c-Myc (Myc) and cancer literatures

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Abstract: c-Myc (Myc) is a regulator gene coding for a transcription factor. The c-Myc protein is a multifunctional, nuclear phosphoprotein that plays a role in cell cycle progression, apoptosis and cellular transformation. The mutated c-Myc is found in many cancers, which makes it be persistently expressed. This causes to the unregulated expression of many genes, some of which are involved in cell proliferation and results in the formation of cancer. Malfunctions in c-Myc have been found in carcinoma of the cervix, colon, breast, lung and stomach, etc. c-Myc is considered as a promising target for anti-cancer drugs.
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Key words: DNA; eternal; life; stem cell; universe

1. Introduction

c-Myc (Myc) is a regulator gene coding for a transcription factor. The c-Myc protein is a multifunctional, nuclear phosphoprotein that plays a role in cell cycle progression, apoptosis and cellular transformation.

The mutated c-Myc is found in many cancers, which makes it be persistently expressed. This causes to the unregulated expression of many genes, some of which are involved in cell proliferation and results in the formation of cancer. Malfunctions in c-Myc have been found in carcinoma of the cervix, colon, breast, lung and stomach, etc. c-Myc is considered as a promising target for anti-cancer drugs.

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 .c-Myc and cancer.

Di, J., T. Duiveman-de Boer, et al. "The stem cell markers Oct4A, Nanog and c-Myc are expressed in ascites cells and tumor tissue of ovarian cancer patients." Cell Oncol (Dordr). 2013 Oct;36(5):363-74. doi: 10.1007/s13402-013-0142-8. Epub 2013 Aug 9.

PURPOSE: The aim of this study was to examine the expression of established stem cell markers in ascites and tumor tissue obtained from ovarian cancer patients. METHODS: Mononuclear cells present in ascites were collected by density gradient centrifugation. Intracellular flowcytometry was used to assess the putative presence of stem cell markers. RT-PCR was used to detect full length Oct4A, a splice variant Oct4B, implicated in glioma and breast cancer, Oct4 pseudogenes and c-Myc. Genes were cloned and sequenced to determine putative mutations. Confocal laser scanning microscopy was performed to localize the markers in ascites cells as well as in tumor tissue. Material from carcinomas other than epithelial ovarian carcinoma served as control. RESULTS: A small quantity of cells in ascites and in tumor tissue of ovarian cancer patients was detected that expresses c-Myc, Oct4A and Nanog. Besides Oct4A, present in the nucleus, also the cytoplasmic resident Oct4B splice variant was detected. Remarkably, c-Myc was found partially in the cytoplasm. Since no mutations in c-Myc were found that could explain the cytoplasmic localization, we hypothesize that this is due an IL-6 induced c-Myc shuttle factor. CONCLUSIONS: The expression of stem cell genes was detected in a small proportion of tumor cells present in ascites as well as in tumor tissue. IL-6 plays an important role in the induction of c-Myc.

Giorello, L., L. Clerico, et al. "Inhibition of cancer cell growth and c-Myc transcriptional activity by a c-Myc helix 1-type peptide fused to an internalization sequence." Cancer Res. 1998 Aug 15;58(16):3654-9.

c-Myc is a nuclear protein with important roles in cell transformation, cell proliferation, and

gene transcription. It has been previously shown that a 14-amino acid (aa) modified peptide (H1-S6A,F8A) derived from the helix 1 (H1) carboxylic region of c-Myc can interfere in vitro with specific c-Myc DNA binding. Here, we have linked the above Myc-derived 14-aa peptide to a 16-aa sequence from the third helix of Antennapedia (Int). It has been repeatedly reported that this 16-aa Antennapedia peptide is able to cross mammalian cell membranes and to work as a vector for short peptides. Using fluorescent (dansylated or rhodaminated) peptides, we have shown that the fusion peptide with the Antennapedia fragment (Int-H1-S6A,F8A) but not the c-Myc derived fragment alone (H1-S6A,F8A) was capable of internalization inside MCF-7 human breast cancer cells. Int-H1-S6A,F8A and H1-S6A,F8A were the only two peptides capable of inhibiting coimmunoprecipitation of the c-Myc/Max heterodimer in vitro. We have treated (continuously for 10-11 days) MCF-7 cells with four different peptides: Int, H1-S6A,F8A, Int-H1-S6A,F8A, and Int-H1wt [a peptide differing from Int-H1-S6A,F8A by 2 aa (S6 and F8) in the H1 region]. In intact MCF-7 cells, Int-H1-S6A,F8A was the only active peptide capable of inducing the following biological effects: (a) inhibition of cloning efficiency on plates; (b) inhibition of cell growth and induction of apoptosis in subconfluent/confluent cells; and (c) inhibition of transcription of two c-Myc-regulated genes (ODC and p53).

