Oral Oncology 98 (2019) 92–95

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Review

LIN28: A cancer stem cell promoter for immunotherapy in head and neck squamous cell carcinoma

Mengxue Li[1], Heng Chen[1], Tianfu Wu*

The State Key Laboratory Breeding Base of Basic Science of Stomatology (Hubei-MOST) & Key Laboratory of Oral Biomedicine Ministry of Education, School & Hospital of Stomatology, Wuhan University, People's Republic of China

ARTICLE INFO

Keywords:
Lin28
Lin28/let-7
PD-L1
Head and neck cancer
Squamous cell carcinoma
Development
Cell reprogramming
Cancer stem cell
Stem cell therapy
Immunotherapy

ABSTRACT

Lin28, a highly conserved RNA-binding protein, plays an important role in differentiation, metabolism, proliferation, pluripotency, and tumourigenicity. Lin28 overexpression promotes tumour-cell proliferation and metastasis in various human cancers, including head and neck cancer. Multiple studies demonstrate that Lin28 critically contributes to anti-tumour immunity and production of cancer stem cells in head and neck squamous cell carcinoma (HNSCC). Thus, Lin28 has potential application in HNSCC treatment.

Introduction

Head and neck cancer is the sixth most prevalent cancer worldwide, and more than 90% are head and neck squamous cell carcinoma (HNSCC) [1,2]. The five-year survival rate of HNSCC patients is approximately 50%, which indicates poor prognosis [3]. Traditional therapy for HNSCC includes surgery, radiotherapy and chemotherapy. In recent years, new treatments have been applied clinically, but the survival rate remains unsatisfactory [4]. Thus, the cancer stem cell (CSC) hypothesis was proposed to explain cancer heterogeneity and therapeutic tolerance; this hypothesis provides a new thinking for preventing tumour metastasis, resistance and recurrence.

Lin28 was first discovered in *Caenorhabditis elegans* as a heterogeneous gene and constitutes a gene network that regulates developmental timing [5]. Lin28 in humans has two homologs, namely, LIN28A and LIN28B. LIN28A locates on human chromosome 1p36.11, whereas LIN28B is sited in 6q21. LIN28A encodes a protein of 209 amino acids, and LIN28B encodes a protein which contains 250 amino acids [6]. LIN28A and LIN28B proteins have similar structures and functions. Both of them contain a cold-shock domain and two Cys-Cys-His-Cys (CCHC)-type zinc fingers, which participate in the combination of Lin28 and its target RNAs [7]. However, they do have certain differences. For example, LIN28B contains a nuclear localisation signal and nucleolar localisation signal, which is responsible for its nucleolar localisation, whereas LIN28A is primarily located in the cytoplasm. This difference in cell localisation also relates to their inhibition of let-7 biosynthesis [8], which leads to different tumour immune responses.

Currently, a growing body of evidence suggests that Lin28 significantly contributes to pluripotency, reprogramming and tumourigenesis [9–12]. Through a thorough study of the functions of Lin28, scholars have found that it regulates cancer cells' proliferation, metabolism and resistance to radiotherapy and chemotherapy and induces CSC formation [13–17]. An increasing number of studies are focusing on the relationship between Lin28 and CSCs, demonstrating that Lin28 can promote the induction of CSCs, thereby contributing to tumour aggressive, metastasis, recurrence and therapeutic tolerance. Moreover, emerging evidence suggests that Lin28 is also involved in anti-tumour immunity. These findings indicate the potential value of targeting Lin28 in HNSCC therapy.

CSCs in HNSCC

Despite the various anti-tumour drugs and therapies that are emerging, the radiotherapy and chemotherapy tolerance of HNSCC is

* Corresponding author at: The State Key Laboratory Breeding Base of Basic Science of Stomatology (Hubei-MOST) & Key Laboratory of Oral Biomedicine Ministry of Education, School & Hospital of Stomatology, Wuhan University, Wuhan 430079, People's Republic of China.
E-mail address: wutianfu@whu.edu.cn (T. Wu).
[1] Present address: 237 Luoyu Road, Hongshan District, Wuhan City 430072, Hubei Province, People's Republic of China.

