Induced pluripotent stem cells (iPSCs) and cancer literatures

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Abstract: Induced pluripotent stem cells (iPSCs) are genetically reprogrammed adult cells that exhibit a pluripotent stem cell-like state similar to embryonic stem cells. There are several key types of pluripotent stem cells: (1) Embryonic stem cells are isolated from the inner cell mass of the blastocyst. (2) Embryonic germ cells are taken from aborted foetuses and these pluripotent cells are derived from very early cells. (3) Embryonic carcinoma or cancer cells are isolated from a type of tumour that sometimes occurs in a foetus. Embryonic germ cells are taken from aborted foetuses and these pluripotent cells are derived from very early cells. These early cells can become sperm and eggs. Embryonic stem cells are isolated from the inner cell mass of the blastocyst. Embryonic carcinoma or cancer cells are isolated from a type of tumour that sometimes occurs in a foetus. Embryonic carcinoma or cancer cells are isolated from a type of tumour that sometimes occurs in a foetus. Cancer stem cells are a subpopulation of cancer cells that can self-renew, propagate, and differentiate into the many types of cells in a tumor. Cancer stem cells are the source of all cells that make up the cancer. Chemotherapy may only destroy the cells that form the bulk of the tumor and leave the cancer stem cells intact and ready to give rise to a recurring tumor.
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1. Introduction

Induced pluripotent stem cells (iPSCs) are genetically reprogrammed adult cells that exhibit a pluripotent stem cell-like state similar to embryonic stem cells. There are several key types of pluripotent stem cells: (1) Embryonic stem cells are isolated from the inner cell mass of the blastocyst. (2) Embryonic germ cells are taken from aborted foetuses and these pluripotent cells are derived from very early cells. (3) Embryonic carcinoma or cancer cells are isolated from a type of tumour that sometimes occurs in a foetus.

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There are many methods to deliver the transcription factors into target cells to generate iPSCs. The first method is retrovirus or lentivirus transduction. The problem of this technique is the genome integration of virus DNA which could possibly alter differentiation potential or other malignant transformation. The second method is adenoviral vectors to induce iPSC. The advantage of adenovirus vector based expression is that the transgenes will not integrate into the house genome, thus reduces the risk of tumorogenesis. The third one is a plasmid based transfection that can avoid the genome integration also. Recently, the Cre-recombinase excisable systems are used in iPSC induction and subsequent transgene removal making the iPSC technology closer to clinic applications.

Literatures

The following gives some recent reference papers on .

Anguera, M. C., R. Sadreyev, et al. "Molecular signatures of human induced pluripotent stem cells highlight sex differences and cancer genes." Cell Stem Cell. 2012 Jul 6;11(1):75-90. doi: 10.1016/j.stem.2012.03.008.

Although human induced pluripotent stem cells (hiPSCs) have enormous potential in regenerative medicine, their epigenetic variability suggests that some lines may not be suitable for human therapy. There are currently few benchmarks for assessing quality. Here we show that X-inactivation markers can be used to separate hiPSC lines into distinct epigenetic classes and that the classes are phenotypically distinct. Loss of XIST expression is strongly correlated with upregulation of X-linked oncogenes, accelerated growth rate in vitro,

and poorer differentiation in vivo. Whereas differences in X-inactivation potential result in epigenetic variability of female hiPSC lines, male hiPSC lines generally resemble each other and do not overexpress the oncogenes. Neither physiological oxygen levels nor HDAC inhibitors offer advantages to culturing female hiPSC lines. We conclude that female hiPSCs may be epigenetically less stable in culture and caution that loss of XIST may result in qualitatively less desirable stem cell lines.

Chen, L., T. Kasai, et al. "A model of cancer stem cells derived from mouse induced pluripotent stem cells." PLoS One. 2012;7(4):e33544. doi: 10.1371/journal.pone.0033544. Epub 2012 Apr 12.

