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Metabolic Reprogramming in Oral Squamous Cell Carcinoma

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Abstract

Oral Squamous Cell Carcinoma (OSCC) is the sixth most common human malignancy worldwide. Metabolic reprogramming is one of the hallmarks of cancer, and metabolic change favors rapid energy production and biosynthetic capabilities. The energy adaptation pathways promote tumor cells to survive, proliferation, and metastasis, which may be induced by hypoxia, free radicals, and nutrient depletion from microenvironment. The stresses of microenvironment also cause cancer cell autophagy, which is the major way to escape from cell death. Thus, many metabolic enzymes have become potential targets for new cancer therapies. Uncovering the intrinsic and extrinsic mechanisms that control the maintenance of cancer metabolism and autophagy is critical for developing novel therapeutic strategies to target cancer progression and recurrence.

Keywords: Oral squamous cell carcinoma; Cancer metabolism; Mitochondrion; Autophagy

Abbreviations

OSCC-Oral Squamous Cell Carcinoma; ATP-Adenosine 5'-triphosphate; OXPHOS-Oxidative Phosphorylation; Acetyl-CoA-Acetyl-coenzyme A; TCA-Tricarboxylic acid; ETC-Electron Transport Chain; ROS-Reactive Oxygen Species; HIF-Hypoxia-Inducible Factor; VEGF-Vascular Endothelial Growth Factor; pVHL-Von Hippel-Lindau; PHD1: Prolyl hydroxylase; ARD1-Arrest-Defective 1 Protein; PI3K-Phosphoinositide 3-kinase; HK II-Hexokinase II; PFK2-Phosphofructokinase 2; GLUT1-Glucose Transporter 1; PKM2-Pyruvate kinase M2; LDH-lactate dehydrogenase; mtDNA-Mitochondrial DNA; mtTFA-Mitochondrial Transcription Factor A; FOXOs-Forkhead Transcription Factors of the O class; FOXO3a-Forkhead-Box Protein O3a; ATG16L1-Autophagy-Related 16-like 1

Introduction

OSCC is one of the 10 most frequent cancers worldwide [1-3], and five-year survival rate is less than 50% [1]. The reason of high mortality in OSCC is metastasis, a process that cancer cells spread from a primary site and form tumors at proximal lymph nodes or distant sites [4-8]. Metabolic reprogramming plays crucial roles in cancer progression, including metastasis. Tumor cells exhibit an altered metabolism that is characterized by elevated uptake of glucose and increased glycolytic rate; this observation was first reported by Otto Warburg [10]. Cancer cells generated the majority of ATP by glycolysis, even when grown in the presence of oxygen. However, recent studies have revealed the additional energy generation dependent on mitochondrial biogenesis [11].To addresses this issue; we aim to review the cancer metabolism and autophagy in OSCC progression. How does cancer cells adapt to microenvironment by using biogenetic reprogramming as a cell survival strategy? How does biogenetic reprogramming modulate a series of oncogenic and/or tumor suppressive signaling pathways? Understanding the metabolic pathways in tumors could contribute to the identification of novel therapeutic target and the development of more effective cancer therapeutic.

Cancer metabolism in microenvironment

Glycolysis and mitochondrial Oxidative Phosphorylation (OXPHOS) are the two main metabolic pathways to generate ATP. Glycolysis produces pyruvate which moving into the mitochondria converts to Acetyl-coenzyme A (acetyl-CoA), then enter the Tricarboxylic Acid (TCA) cycle and OXPHOS, generated up to 36 ATPs upon complete oxidative of one glucose molecule [12]. During OXPHOS, oxygen is reduced to water in mitochondrial Electron Transport Chain (ETC). Under the hypoxia conditions, pyruvate is converted to lactate which completes glycolysis cycle and triggers Warburg effect. As the early tumor expands, cancer cells are exposed to hypoxia condition. Consequently, tumor hypoxia is a poor prognostic factor in malignancy [13-15]. Hypoxia-inducible factor-1α (HIF-1α) is a transcription factor that increases glycolytic capacity and decreases mitochondrial respiration in OSCC [16,17]. Decreased dependence on aerobic respiration becomes advantageous to tumor cells. It also stimulates angiogenesis by up regulating Vascular Endothelial Growth Factor (VEGF) [18]. Under normoxic conditions, the protein is tightly controlled by ubiquitin-dependent degradation; binding to the von Hippel-Lindau (pVHL) tumor suppressor protein [19]. Loss of VHL expression was closely associated with pathologic grading, lymph node metastasis, poor prognosis, and EMT in OSCC [20]. HIF-1α binds to pVHL only after it is hydroxylated by HIF Prolyl hydroxylase (PHD1) [21-23] and acetylated by Arrest-defective 1 protein (ARD1) acetyltransferase [24]. This posttranslational modification (i.e., hydroxylation and acetylation) of HIF-1α protein promotes its association with pVHL and subsequent degradation [25-27]. The Warburg effect that is, an uncoupling of glycolysis from oxygen levels, cannot be explained solely by upregulation of HIF-

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1α. These oxygen-independent mechanisms to activate oncogenesis tumor suppressor genes still need further investigations.