https://doi.org/10.1016/j.oraloncology.2019.09.024
Received 13 June 2019; Received in revised form 19 September 2019; Accepted 24 September 2019
Available online 28 September 2019
1368-8375/ © 2019 Elsevier Ltd. All rights reserved.

increasing, and the mortality rate remains high. Therefore, the CSC hypothesis was proposed to explain cancer heterogeneity and therapeutic tolerance. The CSC hypothesis suggests that tumour tissue consists of heterogeneous cancer cells, and only a small subset of populations can form tumours [18]. These cells are CSCs, which have self-renewal capacity and can form various cell lines that grow into tumours [19]. CSCs share many common characteristics with normal stem cells, such as self-renewal capacity and differentiation ability [18]. Kim et al. [20] classified the currently known CSC surface markers and found that approximately 73% of CSC surface markers are present on embryonic or adult stem cells. Researchers have already discovered CSCs in solid tumours of breast cancer. For example, Al-Hajj et al. [21] found that as few as 100 $CD44^+CD24^-$ cells were able to form tumours in mice, whereas tens of thousands of cells with alternate phenotypes failed to form tumours. Moreover, new tumours formed by passaged $CD44^+CD24^-$ cells contain $CD44^+CD24^-$ tumourigenic cells and the phenotypically diverse populations of non-tumourigenic cells present in the initial tumour. Altogether, CSCs can self-renew and differentiate into other cells that form tumours.

Many studies have suggested that HNSCC is consistent with the theory of CSCs. In HNSCC, CSCs are associated with cancer development, progression, metastasis, recurrence and resistance to radiotherapy and chemotherapy. A research found that HNSCC cells that have high expression levels of CD44, which is a cell surface marker, have a significant tumourigenic potential; the $CD44^+$ subpopulation formed tumours in 20 of 30 implantations, whereas only 1 of 40 implantations of $CD44^-$ cells produced a tumour [3]. In another study, 1000 implanted $ALDH^+CD44^+$ (CD44 high and aldehyde dehydrogenase [$ALDH^+$]) cells sorted from the primary human HNSCC were able to form 13 (out of 15) tumours, and only 2 of the 15 transplants of 10 000 $ALDH^-CD44^-$ cells formed tumours. Further studies demonstrate that $ALDH^+CD44^+$ cells also have self-renewal ability, and xenografts form tumours similar to the initial tumour tissues. Therefore, $ALDH^+CD44^+$ cells are CSCs of HNSCC [22]. Currently, the markers for identifying CSC in head and neck tumours include CD44, ALDH1, CD133 and c-Met [22–24], and stemness markers include Oct-4, Sox2, Nanog, Klf4 and Bmi1 [25–29]. Chinn et al. [30] found that in HNSCC, CSCs ($CD44^+ALDH1^+$ cells) have stronger tumourigenesis and metastasis ability than non-CSCs in vivo; in patients with primary HNSCC, a large proportion of CSCs was related to tumour size and stage. Benzion et al. also found that a high frequency of CD44+ cells correlated with advanced T classification and recurrence [31]. Kulsum et al. [32] confirmed that cells with increased resistance to chemotherapeutic drugs in HNSCC cells express high levels of ALDH1 and CD44, but when ALDH1 is inhibited, these cells become increasingly sensitive to chemotherapeutic drugs. These findings reveal that CSCs are resistant to HNSCC chemotherapy.

Lin28 induces CSCs through reprogramming mechanism in HNSCC

Lin28 is aberrantly expressed in many types of cancer, such as liver [7], lung [33], gastric [16], glioma [34] and esophageal cancers [35] and adrenal tumours[36]. Multiple studies report that LIN28A and LIN28B are overexpressed in HNSCC and correlated with tumour invasion, metastasis and poor patient prognosis [37–41]. Many recent works demonstrate that Lin28 plays an important role in the production of CSCs.

CSCs are believed to be produced from non-CSCs by a reprogramming mechanism which is very similar to that of induced pluripotency stem cell (iPSC) production [42]. In the study conducted by Takahashi and Yamanaka, mature somatic cells can be reprogrammed to iPSC by introducing pluripotent stem cell genes Oct4, Sox2, Klf4 and c-Myc [43]. Meanwhile, Oct4, Sox2, Nanog and Klf4 are the stem markers of CSCs in HNSCC [25].

