膜电位降低, ROS产生增加, 谷胱甘肽、胱硫醚和5-腺苷基同型半胱氨酸减少, 提示PGC-1α缺失的黑色素瘤细胞内有凋亡途径被激活[36]。另一个例子就是雄激素受体-AMP蛋白激酶(AMPK)信号轴能激活PGC-1α的表达, 从而驱动前列腺癌的生长优势[41]。也有证据显示, PGC-1α在野生型p53的肺癌中表达显著高于p53突变型的肿瘤[42]。而在H1944肺癌细胞中使用siRNA敲低PGC-1α后, 细胞增殖受到了抑制。此外, 在代谢应激条件下, PGC-1α能够与p53协同激活细胞周期抑制因子的转录, 并促进线粒体生物合成相关基因的表达。同时, 在PGC-1α敲除的细胞中氧化应激会导致p53诱导的凋亡产生[43]。另一方面, PGC-1α表达的增加可以通过维持氧化磷酸化和糖酵解之间的平衡来防止p53诱导的细胞凋亡[44]。

有研究显示, PGC-1α能通过雌激素相关受体α(ERRα)依赖途径激活VEGF的表达[45]。PGC-1α对HIF-1α活性具有调节作用。提高PGC-1α的表达水平能使耗氧率上升, 并且降低局部氧分压, 从而维

表1 PGC-1α在肿瘤中的作用及作用机制

Table 1 The role and action mechanisms of PGC-1α in cancer

实验方法 Experimental system	细胞类型 Cell type	作用及作用机制 Role and action mechanism	参考文献 Reference
Tumor-promoting functions of PGC-1α			
PGC-1α knockdown	Human prostate cancer PC3, LN-Cap cells	Stimulation of cell proliferation; activation of androgen receptor	[32]
Increased PGC-1α expression in arsenic-induced skin cancer	Skin cancer	Stimulation of cell proliferation; enhanced mitochondrial biogenesis	[33]
Pgc-1α knockout and knockdown by lentivirus-based PGC-1α shRNA	Human colorectal cancer cell line (Colo205)	Stimulation of carcinogenesis and tumor growth; induction of lipogenic enzymes	[34]
PGC-1α overexpression by PGC-1α plasmid	Human embryonic kidney cells, human colorectal cancer SNU-C4 cells, xenograft model	Stimulation of cell proliferation and tumorigenesis; upregulation of Sp1 and ACBP; upregulation of antioxidant enzyme (catalase, SOD)	[35]
PGC-1α shRNA knockdown	Human melanoma PGC-1α-positive A375 cells, xenograft model	Inhibition of apoptosis; decreased ROS production, induction of ROS detoxifying enzymes	[36]
Increased PGC-1α expression in breast cancer cell	Breast cancer cell	Stimulation of cell proliferation; enhanced glutamine-mediated lipid biosynthesis	[39]
Pgc-1α shRNA knockdown	Human prostate cancer cell line (C4-2 cells)	Stimulation of cell proliferation; increased mitochondrial biogenesis	[41]
PGC-1α shRNA knockdown and PGC-1α overexpression	Human breast cancer cell, human melanoma cells	Stimulation of cell proliferation, increased invasion; increased mitochondrial biogenesis and oxidative phosphorylation	[42]
Anticancer functions of PGC-1α			
PGC-1α overexpression by adenovirus infection	Human ovarian cancer cell line (Ho-8910)	Induction of apoptosis; downregulation of Bcl-2 and upregulation of Bax	[31]
PGC-1α overexpression by adenovirus infection	Human hepatoma cell line (HepG2)	Inhibition of cell motility; upregulation of E-cadherin	[51]
PGC-1α overexpression	Human colorectal cancer cell lines (HT29 and HCT116)	Induction of apoptosis; ROS accumulation	[52]
Increased expression of PGC-1α by bezafibrate (PPAR panagonist)	Human cancer cell lines (HeLa, 143B, MDA-MB-231)	Inhibition of cell proliferation and invasion; increased mitochondrial biogenesis	[57]
PGC-1α overexpression	Human prostate cancer cell	Inhibition of cell proliferation and inhibition of metastasis; activation of ERRα-dependent	[58]
PGC-1α overexpression by adenovirus infection, CRISPR-mediated PGC-1α depletion	Human melanoma cell	Transcriptional program; induction of catabolic state Inhibition of metastasis; inhibition of inhibitor of DNA binding protein 2 (ID2) and TCF-mediated gene transcription	[59]