Important signaling pathways in OSCC metabolism

Cancer progression is dependent on the reprogramming of metabolism. Not only may the tumor microenvironment select for altered metabolic pathways, but also can oncogenes drive metabolic changes. The signaling molecule, Ras, a powerful oncogene when mutated, promotes glycolysis [28,29]. Ras was also confirmed as a direct target of miR-206, an important regulator in OSCC to reduce proliferation and invasion/migration [30]. The phosphoinositide 3-kinase (PI3K) is one of the most activated signaling pathways, which links oncogenesis and glucose metabolism in OSCC [31,32]. Mutations in PI3K could provide strong growth and survival signals to tumor cells, and contribute to oncogene activation of the AKT pathway [33,34]. AKT1 is the crucial driver of the aerobic glycolysis pathway to stimulate ATP production, which ensures cells that have bioenergetic capacity to respond to growth signals [35,36]. AKT1 stimulates glycolysis by increasing the membrane translocation of glucose transporters and phosphorylating key glycolytic enzymes, such as hexokinase II (HK II) and Phosphofructokinase 2 (PFK2) [37,38]. In addition to its well-described roles in controlling cell growth and proliferation, the downstream transcription factor, Myc, also has several important effects on OSCC metabolism [39,40], including glutaminolysis [41]. It may predict OSCC patients with poor prognosis [42]. Regulation of metabolism is involved in tumor suppressors, such as p53 [43]. p53 inhibits the glycolytic pathway by declined the transcription activity of the glucose transporter 1 (GLUT1) [44]. Loss of the tumor suppressor protein p53 resulted in Warburg effect. Clinically, numbers of OSCC patients have p53 mutation [45]. Taken together, tumor microenvironment may induce or interact oncogenes and tumor suppressor genes to drive metabolic shifts resulted in OSCC initiation, development, and progression.

Key enzymes of glucose metabolism in OSCC

Glucose is the major source of energy for cells, and GLUT1 is the most important transporter to facilitate the glucose transportation crossing the plasma membranes in humans [46]. GLUT1 is aberrantly expressed in several tumor types. Studies have implicated its expression as a prognostic and diagnostic marker in OSCC clinically [47]. Reduction of VHL [48] and miR-340 [49] playas the switches to contribute the glucose uptake in OSCC by regulating GLUT1 expression.HK are a family of enzymes that catalyze the first phosphorylation of glucose to glucose-6-phosphate.HK II binds to mitochondria is via the outer membrane protein known as the voltage-dependent anion channel VDAC [50]. It has been shown that high expression of HK II correlated with poor prognosis in OSCC, and the precise mechanism is still under investigation [51-52]. PKM2 is involved in OSCC initiation and progression by promoting cell proliferation and migration, and reducing apoptosis critically. Overexpression of PKM2 correlates with aggressive clinicopathological features and poor patients' clinical outcome [53]. In cancer metabolism, lactate is also important in glucose pathway. Lactate is made from pyruvate by lactate dehydrogenase (LDH) enzyme. In tumor microenvironment, excess lactate is secreted, and contributes to an extracellular environment to promote OSCC progression [54]. The key enzyme, LDH, plays as a potential diagnostic marker and therapeutic index in OSCC [55,56]. Collectively, these studies support a model that metabolites, like lactate, facilitate malignant cancer development and metastasis, and could be the potential targets therapeutically in the future.

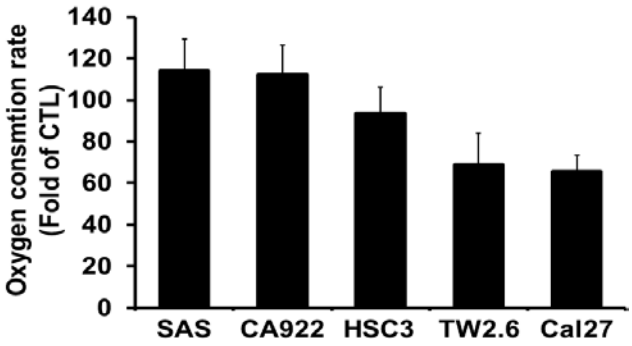

Figure 1: Mitochondrial metabolism is related to malignant behavior in OSCC cell lines. The basal oxygen consumption rate was determinate with a Seahorse XF24 analyzer. The experiment was performed at least 6 times. Error bar indicates S.D. value.

