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REVIEW

SGF29 and Sry pathway in hepatocarcinogenesis

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Abstract

Deregulated c-Myc expression is a hallmark of many human cancers. We have recently identified a role of mammalian homolog of yeast SPT-ADA-GCN5-acetyltransferas (SAGA) complex component, SAGA-associated factor 29 (SGF29), in regulating the c-Myc overexpression. Here, we discuss the molecular nature of SFG29 in SPT3-TAF9-GCN5-acetyltransferase complex, a counterpart of yeast SAGA complex, and the mechanism through which the elevated SGF29 expression contribute to oncogenic potential of c-Myc in hepatocellularcarcinoma (HCC). We propose that the upstream regulation of SGF29 elicited by sex-determining region Y (Sry) is also augmented in HCC. We hypothesize that c-Myc elevation driven by the deregulated Sry and SGF29 pathway is implicated in the male specific acquisition of human HCCs.

Key words: c-Myc; SPT3-TAF9-GCN5-acetyltransferase complex; SGF29; Sry; Hepatocarcinogenesis

Core tip: Deregulated c-Myc expression is a hallmark of many human cancers. We have recently identified a role of mammalian homolog of yeast SPT-ADA-GCN5-acetyltransferas (SAGA) complex component, SAGA-associated factor 29 (SGF29), in regulating the c-Myc overexpression. We propose that the upstream regulation of SGF29 elicited by sex-determining region Y (Sry) is also augmented in hepatocellularcarcinoma (HCC). We hypothesize that c-Myc elevation driven by the deregulated Sry and SGF29 pathway is implicated in the male specific acquisition of human HCCs.

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C-MYC AND HEPATOCARCINOGENESIS

c-*myc* is a protooncogene of the viral homolog of v-*myc* which causes myelocytomatosis[1-4]. The expression of c-Myc is tightly regulated by the many ligand-stimulated receptor signaling under normal condition[5]. The deregulated expression level of c-Myc contributes many aspects of cancer development including proliferation, growth, DNA replication, protein synthesis, metabolism, cell adhesion, angiogenesis, metastasis and immune responses by regulating the transcription of its target genes[6-11]. Only two-fold increase in the expression level of c-Myc can affect cell cycle progression[12]. In over 50% of human cancers, c-Myc is deregulated and/or activated[13-18]. In Burkitt lymphoma, the translocation of c-*myc* gene to the immunoglobulin gene causes the overexpression of c-Myc[19,20]. c-Myc is also highly expressed by the gene amplification in many human and rodent cancers including hepatocellularcacinoma (HCC)[21-23]. The 8q22-24 region including c-*myc* locus is involved in the early onset of HCC and represent the frequent amplification in early HCC[24,25]. In mice models, the expression level of c-Myc is also associated with the development of HCC[26-28]. In colon cancer and T cell leukemia, WNT and Notch signaling pathways are involved in the upregulation of c-Myc, respectively[29-32]. Conversely, suppression of c-Myc expression can cause tumor regression by inducing cell cycle arrest, differentiation, or senescence depending on the cell contexts in mice models. The effect of c-Myc downregulation on tumor regression is permanent in some tumors such as lymphoma and osteosarcoma, whereas in hepatocellular or breast cancers this effect is reversible[33-37]. Thus, inhibiting the c-Myc expression could be a promising therapeutic strategy[38-44].

