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Review

C-myc Contributes to Malignancy of Lung Cancer: A Potential Anticancer Drug Target

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Abstract. *Emerging evidence has provided important information on oncoproteins involved in cancer initiation, progression, metastasis, and resistance to current therapies. C-myc, one of the critical oncoproteins, has been shown to be implicated in enhancing the aggressiveness of many cancers, mainly through its ability to increase cancer cell growth and cellular survival mechanisms. Despite the more precise and earlier detection and the availability of better therapies, lung cancer remains the most dreadful cancer as it causes high mortality rate with relatively poor treatment success. In lung cancer, C-myc is frequently dysregulated and associated with unfavorable patient survival. C-myc plays a role in regulation of lung cancer cell behaviors including growth, resistance, death, and dissemination through the activation of cell cycle driving proteins, an increase in the cellular levels of anti-apoptotic proteins, and the modulation of metabolism. Besides, C-myc has been shown to be important for cancer stem cell (CSC) properties. Taken together, targeting as well as inhibiting C-myc could provide promising means for resolving lung cancer. This review emphasizes on the molecular mechanism by which C-myc influences lung cancer growth, metastasis, drug resistance, and CSC maintenance, and suggests the target proteins that may benefit drug discovery and design.*

Although the specific mechanisms are not clear, there is hypothesis that non-lethal genetic alterations as well as multiple gene lesions could render carcinogenesis (1). The affected genes that associate with cancer can be divided in to several groups. Among them, the proto-oncogenes that acquire active function and tumor suppressor genes that lose their function contribute to the initiation of cancer (2). An oncogene is an altered gene that encodes for a protein that accelerates cell division that warrants uncontrolled tumor growth. In addition, apoptosis resistance as well as immune escape are related to the functions of an oncogene (2-4). Recently, a new concept has been proposed that cancer stem cells (CSCs) playing a key role in carcinogenesis, cancer progression, and poor prognosis require continuously active oncogenes (5). C-myc, which belongs to the myc family, has been shown to regulate carcinogenesis and progression in many cancers (6-9). Besides, recent evidence has pointed its significant role on CSC properties and metastasis of certain cancers including lung cancer (10). C-myc is known to enhance cell survival and growth *via* the induction of its down-stream proteins involved in protein translation, cell cycle drive, apoptosis, and metabolism (11, 12). These effectors of C-myc govern a broad range of cancer cell behaviors and activities, such as cell growth, survival, resistance to chemotherapies, immune surveillance, and metastasis.

As lung cancer is among the most aggressive types of human cancer with a relatively high growth rate and metastatic potential, to understand the role and function of key oncogenes frequently activated in this cancer would lead to better treatment approaches.

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Lung Cancer

Lung cancer is a disease in which cells of the lung tissue cannot control their growth, proliferation, and maintenance of their normal function. This causes the development of tumors that compromise a person's ability to breath and reduce quality of life. The uncontrolled cells will invade neighboring tissues, disseminate, and form new metastasized

tumors throughout the body. Cancer statistics in 2019, showed that lung cancer incidence is slightly decreasing in male but remaining as ever in female due to the changing of smoking behavior.

Generally, lung cancer is classified into 2 types by histology, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). SCLCs are quite rare compared to NSCLCs and account for approximately 15% of all lung cancers, whereas NSCLCs account for about 85% of all lung cancers. SCLCs tend to grow faster than NSCLCs and often metastasize to other organs or lymph nodes, thus they are more responsive to chemotherapy (13). NSCLCs are still being divided into 3 sub-categories, adenocarcinoma, squamous cell carcinoma (SqCC), and large cell carcinoma. The most common type of NSCLC is adenocarcinoma which presents in the outer parts of lung. It has been shown that this subtype occurs with higher frequency in females than in males and develops more frequently in younger age than other subtypes. However, adenocarcinoma can be detected earlier before it starts to metastasize. Squamous-cell carcinoma (epidermoid) accounts for approximately 25-30% of all lung cancers. It initiates from squamous cells in the central parts of the lungs, near bronchi. This subtype is firmly related to cigarette smoking. Large cell (undifferentiated) carcinoma comprises about 10-15% of all lung cancer cases. It can present in any part of the lung but often starts in the central of the lung. It has a tendency to proliferate and metastasize quicker than other subtypes (13).

Although the trends in incidence rate of lung cancer have been declining, it remains the highest leading cause of cancer-related death worldwide (14). Overall the 5-year survival of lung cancer is approximately 19%. Interestingly, the 5-year survival of lung cancer localizing inside the lung is as high as 54%, however, after metastasis the survival rate is only less than 4% (14). Unfortunately, more than half of lung cancer cases were found with metastasis at the time of first diagnosis (14). This information led to the development of strategies of metastasis inhibition as well as investigations on mechanisms of cancer cell dissemination. The new insights regarding cancer cell biology have indicated that there is a small cancer cell population inside the tumor that possesses the properties of stem cells (5, 15, 16). Such cancer cells have been termed cancer stem cells or cancer initiating cells as they were believed to be the original seed of cancer (15). Besides, it has been shown that CSCs are the major cells that disseminate and form distant metastases (16).

C-myc Proto-oncogene

The activation of oncoproteins together with the inactivation of tumor suppressor proteins are the generally accepted concept of initiation of human cancers. The myc proto-oncogenes are gene encoding transcription factors, which are commonly overexpressed in cancer patients and have been intensively investigated as they may be potential targets of cancer treatment (17, 18). Myc associates with the tumorigenesis and tumor maintenance in many human cancers (7, 12, 19). Basically, the myc family proteins comprise L-myc, N-myc and C-myc (6). The structure and their important domains are presented in Figure 1. C-myc is expressed in many kinds of adult tissues while N-myc is found mostly in early developmental stages of neuronal tissues. L-myc is prominently expressed in embryonic brain, kidney and lung tissue (6) but the function of L-myc is not well studied. C-myc exhibits many important functions regarding the regulation of signaling in normal and cancerous cells. C-myc is involved in cell growth, division, differentiation, genome stability, cell survival and death, and angiogenesis (10, 20-23). C-myc functions as a down-stream signal of several growth receptors such as epidermal growth factor receptor (EGFR), transforming growth factor alpha (TGF-α), transforming growth factor beta (TGF-β) receptor, interleukin-6 (IL-6) receptor, Notch receptor, and Frizzled receptor (24). Therefore, C-myc usually responds to growth factors-receptor interaction and contributes to cellular response through its transcriptional activity (25) (Figure 2).

Regarding the mechanism of action, C-myc forms a dimer with Myc - associated factor X (MAX) before binding to E-boxes (CACGTG) in DNA within enhancers and promoters of genes (Figure 2). Its target genes encode for proteins that participate in the regulation of cell growth and proliferation including CDK4, CDC25A, p15, p21, PTMA and E2F1 (12). They are also linked to DNA damage and apoptosis responses as C-myc has been shown to regulate the expression of Bax, Bcl-2 and Mcl-1 (26). In normal cells, overexpression of myc proteins will lead to apoptosis, proliferation arrest, or senescence (11). In addition, the myc protein has been shown to act as a central contributor to the survival and division of cancer cells (8). This myc is recognized as an important therapeutic target as it has been shown to be dysregulated in about 50% of human cancers (27). It is likely that the alteration or dysregulation of myc oncogene contributes to cancer progression and aggressiveness (6-9) and myc has been linked with poor prognosis in several cancers (28). Evidence indicates that myc functions in several steps of carcinogenesis and disease progression including enhancement of cell proliferation, inhibition of apoptosis, and deregulation of differentiation (6-9). It has been widely suggested that C-myc inhibition could be a promising approach for cancer treatment (10, 18, 28, 29). This is supported by many studies indicating that the inactivation or inhibition of C-myc can induce tumor regression by restoration of the normal cell checkpoint mechanisms or induction of proliferation arrest, cellular senescence, and apoptotic mechanisms (8, 30).