Cancer stem cells (CSCs) are capable of continuous proliferation and self-renewal and are proposed to play significant roles in oncogenesis, tumor growth, metastasis and cancer recurrence. CSCs are considered derived from normal stem cells affected by the tumor microenvironment although the mechanism of development is not clear yet. In 2007, Yamanaka's group succeeded in generating Nanog mouse induced pluripotent stem (miPS) cells, in which green fluorescent protein (GFP) has been inserted into the 5'-untranslated region of the Nanog gene. Usually, iPS cells, just like embryonic stem cells, are considered to be induced into progenitor cells, which differentiate into various normal phenotypes depending on the normal niche. We hypothesized that CSCs could be derived from Nanog miPS cells in the conditioned culture medium of cancer cell lines, which is a mimic of carcinoma microenvironment. As a result, the Nanog miPS cells treated with the conditioned medium of mouse Lewis lung carcinoma acquired characteristics of CSCs, in that they formed spheroids expressing GFP in suspension culture, and had a high tumorigenicity in Balb/c nude mice exhibiting angiogenesis in vivo. In addition, these iPS-derived CSCs had a capacity of self-renewal and expressed the marker genes, Nanog, Rex1, Eras, Esg1 and Cripto, associated with stem cell properties and an undifferentiated state. Thus we concluded that a model of CSCs was originally developed from miPS cells and proposed the conditioned culture medium of cancer cell lines might perform as niche for producing CSCs. The model of CSCs and the procedure of their establishment will help study the genetic alterations and the secreted factors in the tumor microenvironment which convert miPS cells to CSCs. Furthermore, the identification of potentially bona fide markers of CSCs, which will help the development of novel anti-cancer therapies, might be possible though the CSC model.

Doi, A., I. H. Park, et al. "Differential methylation of tissue- and cancer-specific CpG island shores distinguishes human induced pluripotent stem cells, embryonic stem cells and fibroblasts." Nat Genet. 2009 Dec;41(12):1350-3. doi: 10.1038/ng.471. Epub 2009 Nov 1.

Induced pluripotent stem (iPS) cells are derived by epigenetic reprogramming, but their DNA methylation patterns have not yet been analyzed on a genome-wide scale. Here, we find substantial hypermethylation and hypomethylation of cytosine-phosphate-guanine (CpG) island shores in nine human iPS cell lines as compared to their parental fibroblasts. The differentially methylated regions (DMRs) in the reprogrammed cells (denoted R-DMRs) were significantly enriched in tissue-specific (T-DMRs; 2.6-fold, $P < 10(-4)$) and cancer-specific DMRs (C-DMRs; 3.6-fold, $P < 10(-4)$). Notably, even though the iPS cells are derived from fibroblasts, their R-DMRs can distinguish between normal brain, liver and spleen cells and between colon cancer and normal colon cells. Thus, many DMRs are broadly involved in tissue differentiation, epigenetic reprogramming and cancer. We observed colocalization of hypomethylated R-DMRs with hypermethylated C-DMRs and bivalent chromatin marks, and colocalization of hypermethylated R-DMRs with hypomethylated C-DMRs and the absence of bivalent marks, suggesting two mechanisms for epigenetic reprogramming in iPS cells and cancer.

Fernandez Tde, S., C. de Souza Fernandez, et al. "Human induced pluripotent stem cells from basic research to potential clinical applications in cancer." Biomed Res Int. 2013;2013:430290. doi: 10.1155/2013/430290. Epub 2013 Oct 28.

The human induced pluripotent stem cells (hiPSCs) are derived from a direct reprogramming of human somatic cells to a pluripotent stage through ectopic expression of specific transcription factors. These cells have two important properties, which are the self-renewal capacity and the ability to differentiate into any cell type of the human body. So, the discovery of hiPSCs opens new opportunities in biomedical sciences, since these cells may be useful for understanding the mechanisms of diseases in the production of new diseases models, in drug development/drug toxicity tests, gene therapies, and cell replacement therapies. However, the hiPSCs technology has limitations including the potential for the development of genetic and epigenetic abnormalities leading to tumorigenicity. Nowadays, basic research in the hiPSCs field has made progress in the application of new strategies with the aim to enable an efficient production of high-quality of hiPSCs for safety and efficacy, necessary to the future

application for clinical practice. In this review, we show the recent advances in hiPSCs' basic research and some potential clinical applications focusing on cancer. We also present the importance of the use of statistical methods to evaluate the possible validation for the hiPSCs for future therapeutic use toward personalized cell therapies.