A recent investigation identified LIN28A and LIN28B as pluripotency factors with the ability to promote reprogramming. LIN28A and LIN28B can function effectively with Nanog, Oct4, and Sox2 in reprogramming to pluripotency; reactivation of endogenous LIN28A and LIN28B is required for maximum reprogramming efficiency [9]. Hayashi et al. found that LIN28A is overexpressed in TOSCC23 cells; SP cells are isolated from TOSCC23 cells and show increased cell proliferation, invasion and enrichment for CSC-like cells, and LIN28A can increase their proliferation, colony formation and invasion [41]. In HNSCC, $CD44^+ALDH1^+$ cells have high tumour-forming ability and are considered CSCs with tumourigenic potential [22]. Chien et al. [17] found that the overexpression of LIN28B increases the percentage of $CD44^+ALDH^+$ cells and their spheroid formation; moreover, LIN28B induces the expression of stemness genes (such as Oct4 and Sox2) and CSCs markers (such as CD44 and ALDH1) and the self-renewal ability of CSCs. LIN28B also determines the efficiency with which normal human oral keratinocytes can be reprogrammed to iPSC through modulating Oct4/Sox2 expression. Haradaet et al. [44] found that cells with CSC-like properties can be generated from a tongue cancer cell line (HSC) by introducing defined reprogramming factors (Oct4, shp53, Sox2, Klf4, l-Myc and LIN28A). The derived cells possess the hallmarks of CSCs and can efficiently generate tumours in a nude mouse model. These results suggest that LIN28A and LIN28B are reprogramming factors that can possibly dedifferentiate oral squamous cancer cells into CSCs. In an investigation about LIN28A small-molecule inhibitors, researchers found that a small-molecule inhibitor called Compound 1632 (N-methyl-N-[3-(3-methyl[1,2,4]triazolo[4,3-b]-pyridazin-6yl]) can inhibit the binding between LIN28A and pre-let-7 through combination with LIN28A; furthermore, C1632 can inhibit cancer cells with overexpressed LIN28A proliferation and spheroid formation and also tumourigenesis and CSC subpopulation [45]. These studies indicate that Lin28 provides a crucial contribution to the production of CSCs in HNSCC, but the specific mechanism needs additional in-depth research.

Lin28/let-7 participates in the regulation of cancer stemness

The microRNA let-7 was also discovered in *C. elegans* as a heterogeneity gene and plays an important role in development [46]. In humans, the let-7 family includes 13 members, namely, let-7a-1, 7a-2, 7a-3, 7b, 7c, 7d, 7e, f7-1, 7f-2, 7g, 7i, mir-98 and mir-202 [6]. In many types of cancer, let-7 is down-regulated in tumour tissues compared with normal tissues; therefore, let-7 is a tumour suppressor microRNA. Its down-expression is associated with a low differentiation of tumour tissues and with the invasiveness and therapeutic tolerance of cancer [47]. Studies also show that inhibition of let-7 expression is associated with cancer stemness in breast cancer, and the overexpression of let-7 can regulate CSCs differentiation and self-renewal [48].

Let-7 is an important target of Lin28. Research shows that LIN28A and LIN28B block the biosynthesis of let-7 by different mechanisms; LIN28A can block let-7 processing in the cytoplasm by Dicer by recruiting the terminal uridyltransferase, TUT4/Zcchc11, thereby leading to pre-let-7 degradation [8]. LIN28B, which is predominantly located in the nucleolus, can inhibit pri-let-7 by a TUT4/Zcchc11-independent mechanism, that is, by blocking the pri-let-7 in the nucleus to prevent another Drosha ribonuclease from processing it, thereby inhibiting the maturation of let-7 [8]. On the other hand, the 3′-untranslated regions (3′-UTR) of Lin28 mRNAs is the let-7 binding site, and mature let-7 family members can repress the expression of Lin28 by directly targeting the 3′-UTR [47]. Thus, Lin28 and let-7 form a double-negative feedback loop; the let-7 molecule can inhibit the translation of Lin28, which in turn blocks the maturation of the let-7 miRNA [49]. It is also involved in the regulation of various biological functions, including the regulation of cancer stemness [49].