C-myc protein levels are increased in about 70% in cancer patients but only 15-20% of the patients have a gene

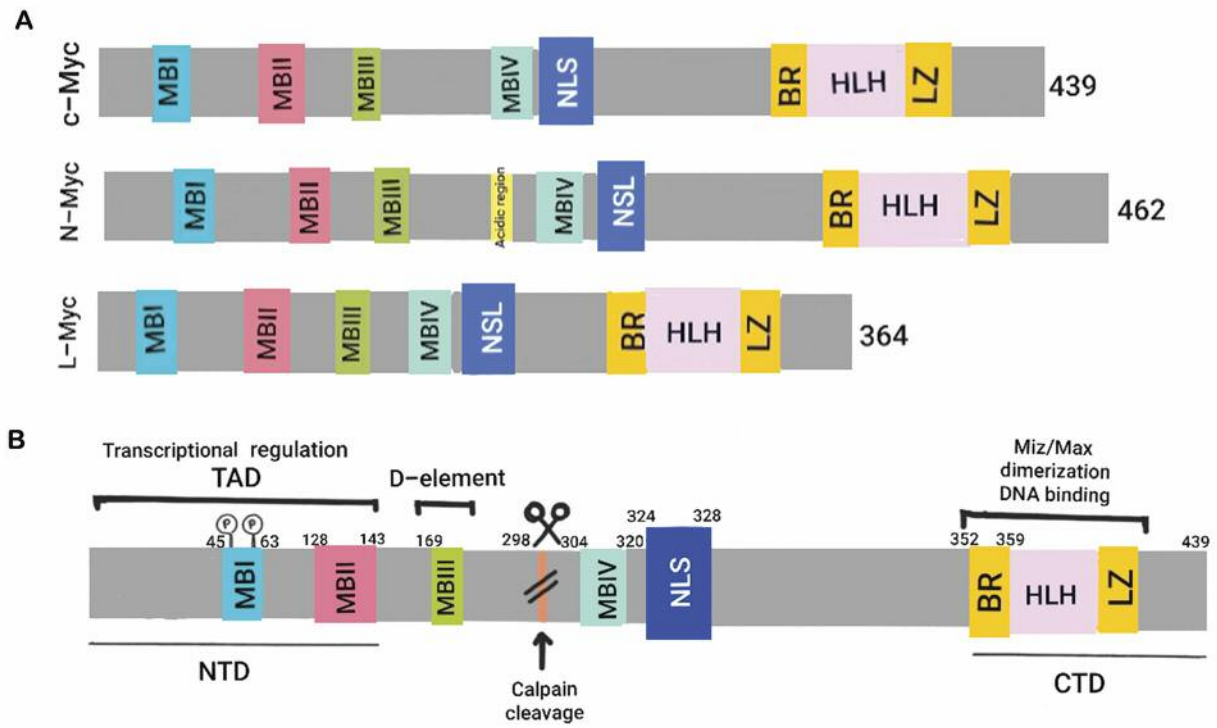

Figure 1. *Schematic display of the myc family members (A) and detail of C-myc protein (B). MBI: Myc-box I, MBII: Myc-box II, MBIII: Myc-box III, MBIV: Myc-box IV, NLS: nuclear localization signal, BR: basic region, HLH: helix-loop-helix, LZ: leucine zipper domain, TAD: transactivation domain, NTD: N-terminal domain CTD: C-terminal domain.*

amplification. Recently, a meta-analysis has shown that the rate of C-myc amplification in cancers varies from 1-50% with an average of about 15.7% (31). It has been accepted that overexpression of C-myc could be the result of the amplification of the gene, however, the frequency of overexpression of the C-myc protein in cancer tissues is much higher (approximately 2 folds) than C-myc amplification (32).

In malignant cancers, an increase in C-myc expression has been linked to malignant phenotypes. Recent studies have indicated that amplification of the C-myc gene is observed in many cancer cell lines including human colon cancer cells and SCLC cells. C-myc oncoprotein has been shown to be overexpressed in about 50-100% of breast cancers (32, 33), in about 50-75% of NSCLC cases (34-36, 37) and also to be critical for the pathogenesis of NSCLC (10). In NSCLC, overexpression of Myc has been shown to be associated with mutated *PHACTR3* and *E2F4* genes (38).

C-myc and Drug Resistance

Drug resistance is the main problem in cancer therapy and has been found to mostly correlate with amplification and overexpression of the c-Myc oncogene (39-41). A study has shown that C-myc is an effective therapeutic target for overcoming drug resistance in acute myeloid leukemia (AML) (42). C-myc expression levels have not only been associated with aggressive phenotypes in many cancers (43), but also with chemotherapy resistance in several cancers, such as melanoma, ovarian cancer, hepatocellular carcinoma, and lung cancer (10, 44, 45). The mechanism through which C-myc contributes to drug resistance may involve increased expression of genes that promote cell survival, genomic instability, and blockage of apoptosis (10, 46).

Drug resistance has been recognized as a long important concern regarding lung cancer therapy. The rate of chemotherapeutic resistance in lung cancer is relatively high (47). Although the targeted therapy, including epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), has been shown to improve the clinical outcome and recommended as a first choice for lung cancer with EGFR mutations (48, 49), the platinum-based drugs as well as other chemotherapeutic agents remain the standard of care for other patients with advanced disease (50). One important platinum-based compound is cisplatin [cis-DDP, cis-diamminedichloroplatinum (II)], which is widely prescribed for the treatment of many human cancers with a high curative effect on lung cancer (51). However, in the process of NSCLC treatment with chemotherapy, cancer frequently