Lin, F. K. and Y. L. Chui "Generation of induced pluripotent stem cells from mouse cancer cells." Cancer Biother Radiopharm. 2012 Dec;27(10):694-700. doi: 10.1089/cbr.2012.1227. Epub 2012 Aug 14.

Reprogramming of cancer cells into induced pluripotent stem cells (iPSCs) opens up the possibility of converting malignant cells into any cell type, including those best suited to be developed as cancer vaccines. Mouse models are needed to evaluate and optimize the therapeutic efficacy of such novel cancer vaccines. However, only human cancer cell lines have been reported as being reprogrammed into iPSCs. Here, we report a proof-of-principle study which shows that mouse cancer cells can be reprogrammed into iPSCs that are capable of subsequent differentiation. Four canonical reprogramming transcription factors, Oct3/4, Sox2, Klf4, and c-Myc, were introduced by plasmid transfection into mouse Lewis lung carcinoma D122 harboring Nanog-GFP reporter. Green fluorescent cells were found clustered into embryonic stem cell (ESC)-like colonies expressing ESC markers, Oct4 and SSEA-1. Bisulfite genomic sequencing analyses of these cells revealed hypomethylation of the Nanog promoter. The expression of a host of pluripotency genes by these reprogrammed cells at levels similar to those of ESCs was confirmed by quantitative real-time PCR. Functional pluripotency of the reprogrammed cells was demonstrated by their ability to form embryoid bodies and differentiate into neuronal progenitors on retinoic acid treatment. This study indicates the feasibility of developing iPSC-based experimental cancer vaccines for immunotherapy in mouse models.

Lin, Y. C., Y. Murayama, et al. "Role of tumor suppressor genes in the cancer-associated reprogramming of human induced pluripotent stem cells." Stem Cell Res Ther. 2014;5(2):58.

Because of their pluripotent characteristics, human induced pluripotent stem cells (iPSCs) possess great potential for therapeutic application and for the study of degenerative disorders. These cells are generated from normal somatic cells, multipotent stem cells, or cancer cells. They express embryonic stem cell markers, such as OCT4, SOX2, NANOG, SSEA-3, SSEA-4, and REX1, and can differentiate into all adult tissue types, both in vitro and in vivo. However, some of the pluripotency-promoting factors have been implicated in tumorigenesis. Here, we describe the merits of tumor suppresser genes as reprogramming factors for the generation of iPSCs without tumorigenic activity. The initial step of reprogramming is induction of the exogenous pluripotent factors to generate the oxidative stress that leads to senescence by DNA damage and metabolic stresses, thus inducing the expression of tumor suppressor genes such as p21CIP1 and p16INK4a through the activation of p53 to be the pre-induced pluripotent stem cells (pre-iPSCs). The later stage includes overcoming the barrier of reprogramming-induced senescence or cell-cycle arrest by shutting off the function of these tumor suppressor genes, followed by the induction of endogenous stemness genes for the full commitment of iPSCs (full-iPSCs). Thus, the reactive oxygen species (ROS) produced by oxidative stress might be critical for the induction of endogenous reprogramming-factor genes via epigenetic changes or antioxidant reactions. We also discuss the critical role of tumor suppressor genes in the evaluation of the tumorigenicity of human cancer cell-derived pluripotent stem cells, and describe how to overcome their tumorigenic properties for application in stem cell therapy in the field of regenerative medicine.

Matsushita, N., H. Kobayashi, et al. "[Establishment of induced pluripotent stem cells from adipose tissue-derived stem cells for dendritic cell-based cancer vaccines]." Gan To Kagaku Ryoho. 2014 Apr;41(4):467-70.