持HIF-1α的稳定性[46]。此外, HIF-2α也是PGC-1α的转录靶点之一, 但其具体的转录机制还不是十分的清楚[47]。ERRα在许多癌症中都存在着高表达, 抑制其活性可以减少细胞增殖。最近许多研究都表明, PGC-1α在肿瘤中与ERRα存在着协同作用[48]。KSR1(kinase suppressor of Ras 1)是Raf/MEK/ERK信号通路中的一种关键蛋白, 其可以通过激活PGC-1α和ERRα来促进癌基因*Ras*诱导的恶性增殖[49]。有趣的是, 部分研究显示PGC-1α在肿瘤转移的开关也扮演着重要的角色。LeBleu等[50]证明, 循环性乳腺上皮癌细胞中PGC-1α表达增加, 线粒体生物合成以及氧化磷酸化增强, 可能与其高转移和患者预后不良相关。此外, 在MDA-MB-231乳腺癌和B16F10黑色素瘤细胞中敲低PGC-1α会减少ATP的生成, 降低肌动蛋白细胞骨架重塑, 以及减弱细胞的内/外渗, 并阻止其转移。LeBleu等[50]通过人类浸润性乳腺癌的临床分析也表明了PGC-1α在侵袭性癌细胞中的表达与转移形成密切相关。

4 PGC-1α的抗肿瘤作用

与上述的PGC-1α促肿瘤作用不同, 有研究表明, PGC-1α也具有抗肿瘤作用。PGC-1α在结肠癌[29]、

乳腺癌[30]和卵巢癌细胞[31]中减少, 在卵巢癌细胞系Ho-8910中过表达PGC-1α可能引起Bcl-2下调和Bax上调而导致细胞凋亡, 提示PGC-1α可能具有抑制肿瘤生长的功能。Lee等[51]发现, 在HepG2人肝癌细胞中通过腺病毒感染来过表达PGC-1α, 能够诱导E-cadherin增加以及细胞活性降低。也有报道显示, 在HT29和HCT116结肠癌细胞中过表达PGC-1α会造成ROS积累导致细胞凋亡的产生。同时PGC-1α的过表达还能减小HT29移植瘤的肿瘤体积, 也提示我们PGC-1α具有肿瘤抑制因子的作用[52]。Zhang等[53]的研究表明, 在VHL-(von Hippel-Lindau-)缺陷型透明肾细胞癌中有较高水平的HIF-1α和糖酵解。而HIF-1α可诱导转录抑制因子Dec1的产生, 从而抑制PGC-1α的表达, 导致线粒体呼吸减弱[54]。此外, 在VHL缺陷的细胞中表达PGC-1α后, 伴随着线粒体功能恢复的同时, 也会诱导氧化应激并抑制肿瘤的生长[54]。这些数据与临床上的透明细胞癌数据一致, 表明高质量的线粒体能够降低肿瘤的侵袭性[55], 并且PGC-1α的低水平表达与患者预后较差相关[54]。我们也发现, PGC-1α通过与热休克因子1协同作用, 能够减弱癌细胞生长所需的应激反应[56]。Wang和Moraes[57]发现, 使用PPAR激动剂(bezafibrate)处理后PGC-1α表达上升, 线粒体生物合成增加, 从而使糖酵解条件下癌细胞的增殖被抑制, 并降低了癌细胞的侵袭性。另外, 利用miRNA-217下调PGC-1α可促进乳腺癌细胞的增殖, 提示PGC-1α具有抑癌作用[27]。最近, Torrano等[58]发现, PGC-1α能够通过一种ERRα依赖的转录程序抑制前列腺癌转移。有研究发现, 侵袭性高的黑素瘤细胞其PGC-1α表达水平都很低。并且, 这些PGC-1α低水平的细胞其与转移相关的如整合素, TGF-β、Wnt信号元件都具有较高的表达水平。此外, PGC-1α基因缺失会提高低侵袭性黑色素瘤细胞的转移能力。与之相反的是, 在黑色素瘤细胞中过表达PGC-1α能够通过直接调控DNA结合蛋白2抑制剂(ID2)和减弱TCF介导的基因转录, 抑制癌细胞转移[59]。