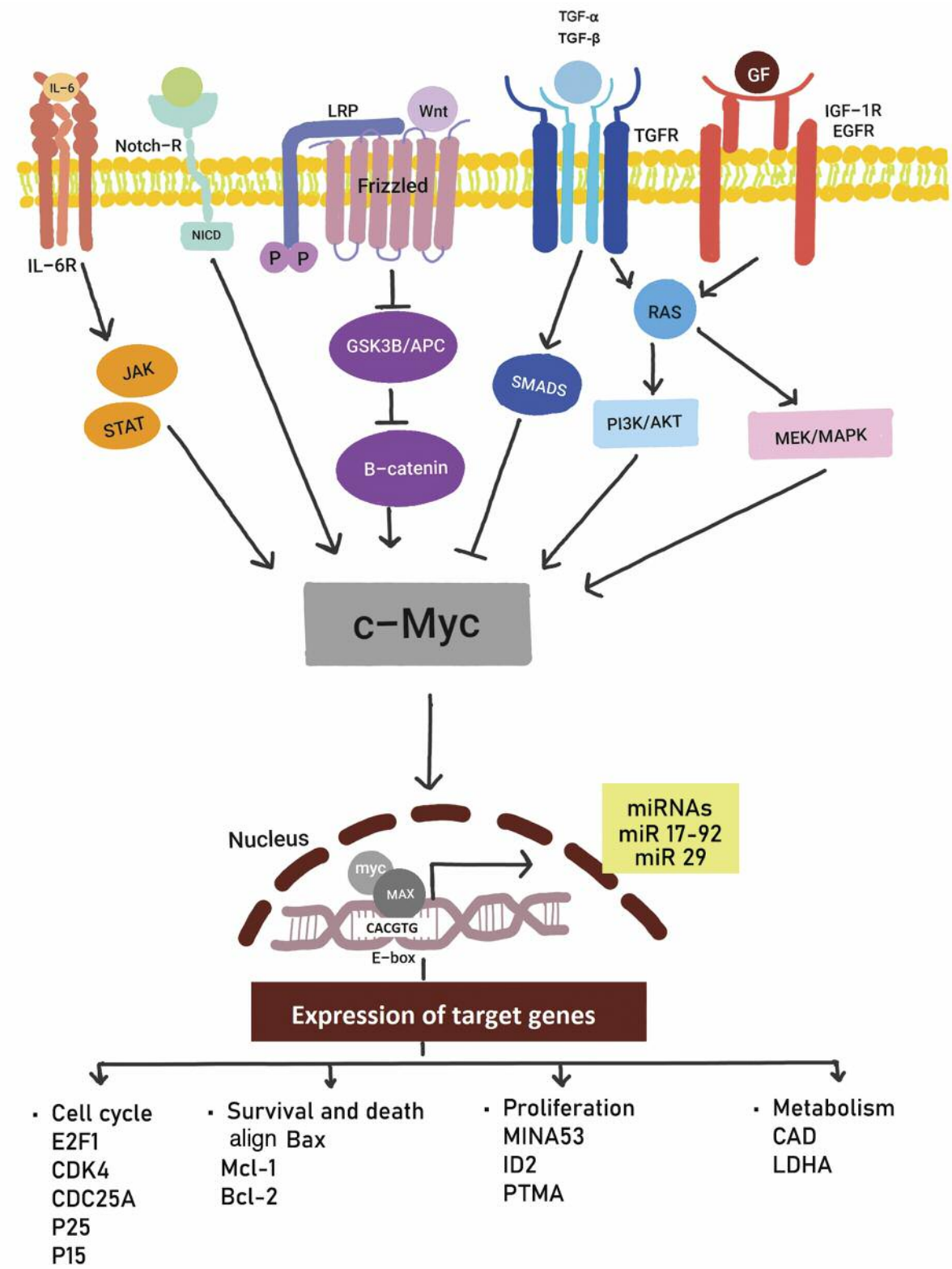

Figure 2. *C-myc can be regulated by several mechanisms, such as JAK/STAT, Wnt/β catenin signaling, Notch signaling and Ras/PI3K/AKT/GSK-3 pathways which increase C-myc levels. Myc will form a dimer with the Myc-associated factor X (MAX) before binding to E-box (CACGTG) within enhancers and promoters of genes. As an important transcription factor, c-myc controls the expression of many genes that affect numerous cellular activities such as cell cycle progression, proliferation, metabolism, survival and death.*

develops primary or acquired resistance to the therapy (52). Therefore, better understanding of the molecular basis of drug resistance in this cancer is important for improving DDP-based chemotherapy and overcoming cancer resistance.

Interestingly, a study has shown that C-myc may associate with cisplatin resistance in lung cancer as niclosamide could enhance cisplatin-mediated apoptosis in cisplatin-resistant cells by attenuating C-myc (53). Cisplatin induces apoptosis of cancer cells *via* a mechanism involving formation of DNA adducts and DNA damage (54, 55). DNA damage mediates p53-dependent increase and decrease in pro-apoptotic and anti-apoptotic members of the Bcl-2 family of proteins, respectively. However, over activated C-myc acts as an inducer of anti-apoptotic proteins including Mcl-1 and Bcl-2 that can sufficiently block cisplatin-mediated death (56). Besides, an interesting study has suggested that the C-myc-mediated drug resistance can be acquired after the cancer cells receive cisplatin (57). It has been shown, in head and neck squamous cell carcinoma, that prior cisplatin treatment could induce resistance to palbociclib *via* a mechanism involving C-myc up-regulation. The results and the underlying mechanism were confirmed by evidence indicating that co-treatment with palbociclib and the C-myc inhibitor JQ1 resulted in a synergistic anti-growth effect (58). Also, studies have shown that c-Myc is an effective therapeutic target for overcoming drug resistance in acute myeloid leukemia (AML) (42).

C-myc Regulates Epithelial-mesenchymal Transition (EMT) and Cancer Stem Cells

Epithelial-mesenchymal transition (EMT) has been reported to be an important process that closely relates with tumor metastasis and chemoresistance. EMT involves a cellular change from epithelial phenotypes toward more motile phenotypes with higher ability to migrate and invade the surrounding tissues (59, 60). Cancer cells change not only their morphology to spindle shape, but they also modify the molecular signaling as demonstrated by alterations in several protein markers such as decrease of E-cadherin and occludin, and induction of N-cadherin, Snail, Slug, Zeb, Twist, and vimentin (61). The EMT process can be driven by many cellular signals including epidermal growth factor receptor, transforming growth factor (TGF), fibroblast growth factor, and hepatocyte growth factor (HGF), Notch, and Wnt/β-catenin pathways (62). It is well accepted that EMT is critical for promoting primary tumor cells to disseminate (63). Besides, it has been suggested that EMT involves the generation of stem-like cancer cells with augmented ability of self-renewal and tumorigenicity (59). Regarding C-myc and EMT regulation, Wolfer and Ramaswamy have reported that the expression of C-myc directly regulates cell migration, invasion, and EMT (64). The amplification of C-myc gene occurs in up to 20%-30% of human cancers, especially in breast cancers (65). In addition, it has been demonstrated, in human breast cancer cells, that overexpression of C-myc could induce EMT (66). The mechanism by which C-myc mediates EMT involves the extracellular signal-regulated kinase (ERK)-dependent GSK-3beta inactivation and snail activation (66).

The new concept of cancer initiation states that cancer is generated from mutated and dysregulated normal stem or progenitor cells (67). Within the tumor, there is a distinguished hierarchy of heterogenous cell populations where cancer stem cells (CSC) are on the apex (68). CSC maintain the unique properties of self-renewal and differentiation of their parental normal stem cells (69). CSCs have been discovered in many cancers including lung cancer and were linked to carcinogenesis, tumor growth and maintenance, chemotherapeutic failure, metastasis, and cancer relapse (10, 70, 71). The role of CSCs in lung cancer has been widely described. Importantly, it has suggested that lung cancer relapse and dissemination is caused by the activity of CSCs and their niches that are not sufficiently affected during therapies (63, 72). Indeed, a number of studies have reported that CSCs are a strong chemoresistant population (72, 73). It has been suggested that targeting these CSCs could be an effective strategy to treat lung cancer with reduced disease relapse (74). In particular, Notch, Wnt/β-catenin, and Hedgehog signals have been widely shown to be critical for CSC properties and maintenance (75). As C-myc is involved in the cellular response to Notch and Wnt/β-catenin activation, C-myc was prohibit the maintenance and function of CSCs. Activation of β-catenin signaling by the interaction of Wnt to Frizzled receptor resulted in increased levels of cellular β-catenin. β-catenin then translocate to the nucleus, where it functions as a transcription factor for C-myc (10, 76). Thus, there is a direct association between C-myc and β-catenin. The role of Wnt/β-catenin signaling on CSC has been widely described (77). Besides, Wnt/β-catenin has been shown to cross talk with several CSC-related pathways including Hedgehog, Notch, and TGFβ/BMP. Wnt/β-catenin has been shown to be critical for CSC survival in many cancers such as lung, breast, ovary, gastric, pancreatic, and colorectal cancers (77, 78). Likewise, C-myc has been shown to be important for the maintenance of CSC properties and chemoresistance of colon cancer stem cells (79). Besides, current studies have pointed out that the contribution of this protein to drug resistance may involve its regulatory role on cancer stem cells (CSCs) (10).