Recently, studies on regenerative stem cell therapy are being encouraged, and efforts to generate dendritic cells, which play important roles in cancer immunotherapy, from stem cells are being made in the field of tumor immunology. Therapeutic acquisition of stem cells has important clinical applications. Studies on induced pluripotent stem(iPS)cells generated from somatic cells with pluripotent genes have advanced in recent years. Stem cells are reported to be found in adipose tissue (adipose-derived stem cells, ADSC). Our goal is to develop a new cancer vaccine by using dendritic cells generated from ADSC. In a preliminary study, we examined whether iPS cells can be generated from ADSC to serve as a source of dendritic cells.We introduced a plasmid with pluripotent genes(OCT3/4, KLF4, SOX2, L-MYC, LIN28, p53-shRNA)into an ADSC strain derived from adipose tissue by electroporation and subsequently cultured the cells for further examination. A colony suggestive of iPS cells from ADSC was observed. OCT3/4, KLF4, SOX2, L-MYC, and LIN28 mRNAs were expressed in the cultured cells, as confirmed by reverse transcriptase-polymerase chain reaction(RT-PCR). On the basis of these results, we confirmed that

iPS cells were generated from ADSC. The method of inducing dendritic cells from iPS cells has already been reported, and the results of this study suggest that ADSC is a potential source of dendritic cells.

Mosca, E., C. Cocola, et al. "Overlapping genes may control reprogramming of mouse somatic cells into induced pluripotent stem cells (iPSCs) and breast cancer stem cells." In Silico Biol. 2010;10(5-6):207-21. doi: 10.3233/ISB-2010-0437.

Recent findings suggest the possibility that tumors originate from cancer cells with stem cell properties. The cancer stem cell (CSC) hypothesis provides an explanation for why existing cancer therapies often fail in eradicating highly malignant tumors and end with tumor recurrence. Although normal stem cells and CSCs both share the capacity for self-renewal and multi-lineage differentiation, suggesting that CSC may be derived from normal SCs, the cellular origin of transformation of CSCs is debatable. Research suggests that the tightly controlled balance of self-renewal and differentiation that characterizes normal stem cell function is dis-regulated in cancer. Additionally, recent evidence has linked an embryonic stem cell (ESC)-like gene signature with poorly differentiated high-grade tumors, suggesting that regulatory pathways controlling pluripotency may in part contribute to the somatic CSC phenotype. Here, we introduce expression profile bioinformatic analyses of mouse breast cells with CSC properties, mouse embryonic stem (mES) and induced pluripotent stem (iPS) cells with an emphasis on how study of pluripotent stem cells may contribute to the identification of genes and pathways that facilitate events associated with oncogenesis. Global gene expression analysis from CSCs and induced pluripotent stem cell lines represent an ideal model to study cancer initiation and progression and provide insight into the origin cancer stem cells. Additionally, insight into the genetic and epigenomic mechanisms regulating the balance between self-renewal and differentiation of somatic stem cells and cancer may help to determine whether different strategies used to generate iPSCs are potentially safe for therapeutic use.

Ohm, J. E., P. Mali, et al. "Cancer-related epigenome changes associated with reprogramming to induced pluripotent stem cells." Cancer Res. 2010 Oct 1;70(19):7662-73. doi: 10.1158/0008-5472.CAN-10-1361. Epub 2010 Sep 14.

The ability to induce pluripotent stem cells from committed, somatic human cells provides tremendous potential for regenerative medicine. However, there is a defined neoplastic potential inherent to such reprogramming that must be understood and may provide a model for understanding key events in tumorigenesis. Using genome-wide assays, we identify cancer-related epigenetic abnormalities that arise early during reprogramming and persist in induced pluripotent stem cell (iPS) clones. These include hundreds of abnormal gene silencing events, patterns of aberrant responses to epigenetic-modifying drugs resembling those for cancer cells, and presence in iPS and partially reprogrammed cells of cancer-specific gene promoter DNA methylation alterations. Our findings suggest that by studying the process of induced reprogramming, we may gain significant insight into the origins of epigenetic gene silencing associated with human tumorigenesis, and add to means of assessing iPS for safety.