The role of mitochondria in cancer metabolism

The traditional view of cancer metabolism relying on glycolysis is due to mitochondrial dysfunction. However, the role of mitochondrial metabolism in modulating cancer progression is developed. Recent studies indicated that mitochondrial activity is essential for cancer cells. Mitochondrion plays important roles as energetic centers. Increased mitochondrial biogenesis promotes tumorigenesis, and loss of Mitochondrial DNA (mtDNA) copy number leads to decrease tumorigenesis due to OXPHOS impairment [57]. Many evidence showed that elevated OXPHOS and mitochondrial activity is associated with cancer aggressiveness. As we know, mitochondrial transcription factor A (mtTFA/TFAM) is necessary for mtDNA maintenance, mitochondrial function and morphology [58-60]. Recent studies indicated that mtTFA significantly correlates to cancer behavior [61,62]. Its expression also highly associated with tumor progression and poor prognosis of patients with endometrial adenocarcinoma [63], and colorectal adenocarcinoma [64]. Loss of mtTFA also inhibited Kras-mediated lung tumorigenesis [65]. Enhanced mitochondrial biogenesis via mtTFA results in aberrant cell proliferation in arsenical skin cancer [66-67]. These data indicate that increased mtTFA may provide more energy for cancer progression. In our preliminary study, we found that advanced invasive OSCC cells, such as SAS and CA922 cells, showed more elevated oxygen consumption rate than less motility cells, including TW2.6 and Cal27 (Figure 1).

Although tumor cells prefer to use glycolysis as major bioenergetic pathway in the presence of oxygen, OXPHOS still play a crucial role in cancer progression. Mitochondrial gene-knockout B16 cells showed delayed subcutaneous tumor growth and failed to form lung tumors. The results suggest that mitochondrial function is required for tumor metastasis [68]. p32/gC1qR/C1QBP/HABP1 is a mitochondrial protein over expressed in certain cancer cells. Fogal V et al. showed that knocked-down p32 expression in human cancer cells strongly shifts their metabolism from OXPHOS to glycolysis. The p32-knockdown cells exhibited reduced synthesis of the mtDNA-

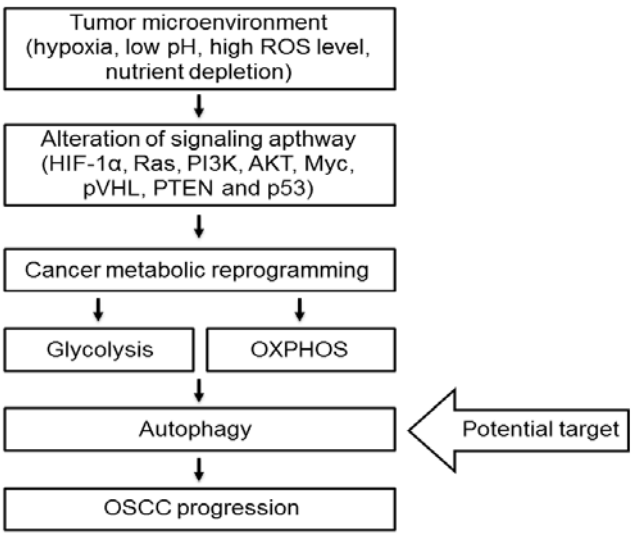

Figure 2: The correlation of tumor metabolism and microenvironment. The metabolic phenotype of OSCC cells is controlled by genetic mutations responding to tumor microenvironment. Abnormal microenvironment conditions, such as hypoxia, low pH, high ROS level, and nutrient depletion elicit reactions from tumor cells, including autophagy. Oncogetic signaling pathways controlling growth and survival often activated by oncoproteins (such as Ras, PI3K, AKT, and Myc) or loss of tumor suppressors (such as p53). The results modify cellular metabolism reflecting to cellular bioenergetics and cancer progression.

encoded OXPHOS polypeptides and less tumorigenicity *in vivo*. The results indicate that tumor cells may use p32 to regulate the balance between OXPHOS and glycolysispathways [69].

Forkhead box O transcription factors (FOXOs) show tumor suppressor function, which are the typical downstream effectorsinPI3K/AKT pathway, and are key regulators of cell cycle, apoptosis and response to oxidative stress [70]. FOXO3a activation results in the nuclear-encoded genes repression of mitochondrial function, and a reduction in mtDNA copy number, mitochondrial respiratory complexes, and respiratory activity [71]. Moreover, Myc could increase mitochondrial biogenesis and functions [72-75]. Mutation or knockdown of p53 promotes mitochondrial biogenesis [76]. These results all suggested that mitochondrial function is essential for tumor formation and progression.