5 结语和展望

如上所述, 人们对PGC-1α在肿瘤进展中的作用进行了大量的研究。然而有趣的是, PGC-1α既可以作为肿瘤的启动子, 也可以作为肿瘤的抑制因子, 例如, 在前列腺癌、皮肤癌、I型子宫内膜癌中, PGC-1α可以促进肿瘤生成, 而在肾透明细胞癌以及肝癌中, PGC-1α又能够抑制肿瘤形成。此外, 在卵巢癌、结肠癌、乳腺癌和黑素瘤中, PGC-1α似乎扮演着促肿瘤和抗肿瘤的双重角色, 目前还没有明确的机制来解释这种矛盾的双重效应, 也许, PGC-1α它既不是肿瘤的帮凶, 也不是肿瘤的敌人, 它只是针对特定的环境对细胞代谢进行调节, 使其能在短时间内利用多种不同类型的营养物质, 从而适应细胞应激。因此, 研究者们认为, PGC-1α在肿瘤上的具体作用还是取决于其组织背景和肿瘤类型, 所以需要进一步研究PGC-1α与其他转录伙伴之间相互作用, 才能更好的了解PGC-1α在癌症中的具体作用。

参考文献 (References)

1 Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144(5): 646-74.

2 Tan Z, Luo X, Xiao L, Tang M, Bode AM, Dong Z, *et al*. The role of PGC1alpha in cancer metabolism and its therapeutic implications. Mol Cancer Ther 2016; 15(5): 774-82.

3 Martinez-Redondo V, Pettersson AT, Ruas JL. The hitchhiker's guide to PGC-1alpha isoform structure and biological functions. Diabetologia 2015; 58(9): 1969-77.

4 Villena JA. New insights into PGC-1 coactivators: redefining their role in the regulation of mitochondrial function and beyond. FEBS J 2015; 282(4): 647-72.

5 Spiegelman BM. Transcriptional control of mitochondrial energy metabolism through the PGC1 coactivators. Novartis Found Symp 2007; 287: 60-3.

6 Olmos Y, Valle I, Borniquel S, Tierrez A, Soria E, Lamas S, *et al*. Mutual dependence of Foxo3a and PGC-1alpha in the induction of oxidative stress genes. J Biol Chem 2009; 284(21): 14476-84.

7 Dominy JE, Jr., Lee Y, Gerhart-Hines Z, Puigserver P. Nutrient-dependent regulation of PGC-1alpha's acetylation state and metabolic function through the enzymatic activities of Sirt1/GCN5. Biochim Biophys Acta 2010; 1804(8): 1676-83.

8 Jager S, Handschin C, St-Pierre J, Spiegelman BM. AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1alpha. Proc Natl Acad Sci USA 2007; 104(29): 12017-22.

9 Ranhotra HS. The orphan estrogen-related receptor alpha and metabolic regulation: new frontiers. J Recept Signal Transduct Res 2015; 35(6): 565-8.

10 Barres R, Osler ME, Yan J, Rune A, Fritz T, Caidahl K, *et al*. Non-CpG methylation of the PGC-1alpha promoter through DNMT3B controls mitochondrial density. Cell Metab 2009; 10(3): 189-98.

11 Su X, Chu Y, Kordower JH, Li B, Cao H, Huang L, *et al*. PGC-1alpha promoter methylation in Parkinson's disease. PLoS One 2015; 10(8): e0134087.

12 Zhang W, Xu J. DNA methyltransferases and their roles in tumorigenesis. Biomark Res 2017; 5: 1.

13 Anderson RM, Barger JL, Edwards MG, Braun KH., O'Connor

CE, Prolla TA, *et al*. Dynamic regulation of PGC-1α localization and turnover implicates mitochondrial adaptation in calorie restriction and the stress response. Aging Cell 2008: 7(1): 101-11.