Purwanti, Y. I., C. Chen, et al. "Antitumor effects of CD40 ligand-expressing endothelial progenitor cells derived from human induced pluripotent stem cells in a metastatic breast cancer model." Stem Cells Transl Med. 2014 Aug;3(8):923-35. doi: 10.5966/sctm.2013-0140. Epub 2014 Jun 27.

Given their intrinsic ability to home to tumor sites, endothelial progenitor cells (EPCs) are attractive as cellular vehicles for targeted cancer gene therapy. However, collecting sufficient EPCs is one of the challenging issues critical for effective clinical translation of this new approach. In this study, we sought to explore whether human induced pluripotent stem (iPS) cells could be used as a reliable and accessible cell source to generate human EPCs suitable for cancer treatment. We used an embryoid body formation method to derive CD133(+)CD34(+) EPCs from human iPS cells. The generated EPCs expressed endothelial markers such as CD31, Flk1, and vascular endothelial-cadherin without expression of the CD45 hematopoietic marker. After intravenous injection, the iPS cell-derived EPCs migrated toward orthotopic and lung metastatic tumors in the mouse 4T1 breast cancer model but did not promote tumor growth and metastasis. To investigate their therapeutic potential, the EPCs were transduced with baculovirus encoding the potent T cell costimulatory molecule CD40 ligand. The systemic injection of the CD40 ligand-expressing EPCs stimulated the secretion of both tumor necrosis factor-alpha and interferon-gamma and increased the caspase 3/7 activity in the lungs with metastatic tumors, leading to prolonged survival of the tumor bearing mice. Therefore, our findings suggest that human iPS cell-derived EPCs have the potential to serve as tumor-targeted cellular vehicles for anticancer gene therapy.

Sachamitr, P., S. Hackett, et al. "Induced pluripotent stem cells: challenges and opportunities for cancer

immunotherapy." Front Immunol. 2014 Apr 17;5:176. doi: 10.3389/fimmu.2014.00176. eCollection 2014.

Despite recent advances in cancer treatment over the past 30 years, therapeutic options remain limited and do not always offer a cure for malignancy. Given that tumor-associated antigens (TAA) are, by definition, self-proteins, the need to productively engage autoreactive T cells remains at the heart of strategies for cancer immunotherapy. These have traditionally focused on the administration of autologous monocyte-derived dendritic cells (moDC) pulsed with TAA, or the ex vivo expansion and adoptive transfer of tumor-infiltrating lymphocytes (TIL) as a source of TAA-specific cytotoxic T cells (CTL). Although such approaches have shown some efficacy, success has been limited by the poor capacity of moDC to cross present exogenous TAA to the CD8(+) T-cell repertoire and the potential for exhaustion of CTL expanded ex vivo. Recent advances in induced pluripotency offer opportunities to generate patient-specific stem cell lines with the potential to differentiate in vitro into cell types whose properties may help address these issues. Here, we review recent success in the differentiation of NK cells from human induced pluripotent stem (iPS) cells as well as minor subsets of dendritic cells (DCs) with therapeutic potential, including CD141(+)XCR1(+) DC, capable of cross presenting TAA to naive CD8(+) T cells. Furthermore, we review recent progress in the use of TIL as the starting material for the derivation of iPSC lines, thereby capturing their antigen specificity in a self-renewing stem cell line, from which potentially unlimited numbers of naive TAA-specific T cells may be differentiated, free of the risks of exhaustion.

Themeli, M., C. C. Kloss, et al. "Generation of tumor-targeted human T lymphocytes from induced pluripotent stem cells for cancer therapy." Nat Biotechnol. 2013 Oct;31(10):928-33. doi: 10.1038/nbt.2678. Epub 2013 Aug 11.