Autophagy as a therapeutic target

Autophagy is an evolutionarily conserved mechanism to adapt adverse microenvironment, including hypoxia, low pH, free radicals, and nutrient depletion. Several energetic sensors, such as AMP-activated protein kinase and mTOR, interacting with autophagy have evolved in metabolism [77,78]. Autophagy is involved in the formation of autophagosomes, and these structures subsequently fuse with lysosomes to form autolysosomes. Then they are delivered for degradation and recycling to maintain cellular homeostasis [79-84]. This is attributed to promote cell survival under conditions of poor nutrient supply or oxidation stress, which are often faced by solid tumors and metastatic cancer cells. Dysregulation of autophagy has been reported in various human cancers, including OSCC. The autophagy-associated proteins were linked to malignancy and an unfavorable prognosis in OSCC [85]. Beclin 1 takes part in the development of autophagy, and potentially plays an important role in the crosstalk between apoptosis and autophagy in OSCC cells [86]. Another pivotal protein, autophagy-related 16-like 1 (ATG16L1), is essential for autophagosome formation. The present study suggested that ATG16L1 may be used as an aggressive phenotype biomarker for OSCC patients, and autophagy impairment contributed to cancer progression [87]. These findings imply that autophagy inhibitors should be developed as a potential agent for adjuvant therapy in OSCC. Taken together, multiple molecular mechanisms induced by microenvironment converging to core cellular metabolism may provide support for ATP generation to maintain energy status, which results in OSCC progression (Figure 2). Increasing evidence indicate that inhibiting autophagy enhances the efficacy of cancer therapies by abolishing resistance and increasing cancer cell death. Since autophagy is often a pro-survival response to radiotherapy, chemotherapy, and target therapy drugs [88-98], suppression of autophagy during ant-cancer therapy has been proposed as a novel therapeutic strategy (Table 1). Therefore, development of new types of autophagy inhibitor for the treatment of cancer has important clinical significance.

Table 1: Effects of cancer treatment on autophagy in preclinical studies.

Treatment	Advantage	Disadvantage	Cancer Type
Irradiation	Genotoxic stress	Autophagy inducer	Breast cancer and OSCC [88,89]
Cisplatin	Genotoxic stress	Autophagy inducer	Esophageal cancer and OSCC [90,91]
Doxorubicin	Genotoxic stress	Autophagy inducer	Breast cancer and OSCC [92,93]
5-Fluorouracil	Thymidylate synthase inhibitor	Autophagy inducer	CRC and OSCC [91-94]
Gefitinib	EGFR tyrosine kinase inhibitor	Autophagy inducer	NSCLC and OSCC [95,96]
Erbitux	EGFR monoclonal antibody	Autophagy inducer	NSCLC and OSCC [97,98]

Conclusion

Cancer cells display multiple metabolic alterations to affect proliferation and progression through dysregulation of oncogenes or tumor suppressors in microenvironment. The studies reviewed here suggest a unity in genes, mitochondria, and metabolic enzymes involved in OSCC, includingHIF-1α, Ras, PI3K, AKT, Myc, p53, mtTFA, GLUT1, HK II, PKM2, and LDH. While unfriendly microenvironment faced by cancer cells, autophagy is an extremely strategy to regulate tumor metabolism. Successful targeting of autophagy in cancer therapy may require molecular basis of distinct components of autophagy, as well as their interactions with other cellular and metabolic processes. The information provided here will be the basis of significant researches to fully clarify OSCC metabolism and potential targets in the future.

References

1. Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and neck cancer. N Engl J Med. 1993; 328: 184-194.
2. Haddad RI, Shin DM. Recent advances in head and neck cancer. N Engl J Med. 2008; 359: 1143-1154.
3. Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. CA Cancer J Clin. 2001; 51: 15-36.
4. Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer. 2003; 3: 453-458.
5. Steeg PS. Tumor metastasis: mechanistic insights and clinical challenges. Nat Med. 2006; 12: 895-904.

6. Sleeman JP. The lymph node as a bridgehead in the metastatic dissemination of tumors. Recent Results Cancer Res. 2000; 157: 55-81.

7. Pepper MS. Lymphangiogenesis and tumor metastasis: myth or reality? Clin Cancer Res. 2001; 7: 462-468.

8. Bonuccelli G, Tsirigos A, Whitaker-Menezes D, Pavlides S, Pestell RG, Chiavarina B, et al. Ketones and lactate "fuel" tumor growth and metastasis: Evidence that epithelial cancer cells use oxidative mitochondrial metabolism. Cell Cycle. 2010; 9: 3506-3514.

9. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144: 646-674.

10. Warburg O. On respiratory impairment in cancer cells. Science. 1956; 124: 259-270.

11. Gordan JD, Thompson CB, Simon MC. HIF and c-Myc: sibling rivals for control of cancer cell metabolism and proliferation. Cancer Cell. 2007; 12: 108-113.

12. Dickens F, Simer F. The metabolism of normal and tumour tissue: The respiratory quotient, and the relationship of respiration to glycolysis. Biochem J. 1930; 24: 1301-1326.

13. Tatum JL, Kelloff GJ, Gillies RJ, Arbeit JM, Brown JM, Chao KS, et al. Hypoxia: importance in tumor biology, noninvasive measurement by imaging, and value of its measurement in the management of cancer therapy. Int J Radiat Biol. 2006; 82: 699-757.

