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Targeting c-Myc as a novel approach for hepatocellular carcinoma

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Abstract

Hepatocelluar carcinoma (HCC) is the most lethal cancer in the world. Most HCC over-express c-Myc, which plays a critical role in regulating cellular growth, differentiation and apoptosis in both normal and neoplastic cells. c-Myc is among the most frequently overexpressed genes in human cancers. Overexpression of c-Myc in hepatic cells leads to development of hepatocellular carcinoma. Here, we review the current progress in understanding physiologic function and regulation of c-Myc as well as its role in hepatic carcinogenesis and discuss the association of c-Myc activation in chronic hepatitis B infection and the upregulation of HIF-1/VEGF. We also explore the possibility of treating HCC by inhibiting c-Myc and examine the pros and cons of such an approach. Although this strategy is currently not available in clinics, with recent advances in better drug design, pharmacokinetics and pharmacogenetics, inhibition of c-Myc might become a novel therapy for HCC in the future.

Key words: Hepatocellular carcinoma; c-Myc; Novel therapy

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a major cause of cancer death worldwide[1]. Each year, approximately 350 000 patients are diagnosed with HCC in China, representing half of the new cases in the world. Surgical resection is the only way to cure this disease, yet most patients are not suitable for surgery because of poor hepatic reserve, comorbidity, or the presence of infiltrative and metastatic nature lesions. With less than 20% response rate, chemotherapy is not a good option either. Therefore it is imperative to develop novel therapeutics. Genetic analyses have revealed that c-Myc over-expression, which is commonly caused by genomic amplification is present in up to 70% of viral and alcohol-related HCC[2]. Furthermore, the presence of c-Myc amplification portends a more advanced and aggressive phenotype, indicating that c-Myc plays a

critical role in pathogenesis of HCC[3,4]. In this review, we will focus on current understanding of c-Myc in hepatic carcinogenesis and its potential as a novel therapeutic target.

PHYSIOLOGIC ROLE OF C-MYC AND ITS REGULATION

c-Myc, together with L-Myc, and N-Myc in the family of c-Myc genes, was first discovered as the cellular homolog of the v-Myc oncogene[5]. The identification of c-Myc as a target for activation by chromosomal translocation in Burkitt's lymphoma resulted in the decade-long studies for its role in carcinogenesis[6]. In fact, c-Myc is the most commonly overexpressed gene in human cancers. In mammalian cells, c-Myc expression is highly regulated and closely tied to cell growth, apoptosis and differentiation[7]. The importance of c-Myc in development was exemplified by the embryonic lethality of c-Myc homologous knockouts[8].

c-Myc proteins consists of over 430 amino acids with 150 amino-terminal residues in the transactivation domain and 90 carboxy-terminal amino acid in the DNA binding and dimerization domain for binding to the obligate partner, Max[5]. To transactivate its downstream genes, c-Myc has to form heterodimers with Max to bind a consensus E-box site in the target promoter. In contrast to c-Myc, Max is a ubiquitous protein, thus the transactivating activity of c-Myc/Max heterodimers relies on the sophisticated control of c-Myc expression. Yet c-Myc is not the only protein that can partner with Max. Mad is another protein that forms heterodimers with Max to regulate c-Myc/Max transactivating activity. Upon differentiation, the binding of target DNA motif switches from c-Myc/Max to Mad/Max[9-11]. Mad protein contains a Sin3-containing domain that recruits Sin3, transcription repressor N-Cor, and histone deacetylase to repress target gene expression, thus adding another layer of control for c-Myc/Max mediated transactivation[12].

However, c-Myc also acts as a transcription repressor, especially for genes regarded to be differentiation markers. For example, when it is recruited by Miz-1 to target DNA binding motif as in the scenario found in p21[13]. Recent studies have found that c-Myc interacts with Miz-1 and recruit DNA methyltransferase DNMT3 to p21 promoter to silence p21 transcription, a critical step during tumorigenesis[14]. Along with the recruitment of DNA methyltransferases, c-Myc also acts as transcription repressor by interacting with histone deacetylases[15]. Other proteins related to cellular differentiation such as CCAAT/enhancer binding proteins and AP-2 have also been shown to be modulated by c-Myc-mediated transcription repression[16,17]. Both the transactivating and transcription-repressive properties are essential for c-Myc-mediated transforming activity.

In the past decades, various approaches have been used to identify c-Myc target genes[18-22]. So far, as many as 15%-20% of human genes can be regulated directly or indirectly by c-Myc. These genes are related to cell cycle control, protein synthesis, cytoskeleton and cell motility, cell metabolism, and microRNA- the small regulatory molecules that regulate the stability and translation of target mRNA[23]. How these genes interact with each other to modulate growth, differentiation, apoptosis, and survival is largely unknown, and it will require tremendous efforts to dissect the intricate networks and elucidate their role in tumorigenesis.

In order fine tune the sophisticated cellular network, the activity of c-Myc is tightly regulated at multiple levels. The half-life of c-Myc is as short as 20-30 min, meaning that its level changes dynamically in response to a broad range of cellular activities. But in cancer cells, the delicate balance of c-Myc expression is deranged by diverse mechanisms such as unidentified epigenetic aberration, dysregulated transcription, altered protein functionality, or resistance to modulation and proteasomal degradation. The story of c-Myc-mediated tumorigenesis is further complicated by a recent finding, indicating that it is not just its overexpression that matters, the levels of expression also determine its cellular response[24]. Low levels of deregulated c-Myc induce proliferation and sensitize cells to apoptotic signals; while high levels of c-Myc activate intrinsic ARF/p53 surveillance pathways. It is conceivable that different levels of c-Myc might trigger distinct subsets of target genes to determine the cell fate.