Cell Regulation and Possible Strategies for Targeting C-myc

C-myc is a 62 kDa protein functioning as a powerful transcription factor regulating several key cellular behaviors including growth, differentiation, and apoptosis. As a transcription factor, C-myc exerts it regulatory roles *via* the promotion of the expression of a significant number of genes (33).

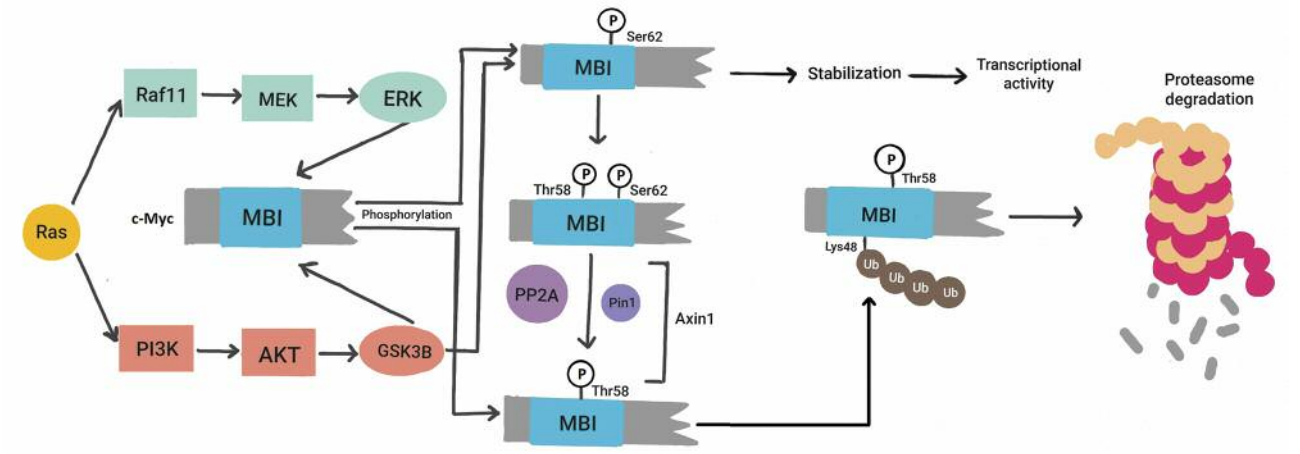

Figure 3. *Kinase cascades in the regulation of C-myc stability and ubiquitin-proteasomal degradation. Myc is stabilized upon phosphorylation at serine 62 (S62) and Threonine 58 (T58) on MBI by ERK and GSK-3β, respectively. Phosphorylation at S62 (p-S62) promotes the stability of c-Myc while p-T58 is recognized as a target for E3 ligase for degradation. In addition, the S62 phosphorylation can be dephosphorylated by PP2A.*

In order to function as transcription factor, the C-myc protein consists of several regions including a non-specific DNA binding region, a nuclear target sequence, a transcriptional activation region, a basic region, a helix-loop-helix (HLH) and a leucine zipper region. C-myc dimerizes with max resulting in the myc/max heterodimer complex that binds to the target DNA sequence or E-BOX (sequence 5'-CANNTG-3') to regulate transcriptional activation of genes involved in cell proliferation, cell cycle regulation, and apoptosis (80, 81). The Myc-Max complex also mediates gene suppression by regulating the transcription of target genes through the binding with Miz-1 (Myc-interacting zinc-finger protein1). In free form, Miz-1 interacts with initiator elements (INR) in the promoters of genes and activates their transcription. Interaction with Myc converts the Miz-1 from activator to repressor that may involve in the decrease of tumor suppressor genes. C-myc also regulates miRNA networks by stimulating miR-17-92 to occlude and suppress dozens of miRs, including Let-7, which affects insulin signaling, miR-23a/b, and glutaminase expression and miR-34a, which regulates lactate dehydrogenase (LDHA) expression (82, 83). The miR-17 cluster contains miRNAs that target PTEN, thereby activating AKT, as well as those that target pro-apoptotic BimL or transcription factor E2F1. miRNAs downstream of C-myc have also been associated with EMT and angiogenesis.

The promoter of the *MYC* gene could be activated by a number of pathways such as Wnt/β-catenin, Jak/STAt, RAS/RAF/MAPK, transforming growth factor-β (TGF-β), and NF-κB (84, 85). Such cellular pathways have been shown to be dysregulated in cancers, which consequently, are characterized by myc over-expression (18, 24, 27, 29). C-myc requires post-translational modifications for controlling its stability and degradation. As C-myc mRNA and protein are relatively short lived (approximately 30 min), the protein function depends on its cellular levels (80). One important regulatory modification of C-myc is phosphorylation. The protein could be phosphorylated at multiple sites. C-myc phosphorylation by protein kinase CK-2 at the C-terminal PEST domain (amino acids 240-262 and amino acids 342-439) could enhance the stability of myc (86). Also, it has been suggested that the stabilization of C-myc in many cancers is associated with increased cell proliferation (87, 88). It is noteworthy that CK-2-mediated phosphorylation of the myc dimerization partner max affects DNA binding of myc-max heterodimer (89, 90). Thus, the kinase activity of CK-2 has been suggested to regulate myc levels as well as its transcription factor function. Likewise, phosphorylation of myc at Thr-58 and Ser-62 is critical for myc degradation (91). Phosphorylation at Ser-62 is a prerequisite for Thr-58 phosphorylation. Ser-62 could be phosphorylated by several kinases including mitogen-activated protein kinase (MAPK), cyclin-dependent kinase 1 (CDK1), and c-JUN N-terminal kinase (JNK) (92-97). Interestingly, Ras signaling that is frequently found to be overactivated in lung cancer has been suggested to enhance myc phosphorylation at Ser-62 (95, 96) (Figure 3). Ras also induces the activation of PI3K/Akt that phosphorylates GSK3 and subsequently results in C-myc stabilization (81, 98). After phosphorylation at Ser-62, GSK3 could phosphorylate Thr-58 of the protein (24). These two sites of phosphorylation of C-myc target the protein for degradation by the ubiquitin-proteasomal degradation (Figure 3). The ubiquitin-proteasomal degradation of C-myc protein has been shown to be a critical process that affects C-myc

function. As C-myc is expressed at low levels, the degradation process of the protein is the factor that regulates its function (81, 98).