14. Bristow RG, Hill RP. Hypoxia and metabolism. Hypoxia, DNA repair and genetic instability. Nat Rev Cancer. 2008; 8: 180-192.

15. Semenza GL. Regulation of cancer cell metabolism by hypoxia-inducible factor 1. Semin Cancer Biol. 2009; 19: 12-16.

16. Chaudhary M, Bajaj S, Bohra S, Swastika N, Hande A. The domino effect: Role of hypoxia in malignant transformation of oral submucous fibrosis. J Oral Maxillofac Pathol. 2015; 19: 122-127.

17. Denko NC. Hypoxia, HIF1 and glucose metabolism in the solid tumour.Nat Rev Cancer. 2008; 8: 705-713.

18. Forsythe JA, Jiang BH, Iyer NV, Agani F, Leung SW, Koos RD, et al. Activation of vascular endothelial growth factor gene transcription by hypoxia-inducible factor 1. Mol Cell Biol. 1996; 16: 4604-4613.

19. Maxwell PH, Wiesener MS, Chang GW, Clifford SC, Vaux EC, Cockman ME, et al. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. Nature. 1999; 399: 271-275.

20. Zhang S, Zhou X, Wang B, Zhang K, Liu S, Yue K, et al. Loss of VHL expression contributes to epithelial-mesenchymal transition in oral squamous cell carcinoma. Oral Oncol. 2014; 50: 809-817.

21. Jaakkola P, Mole DR, Tian YM, Wilson MI, Gielbert J, Gaskell SJ, et al. Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. Science. 2001; 292: 468-472.

22. Ivan M, Kondo K, Yang H, Kim W, Valiando J, Ohh M, et al. HIFalpha targeted for VHL-mediated destruction by proline hydroxylation: implications for O2 sensing. Science. 2001; 292: 464-468.

23. Masson M, Willam C, Maxwell PH, Pugh CW, Ratcliffe PJ. Independent function of two destruction domains in hypoxia-inducible factor-alpha chains activated by prolylhydroxylation. EMBO J. 2001; 20: 5197-5206.

24. Semenza GL. Targeting HIF-1 for cancer therapy. Nat Rev Cancer. 2003; 3: 721-732.

25. Lee JW, Bae SH, Jeong JW, Kim SH, Kim KW. Hypoxia-inducible factor (HIF-1)alpha: its protein stability and biological functions. Exp Mol Med. 2004; 36: 1-12.

26. Semenza GL, Jiang BH, Leung SW, Passantino R, Concordet JP, Maire P, et al. Hypoxia response elements in the aldolase A, enolase 1, and lactate dehydrogenase A gene promotes containessential binding sites for hypoxia-inducible factor 1. J Biol Chem. 1996; 271: 32529-32537.

27. Jiang BH, Zheng JZ, Leung SW, Roe R, Semenza GL. Transactivation and inhibitory domains of hypoxia-inducible factor 1alpha. Modulation of transcriptional activity by oxygen tension. J Biol Chem. 1997; 272: 19253-19260.

28. Dang CV, Semenza GL. Oncogenic alterations of metabolism. Trends Biochem Sci. 1999; 24: 68-72.

29. Ramanathan A, Wang C, Schreiber SL. Perturbational profiling of a cell-line model of tumorigenesis by using metabolic measurements. Proc Natl Acad Sci U S A. 2005; 102: 5992-5997.

30. Lin F, Yao L, Xiao J, Liu D, Ni Z. MiR-206 functions as a tumor suppressor and directly targets K-Ras in human oral squamous cell carcinoma. Onco Targets Ther. 2014; 7: 1583-1591.

31. Wong KK, Engelman JA, Cantley LC. Targeting the PI3K signaling pathway in cancer. Curr Opin Genet Dev. 2010; 20: 87-90.

32. Plas DR, Thompson CB. Akt-dependent transformation: there is more to growth than just surviving. Oncogene. 2005; 24: 7435-7442.

33. Cohen Y, Goldenberg-Cohen N, Shalmon B, Shani T, Oren S, Amariglio N, et al. Mutational analysis of PTEN/PIK3CA/AKT pathway in oral squamous cell carcinoma. Oral Oncol. 2011; 47: 946-950.

34. Chien CM, Lin KL, Su JC, Chuang PW, Tseng CH, Chen YL, et al. Naphtho[1,2-b]furan-4,5-dione induces apoptosis of oral squamous cell carcinoma: involvement of EGF receptor/PI3K/Akt signaling pathway. Eur J Pharmacol. 2010; 636: 52-58.

35. Elstrom RL, Bauer DE, Buzzai M, Karnauskas R, Harris MH, Plas DR, et al. Akt stimulates aerobic glycolysis in cancer cells. Cancer Res. 2004; 64: 3892-3899.

36. Fan Y, Dickman KG, Zong WX. Akt and c-Myc differentially activate cellular metabolic programs and prime cells to bioenergetic inhibition. J Biol Chem. 2010; 285: 7324-7333.