Gokulan, R. and D. Halagowder "Expression pattern of Notch intracellular domain (NICD) and Hes-1 in preneoplastic and neoplastic human oral squamous epithelium: their correlation with c-Myc, clinicopathological factors and prognosis in Oral cancer." Med Oncol. 2014 Aug;31(8):126. doi: 10.1007/s12032-014-0126-1. Epub 2014 Jul 19.

Notch pathway molecules crosstalk with Wnt/beta-catenin signaling cascade in stem cells and tumors. However, the correlation between the expression pattern of Notch intracellular domain NICD, Hes-1 and c-Myc has not been studied in oral squamous cell carcinoma. The aim of this study is to investigate the correlation and prognostic significance of NICD, Hes-1 and c-Myc in oral cancer. Immunohistochemistry was used to study the expression pattern of NICD, Hes-1 and c-Myc in oral preneoplastic and neoplastic tissues. In addition, double immunofluorescence was used to examine the co-localization of NICD, Hes-1 and c-Myc in H314 cells. The expression pattern of NICD and Hes-1 was gradually increased from normal to dysplasia to carcinoma. Interestingly, statistically significant correlation was not observed between NICD, Hes-1 and c-Myc in oral squamous cell carcinoma. Furthermore, NICD+/c-Myc+ and Hes-1+/c-Myc+

double positive cases showed worst survival when compared with other cases in oral cancer. Notch signaling molecules, NICD and Hes-1, are found to be involved in the progression of oral squamous cell carcinoma. Interestingly, NICD, Hes-1 and c-Myc may have independent roles in oral cancer. On the other hand, we have demonstrated that NICD+/c-Myc+ and Hes-1+/c-Myc+ double positivity might be used as independent prognostic indicator of oral carcinoma.

Hofer, E. L., V. La Russa, et al. "Alteration on the expression of IL-1, PDGF, TGF-beta, EGF, and FGF receptors and c-Fos and c-Myc proteins in bone marrow mesenchymal stroma cells from advanced untreated lung and breast cancer patients." Stem Cells Dev. 2005 Oct;14(5):587-94.

Previously, we reported a deficient cloning capacity of the bone marrow (BM) mesenchymal stem cells to give colony-forming unit fibroblast (CFU-F) and an inefficient confluence capacity of BM stromal cells in advanced untreated lung cancer patients (LCP) and breast cancer patients (BCP). Moreover, a decreased level of bFGF at day 7 in the conditioned media from BM CFU-F cultures was found in both cancer groups when compared to the normal range. The current study was specially undertaken, to evaluate the percentage of subconfluent fibroblasts expressing receptors (R) of interleukin-1 (IL-1), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor (TGF-beta), epidermal growth factor (EGF), and the proteins c-Fos and c-Myc in BM primary cultures from untreated LCP and BCP. An immunocytochemical study on subconfluent BM fibroblast cultures from 13 healthy patients, 16 LCP, and 8 BCP was performed, using as primary antibodies, anti-type I of IL-1 R (IL-1R-1), anti-alpha, beta chains of PDGF R (PDGFR-alpha, PDGFR-beta), anti-type I of FGF R (FGFR-I), anti-type I, II, and III of TGF-beta R (TGF-betaR-I, TGF- betaR-II, and TGF-betaR-III), anti-EGF R, anti-c-Fos, and anti-c-Myc. A diminished percentage of subconfluent fibroblasts expressing PDGFR-alpha, TGFbetaR-I, II, III, EGFR, and FGFR-I was found in LCP and BCP compared to healthy patients. A diminished percentage of subconfluent fibroblasts expressing c-Fos and c-Myc was found in patients when compared to healthy patients. The alterations we describe could help to explain the deficiency regarding the proliferative and confluence capacity of BM stroma cells in cancer patients.