A study showed that breast CSCs (BCSCs) express high levels of H19, which functions as a competing endogenous RNA to sponge miRNA let-7, thus increasing the expression level of the pluripotency factor LIN28A. Thus, lncRNA H19, miRNA let-7 and LIN28A form a double-negative feedback loop which has a critical role in the maintenance of

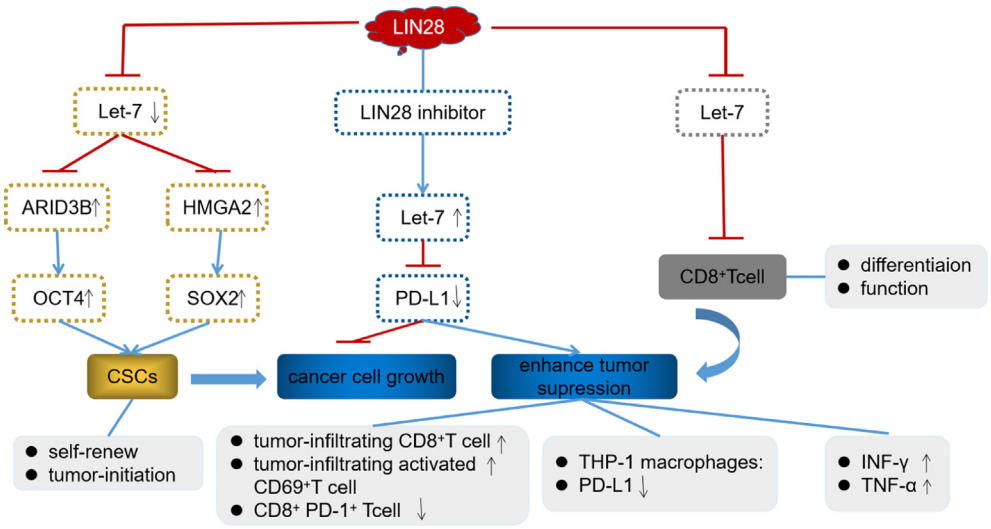

Fig. 1. Role of Lin28 in CSC production and anti-tumour immunity.

BCSCs [12]. Cai et al. [50] found that the Wnt-β-catenin pathway represses let-7 microRNA expression through transactivation of LIN28A to augment BCSC expansion. Yang et al. [51] stated that the expression of LIN28A can maintain the percentage of ALDH1$^+$ tumour cells, which are a "stem cell-like" subpopulation of tumour cells, whereas let-7 negatively regulates ALDH1$^+$ tumour cells through the Lin28/let-7 axis. In oral squamous cancers, the expression levels of LIN28B and let-7 have a strong negative correlation. Further functional experiments have found that LIN28B/let7 regulates the cancer stem-like properties in OSCC. Moreover, the study stated that ARID3B and HMGA2 are downstream factors of the LIN28B/let-7 signalling pathways in the management Oct4 and Sox2 (see Fig. 1). ARID3B and HMGA2 can increase Oct4 and Sox2 expression levels, respectively; however, let-7 combines with the 3'-UTR of ARID3B and HMGA2 and inhibits their expression [17].

Lin28 is involved in anti-tumour immunity

Recently, some studies have demonstrated that LIN28 is closely related to anti-tumour immunity. The two key points of tumour immunotherapy are enhancing the immune response and inhibiting cancer immune evasion. The mechanism of CSCs in cancer immune evasion and immune suppression remains unclear. Some scholars suggest a potential defect in the antigen-presenting functions of CSCs that might lead to the evasion from T cell attacks, and the acquisition of an EMT phenotype of CSCs may be an additional mechanism of immune-escape [52]. Moreover, in HNSCC, research has found that CSCs which are abundant in spheroid culture-derived cells (SDCs) are less sensitive to MHCI antigen-specific CD8$^+$CTL compared with monolayer-derived cells, whereas a high-ALDH-expression SDC group is more sensitive to CD8$^+$CTL than a low-ALDH-expression SDC group [53]. In recent years, investigations conducted on CSC immunity presented a potential immunotherapeutic prospect. Lin28 can promote the percentage of CD44$^+$ALDH1$^+$ cells in tumour tissues [17,51]. Studies on vaccination against the antigen ALDH1A1$^+$ of CSCs have been performed and achieved significant progress. For example, Visus et al. [54] induced ALDHA1-specific CD8$^+$ T cells by applying the ALDHA1 antigen peptide and reported that ALDHA1-specific CD8$^+$ T cells can eliminate ALDH (bright) cells in HNSCC and inhibit tumour growth and metastasis in immune-deficient mice.