A study has demonstrated that suppression of C-myc promotes Fas-mediated apoptosis (99). Another study has shown that degradation of C-myc can affect topoisomerase's function in DNA repair, leading to various types of cancer cells to apoptosis (100). Moreover, decrease in C-myc activity was demonstrated to sensitize cancer cells response to vinca alkaloids treatment (101). In addition, C-myc transcription activities have been shown to strengthen cancer aggressiveness by amplifying survival signaling, inducing EMT, increasing metastasis potentials, as well as enhancing CSC signals. Together with the fact that C-myc is a key regulator of survival and growth of cancer, these results have suggested the C-myc protein as a potential molecular target for cancer treatments. There are several strategies for targeting myc in cancer treatment such as inhibition of the expression of myc protein by disrupting up-stream signals including Wnt/β-catenin, Jak/STAt, RAS/RAF/MAPK, TGF-β, and NF-κB, as well as inhibition of the dimerization between myc and max, and by inducing myc degradation by the ubiquitin-proteasome system (18). The down-regulation of C-myc in cancer cells could promisingly decrease the ability of cells to grow and metastasize, therefore, improving survival and clinical outcome of current therapeutics.

Conflicts of Interest

The Authors declare that they have no conflict of interest regarding this study.

Authors' Contributions

P.C. conceived of the review, wrote the manuscript, and analyzed results of literature research. N.S., and N.N. conducted the review of the literature. All authors discussed the contents and contributed to the final manuscript.

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References

1 Basu AK: DNA damage, mutagenesis and cancer. Int J Mol Sci 19, 2018. PMID: 29570697. DOI: 10.3390/ijms19040970

2 Giancotti FG: Deregulation of cell signaling in cancer. FEBS Lett *588*: 2558-2570, 2014. PMID: 24561200. DOI: 10.1016/j.febslet.2014.02.005

3 Okushi, Mohammad RM, Muqbil I, Lowe L, Yedjou C, Hsu HY, Lin LT, Siegelin MD, Fimognari C, Kumar NB and Dou QP: Broad targeting of resistance to apoptosis in cancer. Semin Cancer Biol *35*: S78-S103, 2015. PMID: 25936818. DOI: 10.1016/j.semcancer.2015.03.001

4 Zahavi DJ and Weiner LM: Tumor mechanisms of resistanceto immune attack. Prog Mol Biol Transl Sci *164*: 61-99, 2019. DOI: 10.1016/bs.pmbts.2019.03.009

5 Efremov YR, Proskurina AS, Potter EA, Dolgova EV, Efremova OV, Taranov OS, Ostanin AA, Chernykh ER, Kolchanov NA and Bogachev SS: Cancer stem cells: emergent nature of tumor emergency. Front Genet *9*, 2018. PMID: 30505319. DOI: 10.3389/fgene.2018.00544

6 Brägelmann J, Böhm S, Guthrie MR, Mollaoglu G, Oliver TG and Sos ML: Family matters: How MYC family oncogenes impact small cell lung cancer. Cell Cycle *16*: 1489-1498, 2017. PMID: 28737478. DOI: 10.1080/15384101.2017.1339849

7 Hoffman B and Liebermann DA: The proto-oncogene c-myc and apoptosis. Oncogene *17*: 3351-3357, 1998. PMID: 9916997. DOI: 10.1038/sj.onc.1202592

8 Gabay, Meital, Yulin Li and DF: MYCActivation is a hallmark of cancer initiation and maintenance meital. *36*: 186-194, 2009. PMID: 24890832. DOI: 10.1101/cshperspect. a014241

9 Kalkat M, De Melo J, Hickman KA, Lourenco C, Redel C, Resetca D, Tamachi A, Tu WB and Penn LZ: MYC deregulation in primary human cancers. Genes (Basel) *8*: 2-30, 2017. PMID: 28587062. DOI: 10.3390/genes8060151

10 Elbadawy M, Usui T, Yamawaki H and Sasaki K: Emerging roles of C-myc in cancer stem cell-related signaling and resistance to cancer chemotherapy: A potential therapeutic target against colorectal cancer. Int J Mol Sci *20*, 2019. PMID: 31083525. DOI: 10.3390/ijms20092340

11 Pelengaris S, Khan M and Evan G: c-MYC: More than just a matter of life and death. Nat Rev Cancer *2*: 764-776, 2002. PMID: 12360279. DOI: 10.1038/nrc904

12 Daniell H: MYC on the path to cancer. Cell *76*: 211-220, 2012. PMID: 22464321. DOI: 10.1016/j.cell.2012.03.003

13 What Is Lung Cancer? | Types of Lung Cancer. Available from: https://www.cancer.org/content/cancer/en/cancer/lung-cancer/about/what-is.html [Last accessed October 7, 2019].

14 Siegel RL, Miller KD and Jemal A: Cancer statistics, 2019. CA Cancer J Clin *69*: 7-34, 2019. PMID: 30620402. DOI: 10.3322/caac.21551

15 Islam F, Gopalan V and Lam AK-Y: Cancer stem cells: role in tumor progression and treatment resistance. Oncogenomics 77-87, 2019. DOI: 10.1016/B978-0-12-811785-9.00006-5

16 Li L and Neaves WB: Normal stem cells and cancer stem cells: The niche matters. Cancer Res *66*: 4553-4557, 2006. PMID: 16651403. DOI: 10.1158/0008-5472.CAN-05-3986

17 Whitfield JR, Beaulieu ME and Soucek L: Strategies to inhibit Myc and their clinical applicability. Front Cell Dev Biol *5*, 2017. PMID: 28280720. DOI: 10.3389/fcell.2017.00010

18 Vita M and Henriksson M: The Myc oncoprotein as a therapeutic target for human cancer. Semin Cancer Biol *16*: 318-330, 2006. PMID: 16934487. DOI: 10.1016/j.semcancer. 2006.07.015

19 Cotter TG: Apoptosis and cancer a genesis of a research field. Nat Rev Cancer *9*: 501-507, 2009. PMID: 19550425. DOI: 10.1038/nrc2663

20 Iritani BM and Eisenman RN: c-Myc enhances protein synthesis and cell size during B lymphocyte development. Proc Natl Acad Sci USA *96*: 13180-13185, 1999. PMID: 10557294. DOI: 10.1073/pnas.96.23.13180

21 Yin XY, Grove L, Datta NS, Long MW and Prochownik EV: C-myc overexpression and p53 loss cooperate to promote genomic instability. Oncogene *18*: 1177-1184, 1999. DOI: 10.1038/sj.onc.1202410

22 Baudino TA, McKay C, Pendeville-Samain H, Nilsson JA, Maclean KH, White EL, Davis AC, Ihle JN and Cleveland JL: c-Myc is essential for vasculogenesis and angiogenesis during development and tumor progression. Genes Dev *16*: 2530-2543, 2002. PMID: 12368264. DOI: 10.1101/gad.1024602

23 Karlsson A, Deb-Basu D, Cherry A, Turner S, Ford J and Felsher DW: Defective double-strand DNA break repair and chromosomal translocations by MYC overexpression. Proc Natl Acad Sci USA *100*: 9974-9979, 2003. PMID: 12909717. DOI: 10.1073/pnas.1732638100

24 Huang H, Weng H, Zhou H and Qu L: Attacking c-Myc: Targeted and combined therapies for cancer. Curr Pharm Des *20*: 6543-6554, 2014. PMID: 25341931. DOI: 10.2174/1381612820666140826153203