14 Hasegawa K, Yasuda T, Shiraishi C, Fujiwara K, Przedborski S, Mochizuki H, *et al*. Promotion of mitochondrial biogenesis by necdin protects neurons against mitochondrial insults. Nat Commun 2016; 7: 10943.

15 Lee M, Beggs SM, Gildea D, Bupp S, Lichtenberg J, Trivedi NS, *et al*. Necdin is a breast cancer metastasis suppressor that regulates the transcription of c-Myc. Oncotarget 2015: 6(31): 31557-68.

16 De Faveri LE, Hurst CD, Platt FM, Taylor CF, Roulson JA, Sanchez-Carbayo M, *et al*. Putative tumour suppressor gene necdin is hypermethylated and mutated in human cancer. Br J Cancer 2013; 108(6): 1368-77.

17 Sohn EJ, Kim J, Hwang Y, Im S, Moon Y, Kang DM. TGF-β suppresses the expression of genes related to mitochondrial function in lung A549 cells. Cell Mol Biol 2012; 58: 1763-7.

18 Barroso WA, Victorino VJ, Jeremias IC, Petroni RC, Ariga SKK, Salles TA, *et al*. High-fat diet inhibits PGC-1alpha suppressive effect on NFkappaB signaling in hepatocytes. Eur J Nutr 2018; 57(5): 1891-900.

19 Ruiz-Andres O, Suarez-Alvarez B, Sánchez-Ramos C, Monsalve M, Sanchez-Niño MD, Ruiz-Ortega M, *et al*. The inflammatory cytokine TWEAK decreases PGC-1α expression and mitochondrial function in acute kidney injury. Kidney Int 2016: 89(2): 399-410.

20 Li J, Ke W, Zhou Q, Wu Y, Luo H, Zhou H, *et al*. Tumour necrosis factor-alpha promotes liver ischaemia-reperfusion injury through the PGC-1alpha/Mfn2 pathway. J Cell Mol Med 2014; 18(9): 1863-73.

21 Shin JH, Ko HS, Kang H, Lee Y, Lee YI, Pletinkova O, *et al*. PARIS (ZNF746) repression of PGC-1alpha contributes to neurodegeneration in Parkinson's disease. Cell 2011; 144(5): 689-702.

22 Bernardini JP, Lazarou M, Dewson G. Parkin and mitophagy in cancer. Oncogene 2017; 36(10): 1315-27.

23 Wang YC, Li Y, Wang XY, Zhang D, Zhang H, Wu Q, *et al*. Circulating miR-130b mediates metabolic crosstalk between fat and muscle in overweight/obesity. Diabetologia 2013; 56(10): 2275-85.

24 Lou C, Xiao M, Cheng S, Lu X, Jia S, Ren Y, *et al*. MiR-485-3p and miR-485-5p suppress breast cancer cell metastasis by inhibiting PGC-1alpha expression. Cell death Dis 2016; 7: e2159.

25 Wang B, Hsu SH, Frankel W, Ghoshal K, Jacob ST. Stat3-mediated activation of microRNA-23a suppresses gluconeogenesis in hepatocellular carcinoma by down-regulating glucose-6-phosphatase and peroxisome proliferator-activated receptor gamma, coactivator 1 alpha. Hepatology 2012; 56(1): 186-97.

26 Roufayel R, Kadry S. Expression of miR-23a by apoptotic regulators in human cancer: A review. Cancer Biol Ther 2017; 18: 269-76.

27 Zhang S, Liu X, Liu J, Guo H, Xu H, Zhang G. PGC-1 alpha interacts with microRNA-217 to functionally regulate breast cancer cell proliferation. Biomed Pharmacother 2017; 85: 541-8.

28 Yin YW, Jin HJ, Zhao W, Gao B, Fang J, Wei J, *et al*. The histone acetyltransferase GCN5 expression is elevated and regulated by c-Myc and E2F1 transcription factors in human colon cancer. Gene Expr 2015; 16(4): 187-96.