Ioannidis, P., L. G. Mahaira, et al. "CRD-BP/IMP1 expression characterizes cord blood CD34+ stem cells and affects c-myc and IGF-II expression in MCF-7

cancer cells." J Biol Chem. 2005 May 20;280(20):20086-93. Epub 2005 Mar 14.

The coding region determinant-binding protein/insulin-like growth factor II mRNA-binding protein (CRD-BP/IMP1) is an RNA-binding protein specifically recognizing c-myc, leader 3' IGF-II and tau mRNAs, and the H19 RNA. CRD-BP/IMP1 is predominantly expressed in embryonal tissues but is de novo activated and/or overexpressed in various human neoplasias. To address the question of whether CRD-BP/IMP1 expression characterizes certain cell types displaying distinct proliferation and/or differentiation properties (i.e. stem cells), we isolated cell subpopulations from human bone marrow, mobilized peripheral blood, and cord blood, all sources known to contain stem cells, and monitored for its expression. CRD-BP/IMP1 was detected only in cord blood-derived CD34(+) stem cells and not in any other cell type of either adult or cord blood origin. Adult BM CD34(+) cells cultured in the presence of 5'-azacytidine expressed de novo CRD-BP/IMP1, suggesting that epigenetic modifications may be responsible for its silencing in adult non-expressing cells. Furthermore, by applying the short interfering RNA methodology in MCF-7 cells, we observed, subsequent to knocking down CRD-BP/IMP1, decreased c-myc expression, increased IGF-II mRNA levels, and reduced cell proliferation rates. These data 1) suggest a normal role for CRD-BP/IMP1 in pluripotent stem cells with high renewal capacity, like the CB CD34(+) cells, 2) indicate that altered methylation may directly or indirectly affect its expression in adult cells, 3) imply that its de novo activation in cancer cells may affect the expression of c-Myc and insulin-like growth factor II, and 4) indicate that the inhibition of CRD-BP/IMP1 expression might affect cancer cell proliferation.

Janghorban, M., A. S. Farrell, et al. "Targeting c-MYC by antagonizing PP2A inhibitors in breast cancer." Proc Natl Acad Sci U S A. 2014 Jun 24;111(25):9157-62. doi: 10.1073/pnas.1317630111. Epub 2014 Jun 9.

The transcription factor c-MYC is stabilized and activated by phosphorylation at serine 62 (S62) in breast cancer. Protein phosphatase 2A (PP2A) is a critical negative regulator of c-MYC through its ability to dephosphorylate S62. By inactivating c-MYC and other key signaling pathways, PP2A plays an important tumor suppressor function. Two endogenous inhibitors of PP2A, I2PP2A, Inhibitor-2 of PP2A (SET oncoprotein) and cancerous inhibitor of PP2A (CIP2A), inactivate PP2A and are overexpressed in several tumor types. Here we show that SET is overexpressed in about 50-60% and CIP2A in about 90% of breast cancers. Knockdown of

SET or CIP2A reduces the tumorigenic potential of breast cancer cell lines both in vitro and in vivo. Treatment of breast cancer cells in vitro or in vivo with OP449, a novel SET antagonist, also decreases the tumorigenic potential of breast cancer cells and induces apoptosis. We show that this is, at least in part, due to decreased S62 phosphorylation of c-MYC and reduced c-MYC activity and target gene expression.

Joensuu, K., J. Hagstrom, et al. "Bmi-1, c-myc, and Snail expression in primary breast cancers and their metastases--elevated Bmi-1 expression in late breast cancer relapses." Virchows Arch. 2011 Jul;459(1):31-9. doi: 10.1007/s00428-011-1096-8. Epub 2011 Jun 3.