25 Stine ZE, Walton ZE, Altman BJ, Hsieh AL and Dang CV: MYC, metabolism, and cancer. Cancer Discov *5*: 1024-1039, 2015. PMID: 26382145. DOI: 10.1158/2159-8290.CD-15-0507

26 Eischen CM, Woo D, Roussel MF and Cleveland JL: Apoptosis triggered by Myc-Induced suppression of Bcl-XL or Bcl-2 is bypassed during lymphomagenesis. Mol Cell Biol *21*: 5063-5070, 2001. PMID: 11438662. DOI: 10.1128/MCB.21.15.5063-5070.2001

27 Chen H, Liu H and Qing G: Targeting oncogenic Myc as a strategy for cancer treatment. Signal Transduct Target Ther *3*, 2018. DOI: 10.1038/s41392-018-0008-7

28 Gustafson WC and Weiss WA: Myc proteins as therapeutic targets. Oncogene *29*: 1249-1259, 2010. PMID: 20101214. DOI: 10.1038/onc.2009.512

29 Carabet LA, Rennie PS and Cherkasov A: Therapeutic inhibition of myc in cancer. Structural bases and computer-aided drug discovery approaches. Int J Mol Sci *20*, 2019. PMID: 30597997. DOI: 10.3390/ijms20010120

30 Felsher DW and Bishop JM: Reversible tumorigenesis by MYC in hematopoietic lineages. Mol Cell *4*: 199-207, 1999. PMID: 10488335. DOI: 10.1016/s1097-2765(00)80367-6

31 Deming SL, Nass SJ, Dickson RB and Trock BJ: C-myc amplification in breast cancer: a meta-analysis of its occurrence and prognostic relevance. Br J Cancer *83*: 1688-1695, 2000. DOI: 10.1054/bjoc.2000.1522

32 Rakesh N: Immunohistochemistry of c-myc expression in breast carcinoma. *In*: Handbook of Immunohistochemistry and *in situ* Hybridization of Human Carcinomas Volume 1 (1st ed). Massachusetts, Academic Press, pp. 395-470, 2004.

33 Locker AP, Dowle CS, Ellis IO, Elston CW, Blarney RW, Sikora K, Evan G and Robins RA: C-myc oncogene product expression and prognosis in operable breast cancer. Br J Cancer *60*: 669-672, 1989. DOI: 10.1016/S1874-5784(04)80050-3

34 Dong QZ, Wang Y, Dong XJ, Li ZX, Tang ZP, Cui QZ and Wang EH: CIP2A is overexpressed in non-small cell lung cancer and correlates with poor prognosis. Ann Surg Oncol *18*: 857-865, 2011. PMID: 20842459. DOI: 10.1245/s10434-010-1313-8

35 Jiang R, Wang X, Jin Z and Li K: Association of nuclear PIM1 expression with lymph node metastasis and poor prognosis in patients with lung adenocarcinoma and squamous cell carcinoma. J Cancer *7*: 324-334, 2016. PMID: 26918046. DOI: 10.7150/jca.13422

36 Xu X, Sun PL, Li JZ, Jheon S, Lee CT and Chung JH: Aberrant Wntl beta-catenin expression is an independent poor prognostic marker of non-small cell lung cancer after surgery. J Thorac Oncol *6*: 716-724, 2011. PMID: 21336184. DOI: 10.1097/JTO.0b013e 31820c5189

37 Kiani A, Abedini A, Adcock IM, Mirenayat MS, Taghavi K, Mortaz E and Kazempour-Dizaji M: Association between vitamin D deficiencies in sarcoidosis with disease activity, course of disease and stages of lung involvements. J Med Biochem *37*: 103-109, 2018. PMID: 30581345. DOI: 10.1515/jomb-2017-0041

38 Dragoj M, Bankovic J, Podolski-Renic A, Buric SS, Pesic M, Tanic N and Stankovic T: Association of overexpressed MYC gene with altered PHACTR3 and E2F4 genes contributes to non-small cell lung carcinoma pathogenesis. J Med Biochem *38*: 188-195, 2019. PMID: 30867647. DOI: 10.2478/jomb-2018-0022

39 Van Waardenburg RC, Prins J, Meijer C, Uges DR, De Vries EG and Mulder NH: Effects of c-myc oncogene modulation on drug resistance in human small cell lung carcinoma cell lines. Anticancer Res *16*: 1963-1970, 1996. PMID: 8712728.

40 Nesbit CE, Tersak JM, and Prochownik EV: Myc oncogenes and human neoplastic disease. Oncogene *18*: 3004-3016, 1999. PMID: 10378696. DOI: 10.1038/sj.onc.1202746

41 Knapp DC, Mata JE, Reddy MT, Devi GR, and Iversen PL: Resistance to chemotherapeutic drugs overcome by c-Myc inhibition in a Lewis lung carcinoma murine model. Anticancer Drugs *14*: 39-47, 2003. PMID: 12544257. DOI: 10.1097/00001813-200301000-00006

42 Xia B, Tian C, Guo S, Zhang L, Zhao D, Qu F, Zhao W, Wang Y, Wu X, Da W, Wei S and Zhang Y: c-Myc plays part in drug resistance mediated by bone marrow stromal cells in acute myeloid leukemia. Leuk Res *39*: 92-99, 2015. PMID: 25443862. DOI: 10.1016/j.leukres.2014.11.004

43 Xu J, Chen Y, and Olopade OI: MYC and breast cancer. Genes Cancer *1*: 629-640, 2010. PMID: 21779462. DOI: 10.1177/1947601910378691

44 Mizutani Y, Fukumoto M, Bonavida B and Yoshida O: Enhancement of sensitivity of urinary bladder tumor cells to cisplatin by c-myc antisense oligonucleotide. Cancer *74*: 2546-2554, 1994. PMID: 7923012. DOI: 10.1002/1097-0142(19941101)74:9<2546::aid-cncr2820740924>3.0.co;2-y

45 Torigoe T, Izumi H, Ishiguchi H, Yoshida Y, Tanabe M, Yoshida T, Igarashi T, Niina I, Wakasugi T, Imaizumi T, Momii Y, Kuwano M and Kohno K: Cisplatin resistance and transcription factors. Curr Med Chem Anticancer Agents *5*: 15-27, 2005. PMID: 15720258. DOI: 10.2174/1568011053352587

46 Kumari A, Folk WP, and Sakamuro D: The dual roles of MYC in genomic instability and cancer chemoresistance. Genes (Basel) *8*: 158, 2017. PMID: 28590415. DOI: 10.3390/genes8060158

47 Wangari-Talbot J and Hopper-Borge E: Drug resistance mechanisms in non-small cell lung carcinoma. J Can Res Updates *2*: 265-282, 2013. PMID: 24634705. DOI: 10.6000/1929-2279.2013.02.04.5

48 Haber DA, Bell DW, Sordella R, Kwak EL, Godin-Heymann N, Sharma SV, Lynch TJ and Settleman J: Molecular targeted therapy of lung cancer: EGFR mutations and response to EGFR inhibitors. Cold Spring Harb Symp Quant Biol *70*: 419-426, 2005. PMID: 16869779. DOI: 10.1101/sqb.2005.70.043