Growing evidence suggests that PD-L1 is often overexpressed in tumour cells, and such overexpression can promote cancer immune evasion and prevent T cells from recognising tumour-specific antigens [55]. According to Chen et al. [56], LIN28A promotes PD-L1 expression by inhibiting the biogenesis of let-7. They also found that treatment with the small compound C1632, an LIN28A inhibitor, suppresses the expression of PD-L1 by up-regulating let-7, increases the percentage of tumour-infiltrating CD8+ T cells and activates CD69+ T cells but decreases the frequency of CD8+ PD1+ T cells *in vivo*. Moreover, C1632 inhibits PD-L1 expression in THP-1 macrophages and increases the levels of TNFα and IFNγ, which are indicators of activated immunity. These results suggest that inhibiting Lin28/let-7 can promote reactivation of anti-tumour immunity in vitro and in vivo through stimulating T cell-mediated immune surveillance. Let-7, which is an important downstream molecule of LIN28A and LIN28B, has recently been discovered to play an important role in anti-tumour immunity. Let-7 miRNA can inhibit the immune response and promote tumour immune evasion [57]. A study showed that let-7 is highly expressed in naive CD8+ T cells, and overexpression of let-7 inhibits the differentiation and function of CD8+ T cells [57]. Reduced let-7 expression enhances CD8$^+$ T cell function, whereas high levels of let-7 reverse this phenomenon; let-7 miRNAs control multiple levels of CD8$^+$T cell differentiation, including proliferation, metabolism and acquisition of effector function. In the absence of the let-7 miRNAs, antigen-specific CTLs exhibit a dramatically enhanced cytotoxic function [58]. These findings suggest that regulating Lin28/let-7 may be a novel target for anti-tumour immunotherapy (see Fig. 1).

Possible medical applications of Lin28

In HNSCC, CSCs are associated with cancer growth, progression, metastasis, recurrence and therapy tolerance. Therefore, targeting CSCs is a significant approach for HNSCC eradication. Lin28, as an oncogene, is overexpressed in a wide range of cancers, and increasing evidence supports that Lin28 plays a significant role in the reprogramming of cancer cells towards additional "CSC-like" phenotypes in HNSCC. Recent studies report that Lin28 is closely related to anti-tumour immunity. Therefore, targeting LIN28A or LIN28B may have dual functions for cancer therapy: (1) suppressing tumours by inhibiting the production of CSCs and (2) stimulating anti-tumour immune responses. Hence, a molecular-based therapeutic strategy of Lin28 may have a great potential clinical value in the treatment of HNSCC, but understanding the specific mechanisms requires further investigation.

Acknowledgements

Mengxue Li and Heng Chen contributed equally to this work.

Declaration of Competing Interest

The authors declare that they have no conflicts of interests.

Funding

This work was supported by a grant of the Wuhan Morning Light Plan of Youth Science and Technology (No. 2017050304010305) and of National Natural Science Foundation of China (No. 81702705) to Tianfu Wu.