Breast cancer is known for its propensity to recur decades after treatment. The biology behind the phenomenon of tumor dormancy is still poorly understood. Bmi-1, c-myc, and Snail are transcription factors that have prognostic roles in several malignancies. In order to reveal whether any of these markers has impact on late relapses, we used immunohistochemistry to study the expression of Bmi-1, c-myc, Snail, and estrogen receptor in 73 primary breast cancers and in their metastatic relapses detected within 2 years, or 5 or 10 years after primary surgery. The expression of Bmi-1 was higher in the metastases than in their corresponding primary tumors in both early and late relapses. The highest expression of Bmi-1 was seen in the very late relapsing tumors (first tumor relapse after 10 years). Previously, Bmi-1 has been reported to function as a marker of tumor stem cells in breast cancer. Our results indicate that metastases, when compared to primary tumors, arise from tumor cells that have retained stem cell properties. We also analyzed the relationship between the expression of these markers and clinical parameters. A significant association between the expression of Bmi-1 and estrogen receptor was found. Nuclear expression of c-myc in primary tumors correlated with an increased risk for axillary lymph node metastasis.

Liu, M., M. C. Casimiro, et al. "p21CIP1 attenuates Ras- and c-Myc-dependent breast tumor epithelial mesenchymal transition and cancer stem cell-like gene expression in vivo." Proc Natl Acad Sci U S A. 2009 Nov 10;106(45):19035-9. doi: 10.1073/pnas.0910009106. Epub 2009 Oct 26.

p21(CIP1/WAF1) is a downstream effector of tumor suppressors and functions as a cyclin-dependent kinase inhibitor to block cellular proliferation. Breast tumors may derive from self-renewing tumor-initiating cells (BT-ICs), which contribute to tumor progression, recurrence, and therapy resistance. The role of p21(CIP1) in regulating

features of tumor stem cells in vivo is unknown. Herein, deletion of p21(CIP1), which enhanced the rate of tumorigenesis induced by mammary-targeted Ha-Ras or c-Myc, enhanced gene expression profiles and immunohistochemical features of epithelial mesenchymal transition (EMT) and putative cancer stem cells in vivo. Silencing of p21(CIP1) enhanced, and expression of p21(CIP1) repressed, features of EMT in transformed immortal human MEC lines. p21(CIP1) attenuated oncogene-induced BT-IC and mammosphere formation. Thus, the in vitro cell culture assays reflect the changes observed in vivo in transgenic mice. These findings establish a link between the loss of p21(CIP1) and the acquisition of breast cancer EMT and stem cell properties in vivo.

Nair, R., D. L. Roden, et al. "c-Myc and Her2 cooperate to drive a stem-like phenotype with poor prognosis in breast cancer." Oncogene. 2014 Jul 24;33(30):3992-4002. doi: 10.1038/onc.2013.368. Epub 2013 Sep 23.

The HER2 (ERBB2) and MYC genes are commonly amplified in breast cancer, yet little is known about their molecular and clinical interaction. Using a novel chimeric mammary transgenic approach and in vitro models, we demonstrate markedly increased self-renewal and tumour-propagating capability of cells transformed with Her2 and c-Myc. Coexpression of both oncoproteins in cultured cells led to the activation of a c-Myc transcriptional signature and acquisition of a self-renewing phenotype independent of an epithelial-mesenchymal transition programme or regulation of conventional cancer stem cell markers. Instead, Her2 and c-Myc cooperated to induce the expression of lipoprotein lipase, which was required for proliferation and self-renewal in vitro. HER2 and MYC were frequently coamplified in breast cancer, associated with aggressive clinical behaviour and poor outcome. Lastly, we show that in HER2(+) breast cancer patients receiving adjuvant chemotherapy (but not targeted anti-Her2 therapy), MYC amplification is associated with a poor outcome. These findings demonstrate the importance of molecular and cellular context in oncogenic transformation and acquisition of a malignant stem-like phenotype and have diagnostic and therapeutic consequences for the clinical management of HER2(+) breast cancer.