37. Robey RB, Hay N. Is Akt the "Warburg kinase"?-Akt-energy metabolism interactions and oncogenesis. Semin Cancer Biol. 2009; 19: 25-31.

38. Manning BD, Cantley LC. AKT/PKB signaling: navigating downstream. Cell. 2007; 129: 1261-1274.

39. Gordan JD, Thompson CB, Simon MC. HIF and c-Myc: sibling rivals for control of cancer cell metabolism and proliferation. Cancer Cell. 2007; 12: 108-113.

40. Dang CV, Le A, Gao P. MYC-induced cancer cell energy metabolism and therapeutic opportunities. Clin Cancer Res. 2009; 15: 6479-6483.

41. Cetindis M, Biegner T, Munz A, Teriete P, Reinert S, Grimm M. Glutaminolysis and carcinogenesis of oral squamous cell carcinoma. Eur Arch Otorhinolaryngol. 2016; 273: 495-503.

42. Segura S, Rozas-Muñoz E, Toll A, Martín-Ezquerra G, Masferrer E, Espinet B, et al. Evaluation of MYC status in oral lichen planus in patients with progression to oral squamous cell carcinoma. Br J Dermatol. 2013; 169: 106-114.

43. Hernández-Reséndiz I, Román-Rosales A, García-Villa E, López-Macay A, Pineda E, Saavedra E, et al. Dual regulation of energy metabolism by p53 in human cervix and breast cancer cells. Biochim Biophys Acta. 2015; 1853: 3266-3278.

44. Dang CV. c-Myc target genes involved in cell growth, apoptosis, and metabolism. Mol Cell Biol. 1999; 19: 1-11.

45. Ara N, Atique M, Ahmed S, Ali Bukhari SG. Frequency of p53 gene mutation and protein expression in oral squamous cell carcinoma. J Coll Physicians Surg Pak. 2014; 24: 749-753.

46. Olson AL, Pessin JE. Structure, function, and regulation of the mammalian facilitative glucose transporter gene family. Annu Rev Nutr. 1996; 16: 235-256.

47. Ayala FR, Rocha RM, Carvalho KC, Carvalho AL, da Cunha IW, Lourenço SV, et al. GLUT1 and GLUT3 as potential prognostic markers for Oral Squamous Cell Carcinoma. Molecules. 2010; 15: 2374-2387.

48. Fukuzumi M, Hamakawa H, Onishi A, Sumida T, Tanioka H. Gene expression of GLUT isoforms and VHL in oral squamous cell carcinoma. Cancer Lett. 2000; 161: 133-140.

49. Xu P, Li Y, Zhang H, Li M, Zhu H. MicroRNA-340 Mediates Metabolic Shift in Oral Squamous Cell Carcinoma by Targeting Glucose Transporter-1. J Oral Maxillofac Surg. 2016; 74: 844-850.

50. Nakashima RA, Mangan PS, Colombini M, Pedersen PL. Hexokinase receptor complex in hepatoma mitochondria: evidence from N,N'-dicyclohexylcarbodiimide-labeling studies for the involvement of the pore-forming protein VDAC. Biochemistry 1986; 25: 1015-1021.

51. Tian M, Zhang H, Higuchi T, Oriuchi N, Nakasone Y, Takata K, et al. Hexokinase-II expression in untreated oral squamous cell carcinoma: comparison with FDG PET imaging. Ann Nucl Med. 2005; 19: 335-338.

52. Yamada T, Uchida M, Kwang-Lee K, Kitamura N, Yoshimura T, Sasabe E, et al. Correlation of metabolism/hypoxia markers and fluorodeoxyglucose uptake in oral squamous cell carcinomas. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012; 113: 464-471.

53. Wang Y, Zhang X, Zhang Y, Zhu Y, Yuan C, Qi B, et al. Overexpression of pyruvate kinase M2 associates with aggressive clinicopathological features and unfavorable prognosis in oral squamous cell carcinoma. Cancer Biol Ther. 2015; 16: 839-845.

54. Chaube B, Malvi P, Singh SV, Mohammad N, Meena AS, Bhat MK. Targeting metabolic flexibility by simultaneously inhibiting respiratory complex I and lactate generation retards melanoma progression. Oncotarget. 2015; 6: 37281-37299.

55. Grimm M, Krimmel M, Hoefert S, Kraut W, Calgéer B, Biegner T, et al. Monitoring a 'metabolic shift' after surgical resection of oral squamous cell carcinomas by serum lactate dehydrogenase. J Oral Pathol Med. 2015.

56. Saluja TS, Spadigam A, Dhupar A, Syed S. Equating salivary lactate dehydrogenase (LDH) with LDH-5 expression in patients with oral squamous cell carcinoma: An insight into metabolic reprogramming of cancer cell as a predictor of aggressive phenotype. Tumour Biol. 2015.