References

[1] Vigneswaran N, Williams MD. Epidemiologic trends in head and neck cancer and aids in diagnosis. Oral Maxillofac Surg Clin North Am 2014;26:123–41.
[2] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. Ca-Cancer J Clin 2011;61:69–90.
[3] Prince ME, Ailles LE. Cancer stem cells in head and neck squamous cell cancer. J Clin Oncol: Off J Am Soc Clin Oncol 2008;26:2871–5.
[4] Pulte D, Brenner H. Changes in survival in head and neck cancers in the late 20th and early 21st century: a period analysis. Oncologist 2010;15:994–1001.
[5] Moss EG, Lee RC, Ambros V. The cold shock domain protein LIN-28 controls developmental timing in C. elegans and is regulated by the lin-4 RNA. Cell. 1997;88:637–46.
[6] Zhou J, Ng SB, Chng WJ. LIN28/LIN28B: an emerging oncogenic driver in cancer stem cells. Int J Biochem Cell Biol 2013;45:973–8.
[7] Guo Y, Chen Y, Ito H, Watanabe A, Ge X, Kodama T, et al. Identification and characterization of lin-28 homolog B (LIN28B) in human hepatocellular carcinoma. Gene 2006;384:51–61.
[8] Piskounova E, Polytarchou C, Thornton JE, LaPierre RJ, Pothoulakis C, Hagan JP, et al. Lin28A and Lin28B inhibit let-7 microRNA biogenesis by distinct mechanisms. Cell 2011;147:1066–79.
[9] Zhang J, Ratanasirintrawoot S, Chandrasekaran S, Wu Z, Ficarro SB, Yu C, et al. LIN28 regulates stem cell metabolism and conversion to primed pluripotency. Cell Stem Cell 2016;19:66–80.
[10] Rehfeld F, Rohde AM, Nguyen DT, Wulczyn FG. Lin28 and let-7: ancient milestones on the road from pluripotency to neurogenesis. Cell Tissue Res 2015;359:145–60.
[11] Gangaraju VK, Lin H. MicroRNAs: key regulators of stem cells. Nat Rev Mol Cell Biol 2009;10:116–25.
[12] Peng F, Li TT, Wang KL, Xiao GQ, Wang JH, Zhao HD, et al. H19/let-7/LIN28 reciprocal negative regulatory circuit promotes breast cancer stem cell maintenance. Cell Death Dis 2017;8:e2569.
[13] Wang H, Zhao Q, Deng K, Guo X, Xia J. Lin28: an emerging important oncogene connecting several aspects of cancer. Tumour Biol: J Int Soc Oncodev Biol Med 2016;37:2841–8.
[14] Ma X, Li C, Sun L, Huang D, Li T, He X, et al. Lin28/let-7 axis regulates aerobic glycolysis and cancer progression via PDK1. Nat Commun 2014;5:5212.
[15] Oh JS, Kim JJ, Byun JY, Kim IA. Lin28-let7 modulates radiosensitivity of human cancer cells with activation of K-Ras. Int J Radiat Oncol Biol Phys 2010;76:5–8.
[16] Teng R, Hu Y, Zhou J, Seifer B, Chen Y, Shen J, et al. Overexpression of Lin28 decreases the chemosensitivity of gastric cancer cells to oxaliplatin, paclitaxel, doxorubicin, and fluorouracil in part via microRNA-107. PLoS ONE 2015;10:e0143716.
[17] Chien CS, Wang ML, Chu PY, Chang YL, Liu WH, Yu CC, et al. Lin28B/Let-7 regulates expression of Oct4 and Sox2 and reprograms oral squamous cell carcinoma cells to a stem-like state. Cancer Res 2015;75:2553–65.
[18] Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. Nature 2001;414:105–11.
[19] Friedmann-Morvinski D, Verma IM. Dedifferentiation and reprogramming: origins of cancer stem cells. EMBO Rep 2014;15:244–53.
[20] Kim WT, Ryu CJ. Cancer stem cell surface markers on normal stem cells. BMB Rep 2017;50:285–98.
[21] Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF. Prospective identification of tumorigenic breast cancer cells. PNAS 2003;100:3983–8.
[22] Krishnamurthy S, Dong Z, Vodopyanov D, Imai A, Helman JI, Prince ME, et al. Endothelial cell-initiated signaling promotes the survival and self-renewal of cancer stem cells. Cancer Res 2010;70:9969–78.