Plummer, H., 3rd, J. Catlett, et al. "c-myc expression correlates with suppression of c-kit protooncogene expression in small cell lung cancer cell lines." Cancer Res. 1993 Sep 15;53(18):4337-42.

The mRNAs encoding the c-kit protooncogene tyrosine kinase receptor and its ligand, hemopoietic stem cell factor, are coexpressed in the majority of small cell lung cancer cell lines, suggesting that an autocrine growth loop may exist. Functional c-kit protein levels correspond well with mRNA levels in these cells. We have observed that those cell lines which express the c-kit gene also express either the L- and N-myc genes; those cell lines which express the c-myc gene do not express the c-kit gene. We have determined, by analyzing several small lung cancer cell lines transfected with a c-myc expression vector, that heterologous expression of c-myc correlates with a marked down-regulation of c-kit expression. Regulation of c-kit expression by the myc gene family may be partly responsible for the differing biological properties of cell lines and tumors which express N- and L-myc versus those that express c-myc.

Reamon-Buettner, S. M. and J. Borlak "Epigenetic silencing of cell adhesion molecule 1 in different cancer progenitor cells of transgenic c-Myc and c-Raf mouse lung tumors." Cancer Res. 2008 Sep 15;68(18):7587-96. doi: 10.1158/0008-5472.CAN-08-0967.

Understanding molecular mechanisms underlying lung cancer is a prerequisite toward treatment. To enable mechanistic investigations into the epigenetic regulation of the tumor suppressor gene cell adhesion molecule 1 (Cadm1) in lung cancer progenitor cells, we developed 10 cell lines from single, spontaneously transformed lung tumor cells isolated from c-Myc and c-Raf double-transgenic mice. Specifically, we investigated Cadm1 promoter hypermethylation, which was significantly induced in transgenic transformed cells. Analysis of 69 CpGs displayed differential methylation pattern between and within progenitor cell lines, and the degree of methylation correlated well with transcriptional repression. Indeed, restoration of Cadm1 gene expression was achieved by treatment with the experimental demethylating drug 5-aza-2'-deoxycytidine. Furthermore, methylation of core CpGs in the binding sites of Sp1, Sp3, and zinc finger 5 along the promoter region of Cadm1 abrogated DNA-protein binding. Treatment with mithramycin A, an inhibitor of Sp1 or Sp3 binding, resulted in reduction of Cadm1 gene expression, therefore suggesting a potential role of Sp1/Sp3 in Cadm1 regulation. Identifying molecular rules for the epigenetic control of tumor suppressor genes enables mechanistic insights into lung cancer growth and opportunities for novel therapies.

Sussman, R. T., M. S. Ricci, et al. "Chemotherapy-resistant side-population of colon cancer cells has a higher sensitivity to TRAIL than the non-SP, a higher expression of c-Myc and TRAIL-receptor DR4."

Cancer Biol Ther. 2007 Sep;6(9):1490-5. Epub 2007 Aug 17.

Cancer stem cells are resistant to chemotherapy and provide an important target for drug development. We found that, surprisingly, the dye-effluxing side population (SP) within SW480 human colon tumor cells, a population defined to possess stem cell characteristics, expresses a 10-fold higher level of pro-apoptotic TRAIL receptor DR4 as compared to non-SP cells. The TRAIL receptors are activated by the anti-tumor host immune system through the TRAIL ligand. SW480 SP-cells express similar levels of another TRAIL receptor (DR5), as non-SP cells. SP-cells from multiple tumorigenic human cell lines, which are most often resistant to chemotherapeutic agents such as etoposide, cisplatin and 5-FU, are more sensitive to TRAIL than non-SP cells. SP-cells express higher levels of c-Myc than non-SP cells which may explain their sensitivity to TRAIL. We have found c-Myc activates DR4 transcription through E-box DNA-response elements located in the DR4 promoter, thereby increasing the expression of cell-surface pro-apoptotic death receptors in TRAIL-resistant cell lines. TRAIL sensitivity of SP-cells may represent a safeguard against malignancy, and therefore, offers a therapeutic window and opportunity.