57. Martinez-Outschoorn UE, Pavlides S, Sotgia F, Lisanti MP. Mitochondrial biogenesis drives tumor cell proliferation. Am J Pathol. 2011; 178: 1949-1952.

58. Bonawitz ND, Clayton DA, Shadel GS. Initiation and beyond: multiplefunctions of the human mitochondrial transcription machinery. Mol Cell. 2006; 24: 813-825.

59. Takamatsu C, Umeda S, Ohsato T, Ohno T, Abe Y, Fukuoh A, et al. Regulation of mitochondrial D-loops by transcriptionfactor A and single-strandedDNA-binding protein. EMBO Rep. 2002; 3: 451-456.

60. Larsson NG, Wang J, Wilhelmsson H, Oldfors A, Rustin P, Lewandoski M, et al. Mitochondrialtranscriptionfactor A is necessary for mtDNAmaintenance and embryogenesis in mice. Nat Genet. 1998; 18: 231-236.

61. Dong X, Ghoshal K, Majumder S, Yadav SP, Jacob ST. Mitochondrial transcription factor A and its downstream targets are up-regulated in a rat hepatoma. J Biol Chem. 2002; 277: 43309-43318.

62. Kidani A, Izumi H, Yoshida Y, Kashiwagi E, Ohmori H, Tanaka T, et al. Thioredoxin2 enhances the damaged DNA binding activity of mtTFA through direct interaction. Int J Oncol. 2009; 35: 1435-1440.

63. Toki N, Kagami S, Kurita T, Kawagoe T, Matsuura Y, Hachisuga T, et al. Expression of mitochondrial transcription factor A in endometrial carcinomas: clinicopathologic correlations and prognostic significance. Virchows Arch. 2010; 456: 387-393.

64. Yoshida Y, Hasegawa J, Nezu R, Kim YK, Hirota M, Kawano K, et al. Clinical usefulness of mitochondrial transcription factor A expression as a predictive marker in colorectal cancer patients treated with FOLFOX. Cancer Sci. 2011; 102: 578-582.

65. Weinberg F, Hamanaka R, Wheaton WW, Weinberg S, Joseph J, Lopez M, et al. Mitochondrial metabolism and ROS generation are essential for Kras-mediated tumorigenicity. Proc Natl Acad Sci USA. 2010; 107: 8788-8793.

66. Han B, Izumi H, Yasuniwa Y, Akiyama M, Yamaguchi T, Fujimoto N, et al. Human mitochondrial transcription factor A functions in both nuclei and mitochondria and regulates cancer cell growth. Biochem Biophys Res Commun. 2011; 408:45-51.

67. 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: 2066-2076.

68. Berridge MV, Tan AS. Effects of mitochondrial gene deletion on tumorigenicity of metastatic melanoma: reassessing the Warburg effect. Rejuvenation Res. 2010; 13: 139-141.

69. Fogal V, Richardson AD, Karmali PP, Scheffler IE, Smith JW, Ruoslahti E. Mitochondrialp32 protein is a critical regulator of tumormetabolism via maintenance of oxidative phosphorylation. Mol Cell Biol. 2010; 30: 1303-1318.

70. Chung HW, Lim JH, Kim MY, Shin SJ, Chung S, Choi BS, et al. High-fat diet-induced renal cell apoptosis and oxidative stress in spontaneously hypertensive rat are ameliorated by fenofibrate through the PPARα-FoxO3a-PGC-1α pathway. Nephrol Dial Transplant. 2012; 27: 2213-2225.

71. Ferber EC, Peck B, Delpuech O, Bell GP, East P, Schulze A. FOXO3a regulates reactive oxygen metabolism by inhibiting mitochondrial gene expression. Cell Death Differ. 2012; 79: 968-979.

72. Dang CV. PKM2 tyrosine phosphorylation and glutamine metabolism signal a different view of the Warburg effect. Sci Signal. 2009; 2: 75.

73. Dang CV, Le A, Gao P. MYC-induced cancer cell energy metabolism and therapeutic opportunities.Clin Cancer Res. 2009; 15: 6479-6483.

74. Dang CV. Rethinking the Warburg effect with Myc micromanaging glutamine metabolism. Cancer Res. 2010; 70: 859-862.

75. Dang CV. Therapeutic Targeting of Myc-Reprogrammed Cancer Cell Metabolism. Cold Spring Harb Symp Quant Biol. 2011; 76: 369-374.

76. Ralph SJ, Rodriguez-Enriquze S, Neuzil J, Saavedra E, Moreno-Sanchez R. The causes of cancer revisited: "mitochondrial malignancy" and ROS-induced oncogenic transformation – why mitochondria are targets for cancer therapy. Mol Aspects Med. 2010; 31: 145-170.

77. Høyer-Hansen M, Jäättelä M. AMP-activated protein kinase: a universal regulator of autophagy? Autophagy. 2007; 3: 381-383.