29 Feilchenfeldt J, Bründler M-A, Soravia C, Tötsch M, Meier CA. Peroxisome proliferator-activated receptors (PPARs) and associated transcription factors in colon cancer: reduced expression of PPARγ-coactivator 1 (PGC-1). Cancer Lett 2004; 203(1): 25-33.

30 Watkins G, Douglas-Jones A, Mansel R, Jiang W. The localisation and reduction of nuclear staining of PPARγ and PGC-1 in human breast cancer. Oncol Rep 2004; 12(2): 483-8.

31 Zhang Y, Ba Y, Liu C, Sun G, Ding L, Gao S, *et al*. PGC-1alpha induces apoptosis in human epithelial ovarian cancer cells through a PPARgamma-dependent pathway. Cell Res 2007; 17(4): 363-73.

32 Shiota M, Yokomizo A, Tada Y, Inokuchi J, Tatsugami K, Kuroiwa K, *et al*. Peroxisome proliferator-activated receptor γ coactivator-1α interacts with the androgen receptor (AR) and promotes prostate cancer cell growth by activating the AR. Mol Endocrinol 2010; 24(1): 114-27.

33 Lee CH, Wu SB, Hong CH, Liao WT, Wu CY, Chen GS, *et al*. Aberrant cell proliferation by enhanced mitochondrial biogenesis via mtTFA in arsenical skin cancers. Am J Pathol 2011; 178(5): 2066-76.

34 Bhalla K, Hwang BJ, Dewi RE, Ou L, Twaddel W, Fang HB, *et al*. PGC1alpha promotes tumor growth by inducing gene expression programs supporting lipogenesis. Cancer Res 2011; 71(21): 6888-98.

35 Shin SW, Yun SH, Park ES, Jeong JS, Kwak JY, Park JI. Overexpression of PGC1alpha enhances cell proliferation and tumorigenesis of HEK293 cells through the upregulation of Sp1 and Acyl-CoA binding protein. Int J Oncol 2015; 46(3): 1328-42.

36 Vazquez F, Lim JH, Chim H, Bhalla K, Girnun G, Pierce K, *et al*. PGC1alpha expression defines a subset of human melanoma tumors with increased mitochondrial capacity and resistance to oxidative stress. Cancer Cell 2013; 23(3): 287-301.

37 Deberardinis RJ, Sayed N, Ditsworth D, Thompson CB. Brick by brick: metabolism and tumor cell growth. Curr Opin Genet Dev 2008; 18(1): 54-61.

38 Hensley CT, Wasti AT, DeBerardinis RJ. Glutamine and cancer: cell biology, physiology, and clinical opportunities. J Clin Invest 2013; 123(9): 3678-84.

39 McGuirk S, Gravel SP, Deblois G, Papadopoli DJ, Faubert B, Wegner A, *et al*. PGC-1α supports glutamine metabolism in breast cancer. Cancer Metab 2013; 1(1): 22.

40 Haq R, Shoag J, Andreu-Perez P, Yokoyama S, Edelman H, Rowe GC, *et al*. Oncogenic BRAF regulates oxidative metabolism via PGC1alpha and MITF. Cancer Cell 2013; 23(3): 302-15.

41 Tennakoon JB, Shi Y, Han JJ, Tsouko E, White MA, Burns AR, *et al*. Androgens regulate prostate cancer cell growth via an AMPK-PGC-1alpha-mediated metabolic switch. Oncogene 2014; 33(45): 5251-61.

42 Taguchi A, Delgado O, Celiktas M, Katayama H, Wang H, Gazdar AF, *et al*. Proteomic signatures associated with p53 mutational status in lung adenocarcinoma. Proteomics 2014; 14(23/24): 2750-9.

43 Sen N, Satija YK, Das S. PGC-1alpha, a key modulator of p53, promotes cell survival upon metabolic stress. Mol Cell 2011; 44(4): 621-34.

44 Chen W, Wang Q, Bai L, Chen W, Wang X, Tellez CS, *et al*.

RIP1 maintains DNA integrity and cell proliferation by regulating PGC-1alpha-mediated mitochondrial oxidative phosphorylation and glycolysis. Cell Death Differ 2014; 21(7): 1061-70.