Progress in adoptive T-cell therapy for cancer and infectious diseases is hampered by the lack of readily available, antigen-specific, human T lymphocytes. Pluripotent stem cells could provide an unlimited source of T lymphocytes, but the therapeutic potential of human pluripotent stem cell-derived lymphoid cells generated to date remains uncertain. Here we combine induced pluripotent stem cell (iPSC) and chimeric antigen receptor (CAR) technologies to generate human T cells targeted to CD19, an antigen expressed by malignant B cells, in tissue culture. These iPSC-derived, CAR-expressing T cells display a phenotype resembling that of innate gammadelta T cells. Similar to CAR-transduced, peripheral blood gammadelta T cells, the iPSC-derived T cells potently inhibit tumor growth in a xenograft model. This approach of generating therapeutic human T cells 'in the dish' may be useful for cancer immunotherapy and other medical applications.

Yan, T., A. Mizutani, et al. "Characterization of cancer stem-like cells derived from mouse induced pluripotent stem cells transformed by tumor-derived extracellular vesicles." J Cancer. 2014 Jul 5;5(7):572-84. doi: 10.7150/jca.8865. eCollection 2014.

Several studies have shown that cancer niche can perform an active role in the regulation of tumor cell maintenance and progression through extracellular vesicles-based intercellular communication. However, it has not been reported whether this vesicle-mediated communication affects the malignant transformation of normal stem cells/progenitors. We have previously reported that the conditioned medium derived from the mouse Lewis Lung Carcinoma (LLC) cell line can convert mouse induced pluripotent stem cells (miPSCs) into cancer stem cells (CSCs), indicating that normal stem cells when placed in an aberrant microenvironment can give rise to functionally active CSCs. Here, we focused on the contribution of tumor-derived extracellular vesicles (tEVs) that are secreted from LLC cells to induce the transformation of miPSCs into CSCs. We isolated tEVs from the conditioned medium of LLC cells, and then the differentiating miPSCs were exposed to tEVs for 4 weeks. The resultant tEV treated cells (miPS-LLCev) expressed Nanog and Oct3/4 proteins comparable to miPSCs. The frequency of sphere formation of the miPS-LLCev cells in suspension culture indicated that the self-renewal capacity of the miPS-LLCev cells was significant. When the miPS-LLCev cells were subcutaneously transplanted into Balb/c nude mice, malignant liposarcomas with extensive angiogenesis developed. miPS-LLCevPT and miPS-LLCevDT, the cells established from primary site and disseminated liposarcomas, respectively, showed their capacities to self-renew and differentiate into adipocytes and endothelial cells. Moreover, we confirmed the secondary liposarcoma development when these cells were transplanted. Taken together, these results indicate that miPS-LLCev cells possess CSC properties. Thus, our current study provides the first evidence that tEVs have the potential to induce CSC properties in normal tissue stem cells/progenitors.

Zhang, D. M., J. J. Li, et al. "Establishment and identification of induced pluripotent stem cells in liver cancer patients." Asian Pac J Trop Med. 2014 Apr;7(4):253-6. doi: 10.1016/S1995-7645(14)60032-8.

OBJECTIVE: To induce pluripotent stem (IPS) cells from fibrocytes that are separated from liver cancer patients. METHODS: The fibrocytes were reprogrammed to IPS cells by lentiviral vector, stained and identified by immunohistochemistry. RESULTS: The IPS cells were successfully established from fibrocytes after infection, and IPS cell clones formed in round shape under a microscopy. The induction rate was 0.013%+/-0.007%. No tumor formed at the back of nude mice within 8 weeks after the inoculation of cell clones. However, tetatoma appeared in nude mice within 1 week after IPS inoculation. A few tumors formed in nude mice within 4 weeks after the inoculation of cell clones. However, subcutaneous tumors formed within 1 week after IPS inoculation. The induced IPS cells showed three germ layers in tetatoma. Nanog and OCT4 in the induced IPS cells showed hypomethylation. SSEA-A, TRA-1-6-, TRA-1-81 and Nanog were highly expressed in the induced IPS cells, indicating the IPS cells possessed the similar ability as the stem cells. CONCLUSIONS: The IPS cells of liver cancer patients can be established effectively from fibrocytes and can be cultured stably in vitro, which provides an approach for the treatment of intermediate or advanced stage liver cancer.

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