78. Wouter, B. G. and Koritzinsky, M. Hypoxia signaling through mTOR and the unfolded protein response in cancer. Nature Rev Cancer. 2008; 8: 851-864.

79. Yang Z, Klionsky DJ. Eaten alive: a history of macroautophagy. Nat Cell Biol. 2010; 12: 814-822.

80. Janku F, McConkey DJ, Hong DS, Kurzrock R. Autophagy as a target for anticancer therapy. Nat Rev Clin Oncol. 2011; 8: 528-539.

81. White E. Deconvoluting the context-dependent role for autophagy in cancer. Nat Rev Cancer. 2012; 12: 401-410.

82. Eskelinen EL. Maturation of autophagic vacuoles in Mammalian cells. Autophagy. 2005; 1: 1-10.

83. Kroemer G, Jäättelä M. Lysosomes and autophagy in cell death control. Nat Rev Cancer. 2005; 5: 886-897.

84. Ravikumar B, Sarkar S, Davies JE, Futter M, Garcia-Arencibia M, Green-Thompson ZW, et al. Regulation of mammalian autophagy in physiology and pathophysiology. Physiol Rev. 2010; 90: 1383-1435.

85. Sakakura K, Takahashi H, Kaira K, Toyoda M, Oyama T, Chikamatsu K. Immunological significance of the accumulation of autophagy components in oral squamous cell carcinoma. Cancer Sci. 2015; 106: 1-8.

86. Jiang LC, Xin ZY, Deborah B, Zhang JS, Yuan DY, Xu K, et al. Inhibition of autophagy augments apoptosis in human oral squamous cell carcinoma under nutrient depletion. J Oral Pathol Med. 2015; 44: 361-366.

87. Tang JY, Hsi E, Huang YC, Hsu NC, Yang WC, Chang HW, et al. Overexpression of autophagy-related 16-like 1 in patients with oral squamous cell carcinoma. Pathol Oncol Res. 2015; 21: 301-305.

88. Apel A, Herr I, Schwarz H, Rodemann HP, Mayer A. Blocked autophagy

sensitizes resistant carcinoma cells to radiation therapy. Cancer Res. 2008; 68: 1485-1494.

89. Wu SY, Liu YW, Wang YK, Lin TH, Li YZ, Chen SH, et al. Ionizing radiation induces autophagy in human oral squamous cell carcinoma. J BUON. 2014;19: 137-144.

90. Liu D, Yang Y, Liu Q, Wang J. Inhibition of autophagy by 3-MA potentiates cisplatin-induced apoptosis in esophageal squamous cell carcinoma cells. Med Oncol. 2011; 28: 105-111.

91. Lee YR, Wu WC, Ji WT, Chen JY, Cheng YP, Chiang MK, et al. Reversine suppresses oral squamous cell carcinoma via cell cycle arrest and concomitantly apoptosis andautophagy. J Biomed Sci. 2012; 19: 9.

92. Zhou J, Li G, Zheng Y, Shen HM, Hu X, Ming QL, et al. A novel autophagy/mitophagy inhibitor liensinine sensitizes breast cancer cells to chemotherapy through DNML1L-mediated mitochondrial fission. Autophagy. 2015; 11: 1259-1279.

93. Saiyin W, Wang D, Li L, Zhu L, Liu B, Sheng L, Li Yet al. Sequential release of autophagy inhibitor and chemotherapeutic drug with polymeric delivery system for oral squamous cell carcinoma therapy. Mol Pharm. 2014; 11: 1662-1675.

94. Li J, Hou N, Faried A, Tsutsumi S, Kuwano H. Inhibition of autophagy augments 5-fluorouracil chemotherapy in human colon cancer *in vitro* and *in vivo* model. Eur J Cancer. 2010; 46: 1900-1909.

95. Han W, Pan H, Chen Y, Sun J, Wang Y, Li J, et al. EGFR tyrosine kinase inhibitors activate autophagy as a cytoprotective response in human lung cancer cells. PLos One. 2011; 6: e18691.

96. Shintani S, Li C, Mihara M, Terakado N, Yano J, Nakashiro K, et al. Enhancement of tumor radioresponse by combined treatment with gefitinib (Iressa, ZD1839), an epidermal growth factor receptor tyrosine kinase inhibitor, is accompanied by inhibition of DNA damage repair and cell growth in oral cancer. Int J Cancer. 2003; 107: 1030-1037.

97. Li X, Lu Y, Pan T, Fan Z. Roles of autophagy in cetuximab-mediated cancer therapy against EGFR. Autophagy. 2010; 6: 1066-1077.

98. Dai W, Li Y, Zhou Q, Xu Z, Sun C, Tan X, et al. Cetuximab inhibits oral squamous cell carcinoma invasion and metastasis via degradation of epidermal growth factor receptor. J Oral Pathol Med. 2013; 43: 250-257.

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