TRANSCRIPTIONAL REGULATION OF C-MYC *VIA* SPT3-TAF9-GCN5-ACETYLTRANSFERASE

c-Myc has N-terminal transcriptional regulatory domain consisting of Myc boxes (Mb) Ⅰ, Ⅱ, Ⅲ, Ⅳ and nuclear localization signal. The basic Helix-Loop-Helix leucine-Zipper (bHLHZ) domains encompasses C-terminal region of c-Myc[45-50]. In the nucleus, c-Myc heterodimerizes with Max through their bHLHZ domains to bind to the E-box sequence (5'-CACGTG-3') in the gene regulatory region[51-54]. The E-box sequences mainly exist in the promoter or intron 1 of the target genes. Although E-boxes are occupied with other E-box-binding transcription factors including ChREBP, SREBP, HIF-1, NRF1, USF, TFE3, Clock, and Bmal to regulate cellular homeostasis in quiescent state, c-Myc is replaced with these factors upon its induction by ligand stimulation[11]. Genome-wide screening for c-Myc-bound target genes using chromatin immunoprecipitation (ChIP)-sequencing reveal that around 6000 genes can be bound with c-Myc in human genome[55]. Of these genes, a set of 300 genes are actually inducible by c-Myc and are involved in nucleotide metabolism, ribosome biogenesis, RNA processing, and DNA replication[56]. These genes are also suggested to be induced in c-Myc-overexpressing transformed cells. c-Myc can recruit some cofactor complexes including histone acetyltransferases, ubiquitin ligases, and kinases, and the N-terminal region of MbI and MbⅡ domains are required for the transcriptional activation and malignant transformation activities[57-59]. These domains can recruit three classes of histone acetyltransferase (HAT) complexes including SPT3-TAF9-GCN5-acetyltransferase (STAGA) complex[60], p300/CBP-associated factor (PCAF) complex[61,62] and the TIP60-containing complex[63] to activate the adjacent gene transcription. Of these three classes of HAT complexes, STAGA complex is thought to be responsible for the transactivation of c-Myc, because the only direct interaction between STAGA and c-Myc is demonstrated[64]. The *Saccharomyces cerevisiae* SPT-ADA-GCN5-acetyltransferase (SAGA) complex is the 1.8 MDa transcriptional coactivator that is highly conserved counterpart of STAGA complex consisting of 18 to 20 proteins[65-71]. The detailed information about these complexes is derived from the studies of yeast SAGA complex. SAGA is essential for about 10% of whole gene transcription[65,66,70,72]. The SAGA complex subunits are classified into four functional groups. The first group includes GCN5 acetyltransferase, ADA2B, ADA3 and SAGA-associated factor 29 (SGF29) regulating the acetylation of multiple lysine residues of histone H3 including H3K9, H3K14, H3K18 and H3K23[73-76]. The acetylation of histones is significantly implicated in the activation state of transcription[77-79]. Moreover, GCN5 can bind to the acetylation mark of histone H3 by its bromo domain[80]. The second group constitutes the ubiquitin-specific protease Ubp8, SGF11, SGF73 and SUS1 to perform the deubiquitinaion of H2B[81,82]. Deubiquitination of Lys123 of histone H2B eventually induce the phosphorylation of the C-terminal domain of RNA polymerase Ⅱ (Pol Ⅱ) to facilitate release of Pol Ⅱ into transcription elongation[83,84]. The third group contains TATA-binding protein (TBP)-associated factor (TAF) proteins that are also incorporated in the general transcription factor TFIID[67,68]. Since a complex consisting of the histone-fold domains of TAF6, TAF9, TAF12 and ADA1 have structural resemblance to the histone octamer, TAF proteins make the structural backbone of the SAGA complex[85]. The last group consists of Tra1 and SPT proteins to tether the SAGA complex to the specific transcriptional activators[67,86-91]. SPT proteins are also reported to be required for the recruitment of TBP to the target gene promoters[69,92-94]. These subunits cooperatively recruit the Pol Ⅱ and assemble the preinitiation complex to induce the target

gene transcription. Of these components, Tra1 and TAF proteins are essential for cellular viability in yeast[95,96]. Most of these components are highly conserved between yeast and human. The human orthologue of Tra1, Transactivation/transformation-associated protein (TRRAP), can interact with the Mb Ⅰ and Mb Ⅱ domains of c-Myc, which is essential for malignant transformation and for the hyperacetylation of histone H3 and H4[64,97-102]. In addition, TRRAP is implicated in the transactivation and transformation activity of E2F1, E2F4, p53, and E1A[98,103-105]. The acetyltransferase activity of human GCN5 is also reported to be involved in the malignant transformation potential of c-Myc[99]. Thus, STAGA complex has significant role in the c-Myc-mediated onset of many human malignancies.