ROLE OF C-MYC DURING HEPATIC CARCINOGENESIS

The association of c-Myc with liver carcinogenesis was first identified by the high expression of c-Myc in chronic liver disease and HCC[25,26] and the frequent c-Myc amplification in liver cancer tissue, which is commonly seen in patients at younger age and with poor prognosis[3,4,25]. Using a chemically-induced liver cancer model, the expression of c-Myc is increased in proportion to hepatic injury but not in normal liver[27]. Studies on the HBV, whose chronic infection is often associated with HCC in Asian countries, also identified that HBx has been implicated in HBV-mediated HCC[28]. HBx transforms hepatocytes through multiple mechanisms. One of the critical genes activated by HBx is c-Myc[29,30]. In turn, activation of c-Myc accelerates HBx-mediated oncogenic potential[31], further underscoring the importance of c-Myc in HCC development. One of the downstream genes activated by c-Myc in HCC is human telomerase reverse transcriptase (hTERT), which has two c-Myc-binding E-boxes in its core promoter and is a direct target of c-Myc[32]. The activation of hTERT by c-Myc in HCC has important clinical significance. Inhibition of hTERT activity by either RNAi, or lipid-conjugated oligonucleotides leads to tumor regression in xenogenic HCC models[33, 34].

Another gene that interacts with c-Myc during hepatocarcinogenesis is HIF-1α, which is upregulated

during hypoxia and induces angiogenesis. HIF-1α cooperates with c-Myc to enhance the expression of vascular-endothelial growth factor-A (VEGFA), a critical gene for angiogenesis[35]. Both HBx and HCV infection have been found to stabilize HIF-1α expression in HCC cells[36,37]. Such stabilization could be critical in promoting hepatic carcinogenesis and be responsible for the drug resistance in HCC[38].

TARGETING C-MYC IN HEPATOCELLULAR CARCINOMA

Given the importance of c-Myc in HCC carcinogenesis, it is not surprising that c-Myc is an attractive target for developing novel therapies. The first evidence that down-regulation of c-Myc can be used as a strategy to treat HCC comes from an inducible c-Myc animal model, in which inactivation of c-Myc induced the regression and differentiation of liver tumors[39], yet could not eradicate them. This finding also echoes the recent discovery that, among the four factors required to maintain stem cell phenotypes, c-Myc is crucial[40-42]. Subsequent studies have indicated that in cells with intact p53, Rb and p16 signaling, inactivation of c-Myc leads to cell senescence[43]. This is also consistent with current knowledge on the relationship between cell senescence and hTERT. In addition, using antisense oligonucleotide strategies to downregulate c-Myc also inhibits HCC growth *in vitro*[44]. Recently small-molecule inhibitors that interfere with the c-Myc/Max heterodimerization have also been developed to block c-Myc-mediated transactivation[45]. Testing one of these small molecule c-Myc inhibitors, 10058-F4, in HCC reveals that 10058-F4 inhibited the growth of HCC cells *in vitro*, blocked the binding of E-box, and downregulated hTERT activity. Furthermore, c-Myc inhibition further sensitizes the chemotherapeutic agents against HCC[46]. However, the use of these small molecule c-Myc inhibitors *in vivo* has been less encouraging, probably due to rapid metabolism, resulting in low concentrations in tumors[47]. Subsequent development of c-Myc-Max inhibitors has tried to improve the activity with better pharmacokinetic profiles[48]. Hopefully these new compounds could better inhibit HCC in future *in vivo* studies.

Currently another small molecule compound, CX-3453 (Quarfloxin), which targets c-Myc by reducing c-Myc mRNA, is now in phase Ⅱ clinical trials (NCT00780663) for neuroendocrine carcinoma. Likewise, CX-3543 also inhibits VEGF expression. Since the small molecule VEGFR inhibitor, sorafenib, has been approved for treating advanced HCC[49]. Testing this compound in HCC might shed more light on its potential for future HCC therapy.

However, some caveats are noteworthy in targeting c-Myc in HCC. First, in a transgenic model, re-activation of c-Myc leads to regrowth of tumors, indicating that this approach might target more mature cancer cells, instead of cancer stem cells. A combination with other strategies, such as chemotherapy or agents that target other critical pathways might be needed to enhance anti-cancer effects. In addition, there is concern about systemic toxicity upon c-Myc inhibition, especially in patients with impaired hepatic reserve. In an animal model, knocking down c-Myc expression does not impair liver regeneration, but the architecture of c-Myc-deficient hepatic tissues is disorganized with hypertrophied hepatocytes[50]. The less-than-anticipated toxicity in adult animals indicates that c-Myc might be dispensable in adult but not in neonatal tissues. Further investigation is crucial to determine whether the disorganized hepatic tissues still function like normal tissues and whether disorganized hepatic cells are prone to transformation.

CONCLUSION

Since the first discovery of its oncogenic properties in Burkitt's lymphoma more than two decades ago, the role of c-Myc in normal and neoplastic cells has been extensively studied[51]. Although its critical functions in regulating cell physiology and in carcinogenesis have been well-recognized, the development of c-Myc as a therapeutic target lags far behind basic research. Reasons for such a slow progress are related to the sophisticated regulation of its expression and concerns of potential catastrophic events upon its inhibition. Indeed, even minor differences in its expression level might have divergent consequences[24]. Yet, with the advances in drug design, and in imaging tools to monitor cellular activity, it is now possible to better target c-Myc and investigate its potential as a novel therapeutic agent for HCC.

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