49 Sgambato A, Casaluce F, Maione P, Rossi A, Rossi E, Napolitano A, Palazzolo G, Bareschino MA, Schettino C, Sacco

PC, Ciadiello F and Gridelli C: The role of EGFR tyrosine kinase inhibitors in the first-line treatment of advanced non small cell lung cancer patients harboring EGFR mutation. Curr Med Chem *19*: 3337-3352, 2012. PMID: 22664249. DOI: 10.2174/092986712801215973

50 Baxevanos P and Mountzios G: Novel chemotherapy regimens for advanced lung cancer: have we reached a plateau? Ann Transl Med *6*: 139, 2018. PMID: 29862228. DOI: 10.21037/atm.2018.04.04

51 Dasari S and Tchounwou PB: Cisplatin in cancer therapy: molecular mechanisms of action. Eur J Pharmacol *740*: 364-378, 2014. PMID: 25058905. DOI: 10.1016/j.ejphar.2014.07.025

52 Tsvetkova E and Goss GD: Drug resistance and its significance for treatment decisions in non-small-cell lung cancer. Curr Oncol *19*(Suppl 1): S45-51, 2012. PMID: 22787410. DOI: 10.3747/co.19.1113

53 Zuo Y, Yang D, Yu Y, Xiang M, Li H, Yang J, Li J, Jiang D, Zhou H, Xu Z and Yu Z: Niclosamide enhances the cytotoxic effect of cisplatin in cisplatin-resistant human lung cancer cells *via* suppression of lung resistance-related protein and c-myc. Mol Med Rep *17*: 3497-3502, 2018. PMID: 29257330. DOI: 10.3892/mmr.2017.8301

54 Prestayko AW, D'Aoust JC, Issell BF and Crooke ST: Cisplatin (*cis*-diamminedichloroplatinum II). Cancer Treat Rev *6*: 17-39, 1979. PMID: 378370. DOI: 10.1016/s0305-7372(79)80057-2

55 Schwarzenbach H and Gahan PB: Resistance to cis- and carboplatin initiated by epigenetic changes in ovarian cancer patients. Cancer Drug Resist *2*: 271-296, 2019. DOI: 10.20517/cdr.2019.010

56 Adams J and Cory S: The Bcl-2 apoptotic switch in cancer development and therapy. Oncogene *26*: 1324-1337, 2007. PMID: 17322918. DOI: 10.1038/sj.onc.1210220

57 Parker A, Vaux L, Patterson AM, Modasia A, Muraro D, Fletcher AG, Byrne HM, Maini PK, Watson AJM and Pin C: Elevated apoptosis impairs epithelial cell turnover and shortens villi in TNF-driven intestinal inflammation. Cell Death Dis *10*: 108, 2019. PMID: 30728350. DOI: 10.1038/s41419-018-1275-5

58 Robinson AM, Rathore R, Redlich NJ, Adkins DR, VanArsdale T, Van Tine BA and Michel LS: Cisplatin exposure causes c-Myc-dependent resistance to CDK4/6 inhibition in HPV-negative head and neck squamous cell carcinoma. Cell Death Dis *10*: 867, 2019. DOI: 10.1038/s41419-019-2098-8

59 Mittal V: Epithelial mesenchymal transition in tumor metastasis. Annu Rev Pathol *13*: 395-412, 2018. PMID: 29414248. DOI: 10.1146/annurev-pathol-020117-043854

60 Raja R, Pandey A and Kumar P: Epithelial to mesenchymal plasticity: role in cancer progression. Front Biosci (Landmark Ed) *25*: 838-873, 2020. PMID: 31585920.

61 Lamouille S, Xu J and Derynck R: Molecular mechanisms of epithelial–mesenchymal transition. Nat Rev Mol Cell Biol *15*: 178-196, 2014. PMID: 24556840. DOI: 10.1038/nrm3758

62 Lindsey S and Langhans SA: Crosstalk of oncogenic signaling pathways during epithelial mesenchymal transition. Front Oncol *4*: 358, 2014. PMID: 25566498. DOI: 10.3389/fonc.2014.00358

63 Banyard J and Bielenberg DR: The role of EMT and MET in cancer dissemination. Connect Tissue Res *56*: 403-413, 2015. PMID: 26291767. DOI: 10.3109/03008207.2015.1060970

64 Wolfer A and Ramaswamy S: MYC and metastasis. Cancer Res *71*: 2034-2037, 2011. PMID: 21406394. DOI: 10.1158/0008-5472.CAN-10-3776

65 Watson PH, Safneck JR, Le K, Dubik D and Shiu RP: Relationship of c-Myc amplification to progression of breast cancer from *in situ* to invasive tumor and lymph node metastasis. J Natl Cancer Inst *85*: 902-907, 1993. PMID: 8492318. DOI: 10.1093/jnci/85.11.902

66 Cho KB, Cho MK, Lee WY and Kang KW: Overexpression of c-myc induces epithelial mesenchymal transition in mammary epithelial cells. Cancer Lett *293*: 230-239, 2010. PMID: 20144848. DOI: 10.1016/j.canlet.2010.01.013

67 Afify SM and Seno M: Conversion of stem cells to cancer stem cells: undercurrent of cancer initiation. Cancers (Basel) *11*: 345, 2019. PMID: 30862050. DOI: 10.3390/cancers11030345

68 Wang W, Quan Y, Fu Q, Liu Y, Liang Y, Wu J, Yang G, Luo C, Ouyang Q and Wang Y: Dynamics between cancer cell subpopulations reveals a model coordinating with both hierarchical and stochastic concepts. PLoS One *9*: e84654, 2014. PMID: 24416258. DOI: 10.1371/journal.pone.0084654

69 Pal A, Valdez KE, Carletti MZ and Behbod F: Targeting the perpetrator: breast cancer stem cell therapeutics. Curr Drug Targets *11*: 1147-1156, 2010. PMID: 20545606. DOI: 10.2174/138945010792006843

70 Bu Y and Cao D: The origin of cancer stem cells. Front Biosci (Schol Ed) *4*: 819-830, 2012. PMID: 22202093. DOI: 10.2741/s302

71 Shen Y and Cao D: Hepatocellular carcinoma stem cells: Origins and roles in hepatocarcinogenesis and disease progression. Front Biosci *4*: 1157-1169, 2012. PMID: 22201943. DOI: 10.2741/448

72 Phi LTH, Sari IN, Yang YG, Lee SH, Jun N, Kim KS, Lee YK and Kwon HY: Cancer stem cells (CSCs) in drug resistance and their therapeutic implications in cancer treatment. Stem Cells Int *2018*: 5416923, 2018. PMID: 29681949. DOI: 10.1155/2018/5416923

73 Abdullah LN and Chow EK: Mechanisms of chemoresistance in cancer stem cells. Clin Transl Med *2*: 3, 2013. PMID: 23369605. DOI: 10.1186/2001-1326-2-3

74 Zakaria N, Satar NA, Abu Halim NH, Ngalim SH, Yusoff NM, Lin J and Yahaya BH: Targeting lung cancer stem cells: research and clinical Impacts. Front Oncol *7*: 80, 2017. PMID: 28529925. DOI: 10.3389/fonc.2017.00080

75 Khan AQ, Ahmed EI, Elareer NR, Junejo K, Steinhoff M and Uddin S: Role of miRNA-regulated cancer stem cells in the pathogenesis of human malignancies. Cells *8*: 840, 2019. PMID: 31530793. DOI: 10.3390/cells8080840