Trumpp, A. "c-Myc and activated Ras during skin tumorigenesis: cooperation at the cancer stem cell level?" Ernst Schering Found Symp Proc. 2006;(5):13-26.

Mutations leading to overexpression and activation of the oncogenes Myc and Ras are among the most frequent lesions known to occur in human and murine cancers. These genes are also the pioneering example for oncogene cooperation during tumorigenesis, whereby the anticancer effects of Myc deregulation (apoptosis) and oncogenic Ras (senescence) are antagonized and therefore canceled out by each other. Here I review the role of endogenous and overexpressed c-Myc in murine skin, focusing primarily on epidermal stem cells. In addition, recent data suggesting an essential role for the endogenous c-Myc-p21(CIP1) pathway in Ras-driven skin tumorigenesis are discussed.

Wang, C., M. P. Lisanti, et al. "Reviewing once more the c-myc and Ras collaboration: converging at the cyclin D1-CDK4 complex and challenging basic concepts of cancer biology." Cell Cycle. 2011 Jan 1;10(1):57-67. Epub 2011 Jan 1.

The c-myc is a proto-oncogene that manifests aberrant expression at high frequencies in most types of human cancer. C-myc gene amplifications are often observed in various cancers as well. Ample studies have also proved that c-myc has a potent oncogenicity, which can be further enhanced by collaborations with other oncogenes such as Bcl-2 and activated Ras. Studies on the collaborations of c-myc with Ras or other genes in oncogenicity have established several basic concepts and have disclosed their underlying mechanisms of tumor biology, including "immortalization" and "transformation". In many cases, these collaborations may converge at the cyclin D1-CDK4 complex. In the meantime, however, many results from studies on the c-myc, Ras and cyclin D1-CDK4 also challenge these basic concepts of tumor biology and suggest to us that the immortalized status of cells should be emphasized. Stricter criteria and definitions for a malignantly transformed status and a benign status of cells in culture also need to be established to facilitate our study of the mechanisms for tumor formation and to better link up in vitro data with animal results and eventually with human cancer pathology.

Wang, J., H. Wang, et al. "c-Myc is required for maintenance of glioma cancer stem cells." PLoS One. 2008;3(11):e3769. doi: 10.1371/journal.pone.0003769. Epub 2008 Nov 20.

BACKGROUND: Malignant gliomas rank among the most lethal cancers. Gliomas display a striking cellular heterogeneity with a hierarchy of differentiation states. Recent studies support the existence of cancer stem cells in gliomas that are functionally defined by their capacity for extensive self-renewal and formation of secondary tumors that phenocopy the original tumors. As the c-Myc oncoprotein has recognized roles in normal stem cell biology, we hypothesized that c-Myc may contribute to cancer stem cell biology as these cells share characteristics with normal stem cells. METHODOLOGY/PRINCIPAL FINDINGS: Based on previous methods that we and others have employed, tumor cell populations were enriched or depleted for cancer stem cells using the stem cell marker CD133 (Prominin-1). We characterized c-Myc expression in matched tumor cell populations using real time PCR, immunoblotting, immunofluorescence and flow cytometry. Here we report that c-Myc is highly expressed in glioma cancer stem cells relative to non-stem glioma cells. To interrogate the significance of c-Myc expression in glioma cancer stem cells, we targeted its expression using lentivirally transduced short hairpin RNA (shRNA). Knockdown of c-Myc in glioma cancer stem cells reduced proliferation with concomitant cell cycle arrest in the G(0)/G(1) phase and increased apoptosis. Non-stem glioma cells displayed limited dependence on c-Myc expression for survival and proliferation. Further, glioma cancer stem cells with decreased c-Myc levels

failed to form neurospheres in vitro or tumors when xenotransplanted into the brains of immunocompromised mice. These findings support a central role of c-Myc in regulating proliferation and survival of glioma cancer stem cells. Targeting core stem cell pathways may offer improved therapeutic approaches for advanced cancers.

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