[23] Sun S, Wang Z. Head neck squamous cell carcinoma c-Met(+) cells display cancer stem cell properties and are responsible for cisplatin-resistance and metastasis. Int J Cancer 2011;129:2337–48.
[24] Wu Y, Wu PY. CD133 as a marker for cancer stem cells: progresses and concerns. Stem Cells Dev 2009;18:1127–34.
[25] Patel SS, Shah KA, Shah MJ, Kothari KC, Rawal RM. Cancer stem cells and stemness markers in oral squamous cell carcinomas. Asian Pac J Cancer Prev 2014;15:8549–56.
[26] Tsai LL, Yu CC, Chang YC, Yu CH, Chou MY. Markedly increased Oct4 and Nanog expression correlates with cisplatin resistance in oral squamous cell carcinoma. J Oral Pathol Med: Off Publ Int Assoc Oral Pathol Am Acad Oral Pathol 2011;40:621–8.
[27] Moral M, Segrelles C, Martinez-Cruz AB, Lorz C, Santos M, Garcia-Escudero R, et al. Transgenic mice expressing constitutively active Akt in oral epithelium validate KLFA as a potential biomarker of head and neck squamous cell carcinoma. In Vivo (Athens, Greece) 2009;23:653–60.
[28] Yu CC, Lo WL, Chen YW, Huang PI, Hsu HS, Tseng LM, et al. Bmi-1 regulates snail expression and promotes metastasis ability in head and neck squamous cancer-derived ALDH1 positive cells. J Oncol 2011.
[29] Bourguignon LY, Wong G, Earle C, Chen L. Hyaluronan-CD44v3 interaction with Oct4-Sox2-Nanog promotes miR-302 expression leading to self-renewal, clonal formation, and cisplatin resistance in cancer stem cells from head and neck squamous cell carcinoma. J Biol Chem 2012;287:32800–24.
[30] Chinn SB, Darr OA, Owen JH, Bellile E, McHugh JB, Spector ME, et al. Cancer stem cells: mediators of tumorigenesis and metastasis in head and neck squamous cell carcinoma. Head Neck 2015;37:317–26.
[31] Joshua B, Kaplan MJ, Doweck I, Pai R, Weissman IL, Prince ME, et al. Frequency of cells expressing CD44, a head and neck cancer stem cell marker: correlation with tumor aggressiveness. Head Neck 2012;34:42–9.
[32] Kulsum S, Sudheendra HV, Pandian R, Ravindra DR, Siddappa G, Chevour P, et al. Cancer stem cell mediated acquired chemoresistance in head and neck cancer can be abrogated by aldehyde dehydrogenase 1 A1 inhibition. Mol Carcinog 2017;56:694–711.
[33] Pan L, Gong Z, Zhong Z, Dong Z, Liu Q, Le Y, et al. Lin-28 reactivation is required for let-7 repression and proliferation in human small cell lung cancer cells. Mol Cell Biochem 2011;355:257–63.
[34] Qin R, Zhou J, Chen C, Xu T, Yan Y, Ma Y, et al. LIN28 is involved in glioma carcinogenesis and predicts outcomes of glioblastoma multiforme patients. PLoS ONE 2014;9:e86446.
[35] Hamano R, Miyata H, Yamasaki M, Sugimura K, Tanaka K, Kurokawa Y, et al. High expression of Lin28 is associated with tumour aggressiveness and poor prognosis of patients in oesophagus cancer. Br J Cancer 2012;106:1415–23.
[36] Faria AM, Sbiera S, Ribeiro TC, Soares IC, Mariani BM, Freire DS, et al. Expression of LIN28 and its regulatory microRNAs in adult adrenocortical cancer. Clin Endocrinol 2015;82:481–8.
[37] Wu TF, Jia J, Xiong XP, He HJ, Bu LL, Zhao ZL, et al. Increased expression of Lin28B associates with poor prognosis in patients with oral squamous cell carcinoma. PLoS ONE 2013;8.
[38] Wang DM, Zhu YM, Wang YL, Li ZW, Yuan CP, Zhang W, et al. The pluripotency factor LIN28B is involved in oral carcinogenesis and associates with tumor aggressiveness and unfavorable prognosis. Cancer Cell Int 2015;15.
[39] Sterenczak KA, Eckardt A, Kampmann A, Willenbrock S, Eberle N, Langer F, et al. HMGA1 and HMGA2 expression and comparative analyses of HMGA2, Lin28 and let-7 miRNAs in oral squamous cell carcinoma. BMC Cancer 2014;14:694.