76 Morin PJ: Beta-catenin signaling and cancer. Bioessays *21*: 1021-1030, 1999. PMID: 10580987. DOI: 10.1002/(SICI)1521-1878(199912)22:1<1021::AID-BIES6>3.0.CO;2-P

77 Katoh M: Canonical and non-canonical WNT signaling in cancer stem cells and their niches: Cellular heterogeneity, omics reprogramming, targeted therapy and tumor plasticity (Review). Int J Oncol *51*: 1357-1369, 2017. PMID: 29048660. DOI: 10.3892/ijo.2017.4129

78 Takebe N, Miele L, Harris PJ, Jeong W, Bando H, Kahn M, Yang SX and Ivy SP: Targeting Notch, Hedgehog, and Wnt pathways in cancer stem cells: clinical update. Nat Rev Clin Oncol *12*: 445-464, 2015. PMID: 25850553. DOI: 10.1038/nrclinonc.2015.61

79 Zhang HL, Wang P, Lu MZ, Zhang SD and Zheng L: c-Myc maintains the self-renewal and chemoresistance properties of colon cancer stem cells. Oncol Lett *17*: 4487-4493, 2019. PMID: 30944638. DOI: 10.3892/ol.2019.10081

80 Conacci-Sorrell M, McFerrin L and Eisenman RN: An overview of MYC and its interactome. Cold Spring Harb Perspect Med *4*, 2014. PMID: 24384812. DOI: 10.1101/cshperspect.a014357

81 Farrell AS and Sears RC: MYC degradation. Cold Spring Harb Perspect Med *4*: 2014. PMID: 24591536. DOI: 10.1101/cshperspect.a014365

82 Mihailovich M, Bremang M, Spadotto V, Musiani D, Vitale E, Varano G, Zambelli F, Mancuso FM, Cairns DA, Pavesi G, Casola S and Bonaldi T: miR-17-92 fine-tunes MYC expression and function to ensure optimal B cell lymphoma growth. Nat Commun *6*, 2015. PMID: 26555894. DOI: 10.1038/ncomms9725

83 Wang X, Zhao X, Gao P and Wu M: c-Myc modulates microRNA processing *via* the transcriptional regulation of Drosha. Sci Rep, 2013. PMID: 23735886. DOI: 10.1038/srep01942

84 Liu J and Levens D: Making Myc. CTMI *302*: 1-32, 2006. DOI: 10.1007/3-540-32952-8_1

85 Clevers H: Wnt breakers in colon cancer. Cancer Cell *5*: 5-6, 2004. PMID: 14749120. DOI: 10.1016/s1535-6108(03)00339-8

86 Channavajhala P and Seldin DC: Functional interaction of protein kinase CK2 and c-Myc in lymphomagenesis. Oncogene *21*: 5280-5288, 2002. PMID: 12149649. DOI: 10.1038/sj.onc.1205640

87 Litchfield DW: Protein kinase CK2: Structure, regulation and role in cellular decisions of life and death. Biochem J *369*: 1-15, 2003. PMID: 12396231. DOI: 10.1042/BJ20021469

88 Ahmed K, Gerber DA and Cochet C: Joining the cell survival squad: an emerging role for protein kinase CK2. Trends Cell Biol *12*: 226-230, 2002. PMID: 12062170. DOI: 10.1016/s0962-8924(02)02279-1

89 Berberich SJ and Cole MD: Casein kinase II inhibits the DNA-binding activity of Max homodimers but not Myc/Max heterodimers. Genes Dev *6*: 166-176, 1992. PMID: 1737614. DOI: 10.1101/gad.6.2.166

90 Krippner-Heidenreich A, Talanian RV, Sekul R, Kraft R, Thole H, Ottleben H and Lüscher B: Targeting of the transcription factor max during apoptosis: Phosphorylation-regulated cleavage by caspase-5 at an unusual glutamic acid residue in position P1. Biochem J *358*: 705-715, 2001. PMID: 11535131. DOI: 10.1042/0264-6021:3580705

91 Sears RC: The life cycle of c-Myc: From synthesis to degradation. Cell Cycle *3*: 1133-1137, 2004. PMID: 15467447. DOI: 10.4161/cc.3.9.1145

92 Benassi B, Fanciulli M, Fiorentino F, Porrello A, Chiorino G, Loda M, Zupi G and Biroccio A: c-Myc phosphorylation is required for cellular response to oxidative stress. Mol Cell *21*: 509-519, 2006. PMID: 16483932. DOI: 10.1016/j.molcel.2006.01.009

93 Lutterbach B and Hann SR: c-Myc transactivation domain-associated Kinases: questionable role for Map kinases in c-Myc phosphorylation. J Cell Biochem *72*: 483-491, 1999. PMID: 10022608. DOI: 10.1002/(sici)1097-4644(19990315)72:4<483::aid-jcb4>3.0.co;2-i

94 Lutterbach B and Hann SR: Hierarchical phosphorylation at N-terminal transformation-sensitive sites in c-Myc protein is regulated by mitogens and in mitosis. Mol Cell Biol *14*: 5510-5522, 1994. PMID: 8035827. DOI: 10.1128/mcb.14.8.5510

95 Sears R, Nuckolls F, Haura E, Taya Y, Tamai K and Nevins JR: Multiple Ras-dependent phosphorylation pathways regulate Myc protein stability. Genes Dev *14*: 2501-2514, 2000. PMID: 11018017. DOI: 10.1101/gad.836800

96 Sears R, Leone G, DeGregori J and Nevins JR: Ras enhances Myc protein stability. Mol Cell *3*: 169-179, 1999. PMID: 10078200. DOI: 10.1016/s1097-2765(00)80308-1

97 Noguchi K, Kitanaka C, Yamana H, Kokubu A, Mochizuki T and Kuchino Y: Regulation of c-Myc through phosphorylation at Ser-62 and Ser-71 by c-Jun N-terminal kinase. JBC *274*: 32580-32587, 1999. PMID: 10551811. DOI: 10.1074/jbc.274.46.32580

98 Amati B and Sanchez-Arévalo Lobo VJ: MYC degradation: Deubiquitinating enzymes enter the dance. Nat Cell Biol *9*: 729-731, 2007. DOI: 10.1038/ncb0707-729

99 Zhang J, Zhou L, Nan Z, Yuan Q, Wen J, Xu M, Li Y, Li B, Wang P, Liu C, Ma Y, Chen S and Xie S: Knockdown of c-Myc activates Fas-mediated apoptosis and sensitizes A549 cells to radiation. Oncol Rep *38*: 2471-2479, 2017. PMID: 28849062. DOI: 10.3892/or.2017.5897

100 Chen J, Li W, Cui K, Ji K, Xu S and Xu Y: Artemisitene suppresses tumorigenesis by inducing DNA damage. Oncogene 37: 5079-5087, 2018. DOI: 10.1038/s41388-018-0331-z

101 Bressin C, Bourgarel-Rey V, Carré M, Pourroy B, Arango D, Braguer D and Barra Y: Decrease in c-Myc activity enhances cancer cell sensitivity to vinblastine. Anticancer Drugs *17*: 181-187, 2006. PMID: 16428936. DOI: 10.1097/00001813-200602000-00009

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