45 Arany Z, Foo SY, Ma Y, Ruas JL, Bommi-Reddy A, Girnun G, *et al*. HIF-independent regulation of VEGF and angiogenesis by the transcriptional coactivator PGC-1alpha. Nature 2008; 451(7181): 1008-12.

46 O'Hagan KA, Cocchiglia S, Zhdanov AV, Tambuwala MM, Cummins EP, Monfared M, *et al*. PGC-1 is coupled to HIF-1-dependent gene expression by increasing mitochondrial oxygen consumption in skeletal muscle cells. Proc Natl Acad Sci USA 2009; 106(7): 2188-93.

47 Rasbach KA, Gupta RK, Ruas JL, Wu J, Naseri E, Estall JL, *et al*. PGC-1alpha regulates a HIF2alpha-dependent switch in skeletal muscle fiber types. Proc Natl Acad Sci USA 2010; 107(50): 21866-71.

48 Girnun GD. The diverse role of the PPARgamma coactivator 1 family of transcriptional coactivators in cancer. Semin Cell Dev Biol 2012; 23(4): 381-8.

49 Fisher KW, Das B, Kortum RL, Chaika OV, Lewis RE. Kinase suppressor of ras 1 (KSR1) regulates PGC1alpha and estrogen-related receptor alpha to promote oncogenic Ras-dependent anchorage-independent growth. Mol Cell Biol 2011; 31(12): 2453-61.

50 LeBleu VS, O'Connell JT, Gonzalez Herrera KN, Wikman H, Pantel K, Haigis MC, *et al*. PGC-1alpha mediates mitochondrial biogenesis and oxidative phosphorylation in cancer cells to promote metastasis. Nat Cell Biol 2014; 16(10): 992-1003.

51 Lee HJ, Su Y, Yin PH, Lee HC, Chi CW. PPARγ_PGC-1α pathway in E-cadherin expression and motility of HepG2 cells. Anticancer Res 2009; 29(12): 5057-63.

52 D'Errico I, Salvatore L, Murzilli S, Lo Sasso G, Latorre D, Martelli N, *et al*. Peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC1alpha) is a metabolic regulator of intestinal epithelial cell fate. Proc Natl Acad Sci USA 2011; 108(16): 6603-8.

53 Zhang H, Gao P, Fukuda R, Kumar G, Krishnamachary B, Zeller KI, *et al*. HIF-1 inhibits mitochondrial biogenesis and cellular respiration in VHL-deficient renal cell carcinoma by repression of C-MYC activity. Cancer Cell 2007; 11(5): 407-20.

54 LaGory EL, Wu C, Taniguchi CM, Ding CC, Chi JT, von Eyben R, *et al*. Suppression of PGC-1alpha is critical for reprogramming oxidative metabolism in renal cell carcinoma. Cell Rep 2015; 12(1): 116-27.

55 Simonnet H, Alazard N, Pfeiffer K, Gallou C, Béroud C, Demont J, *et al*. Low mitochondrial respiratory chain content correlates with tumor aggressiveness in renal cell carcinoma. Carcinogenesis 2002; 23(5): 759-68.

56 Roeder NMaRG. Direct link between metabolic regulation and the heat-shock response through the transcriptional regulator PGC-1α. Proc Natl Acad of Sci USA 2015; 112(42): E5669-78.

57 Wang X, Moraes CT. Increases in mitochondrial biogenesis impair carcinogenesis at multiple levels. Mol Oncol 2011; 5(5): 399-409.

58 Torrano V, Valcarcel-Jimenez L, Cortazar AR, Liu X, Urosevic J, Castillo-Martin M, *et al*. The metabolic co-regulator PGC1alpha suppresses prostate cancer metastasis. Nat cell Biol 2016; 18(6): 645-56.

59 Luo C, Lim JH, Lee Y, Granter SR, Thomas A, Vazquez F, *et al*. A PGC1alpha-mediated transcriptional axis suppresses melanoma metastasis. Nature 2016; 537(7602): 422-6.