[40] Lin WT, Shieh TM, Yang LC, Wang TY, Chou MY, Yu CC. Elevated Lin28B expression is correlated with lymph node metastasis in oral squamous cell carcinomas. J Oral Pathol Med 2015;44:823–30.
[41] Hayashi S, Tanaka J, Okada S, Isobe T, Yamamoto G, Yasuhara R, et al. Lin28a is a putative factor in regulating cancer stem cell-like properties in side population cells of oral squamous cell carcinoma. Exp Cell Res 2013;319:1220–8.
[42] Castellanos A, Vicente-Duenas C, Campos-Sanchez E, Cruz JJ, Garcia-Criado FJ, Garcia-Cenador MB, et al. Cancer as a reprogramming-like disease: implications in tumor development and treatment. Semin Cancer Biol 2010;20:93–7.
[43] Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006;126:663–76.
[44] Harada K, Ferdous T, Cui D, Kuramitsu Y, Matsumoto T, Ikeda E, et al. Induction of artificial cancer stem cells from tongue cancer cells by defined reprogramming factors. BMC Cancer 2016;16:548.
[45] Roos M, Pradere U, Ngondo RP, Behera A, Allegrini S, Civenni G, et al. A small-molecule inhibitor of Lin28. ACS Chem Biol 2016;11:2773–81.
[46] Reinhart BJ, Slack FJ, Basson M, Pasquinelli AE, Bettinger JC, Rougvie AE, et al. The 21-nucleotide let-7 RNA regulates developmental timing in Caenorhabditis elegans. Nature 2000;403:901–6.
[47] Boyerinas B, Park SM, Hau A, Murmann AE, Peter ME. The role of let-7 in cell differentiation and cancer. Endocr Relat Cancer 2010;17:F19–36.
[48] Yu F, Yao H, Zhu P, Zhang X, Pan Q, Gong C, et al. let-7 regulates self renewal and tumorigenicity of breast cancer cells. Cell 2007;131:1109–23.
[49] Farzaneh M, Attari F, Khoshnam SE. Concise review: LIN28/let-7 signaling, a critical double-negative feedback loop during pluripotency, reprogramming, and tumorigenicity. Cell Reprogram 2017;19:289–93.
[50] Cai WY, Wei TZ, Luo QC, Wu QW, Liu QF, Yang M, et al. The Wnt-beta-catenin pathway represses let-7 microRNA expression through transactivation of Lin28 to augment breast cancer stem cell expansion. J Cell Sci 2013;126:2877–89.
[51] Yang X, Lin X, Zhong X, Kaur S, Li N, Liang S, et al. Double-negative feedback loop between reprogramming factor LIN28 and microRNA let-7 regulates aldehyde dehydrogenase 1-positive cancer stem cells. Cancer Res 2010;70:9463–72.
[52] Qian X, Ma C, Nie X, Lu J, Lenarz M, Kaufmann AM, et al. Biology and immunology of cancer stem(-like) cells in head and neck cancer. Crit Rev Oncol/Hematol 2015;95:337–45.
[53] Liao T, Kaufmann AM, Qian X, Sangvatanakul V, Chen C, Kube T, et al. Susceptibility to cytotoxic T cell lysis of cancer stem cells derived from cervical and head and neck tumor cell lines. J Cancer Res Clin Oncol 2012;139:159–70.
[54] Visus C, Wang Y, Lozano-Leon A, Ferris RL, Silver S, Szczepanski MJ, et al. Targeting ALDH(bright) human carcinoma-initiating cells with ALDH1A1-specific CD8(+) T cells. Clin Cancer Res: Off J Am Assoc Cancer Res 2011;17:6174–84.
[55] Chikuma S. Basics of PD-1 in self-tolerance, infection, and cancer immunity. Int J Clin Oncol 2016;21:448–55.
[56] Chen Y, Xie C, Zheng X, Nie X, Wang Z, Liu H, et al. LIN28/let-7/PD-L1 pathway as a target for cancer immunotherapy. Cancer Immunol Res 2019;7:487–97.
[57] Gilles ME, Slack FJ. Let-7 microRNA as a potential therapeutic target with implications for immunotherapy. Expert Opin Therapeut Targets 2018;22:929–39.
[58] Pobezinsky LA, Wells AC. Let's fight cancer: let-7 is a tool to enhance antitumor immune responses. Future Oncol (Lond, Engl) 2018;14:1141–5.