INVOLVEMENT OF SGF29 IN HEPATOCARCINOGENESIS

The critical factor in transformation activity of c-Myc other than TRRAP and GCN5 is SGF29 which is also conserved between yeast and mammals. SGF29 is originally identified using the mass spectrometric analysis of yeast SAGA[81]. By directly interacting with ADA3, SGF29 is incorporated into the STAGA complex[106]. The structural domains of SGF29 are N-terminal coiled-coil domain and C-terminal double Tudor domains[107,108]. Tudor domain is originally cloned in Drosophila, and to date, about 30 Tudor-containing proteins have been identified in mammals such as SGF29, 53BP1, Spindlin1 and UHRF1 most of which can bind to a methylated lysine[75,109-115]. The Tudor domain-containing proteins belong to so-called histone reader proteins that can recognize the various sites for post-translational histone modifications including methylation, acetylation, ubiquitination, and phosphorylation[116]. The histone readers recruit specific protein complexes at the site of histone modifications. These modifications are referred to as histone code to regulate chromatin organization and gene transcription. Many human disorders are associated with the misreading of histone codes[117-119]. The Tudor domains of SGF29 specifically recognize the histone H3K4me3/2 sites in a manner of preference to tri-methylation in yeast and human cells[75,110]. Because tri-methylation of histone H3K4 is prerequisite for subsequent acetylation of histone H3[120] and no other subunits of SAGA complex harbor the Tudor domain, only SGF29 mediates a direct connection between histone H3K4me3/2 and acetylation of histone H3. Knocking down the yeast SGF29 or its mutated form of it decrease the acetylation levels of histone H3 without disturbing the integrity of SAGA complex because of the loss of its ability to bind histone H3K4me3/2 and to load SAGA complex at target gene promoters[67,75,121]. The histone H3K4me3/2 is frequently observed in the active promoter region of genes, and the histone H3 in the E-box sequences are also reported to be highly methylated[122-126]. These methylation of histone H3K4 in E-box occur prior to the induction of acetylation of H3 by c-Myc expression[127]. Because c-Myc is not thought to directly recognize these histone markers, SGF29 in the STAGA complex may help to recruit c-Myc to the E-box in cooperation with TRRAP[106]. The loaded c-Myc induces the local histone acetylation at the site of E-box leading to histone unwinding and significant induction of downstream target gene transcription[128]. In normal organs, SGF29 is robustly expressed in testis and modestly in thymus, spleen and lung. In rat hepatomas, three out of five cell lines overexpress SGF29 together with c-Myc[106]. In the presence of c-Myc, SGF29 enhance the transcriptional activating activity of the promoter of a c-Myc target gene, ornithine decarboxylase (ODC)[129,130], *in vitro*. Conversely, the deletion of SGF29 expression causes the decrease in this promoter activity in rat hepatoma K2 cells. The downregulation of SGF29 also abrogates the colony forming ability of K2 cells in soft agar and tumorigenicity in nude mice concomitant with the decreased expression of c-Myc target genes such as ODC, lactate dehydrogenase-A (LDH-A)[131,132] and metastasis-associated protein 1 (MTA1)[133], whereas growth rate in monolayer culture is not affected. Moreover, the lowered expression level of SGF29 suppresses the metastatic ability of K2 cells to lung[106]. Taken together, the increased SGF29 expression is closely associated with the oncogenic potential of c-Myc by controlling its target gene expression.

MALE SPECIFIC HEPATOCARCINOGENESIS AND SRY

How could the factor(s) cause the deregulated expression of SGF29? The *in silico* search for the transcription factor binding site in the promoter region of rat SGF29 gene predicts that ten transcriptional factors could bind this region[134]. These factors contain c-Myc, sex-determining region Y (Sry), AML-1a and GATA-1. Given that there are seven high-mobility group (HMG)-boxes (5'-AACAAAG-3'), Sry-binding DNA element, and high-expression level of SGF29 in testis, Sry may be the most potent regulator of SGF29 overexpression. Indeed, SGF29 is shown to be a novel Sry target gene because Sry can directly bind the proximal promoter region of rat *SGF29* gene and increase *SGF29* transcript[134]. Sry is originally identified as the male sex-determining gene and is located in the male-specific region of the Y chromosome[135-137]. Induction of Sry expression in the genital ridges drives the testis differentiation and causes the activation of Sox9 to induce the downstream target genes required for male development[138-140]. Sry is not so highly conserved in its N-terminal region among mammals, but these proteins harbor the same ability to control the sex determination in developmental process in a spatiotemporally regulated manner[141-143]. The highly conserved HMG DNA-binding domain of Sry elicits the crucial function in developmental process[139,144,145]. In general, transcription factor have

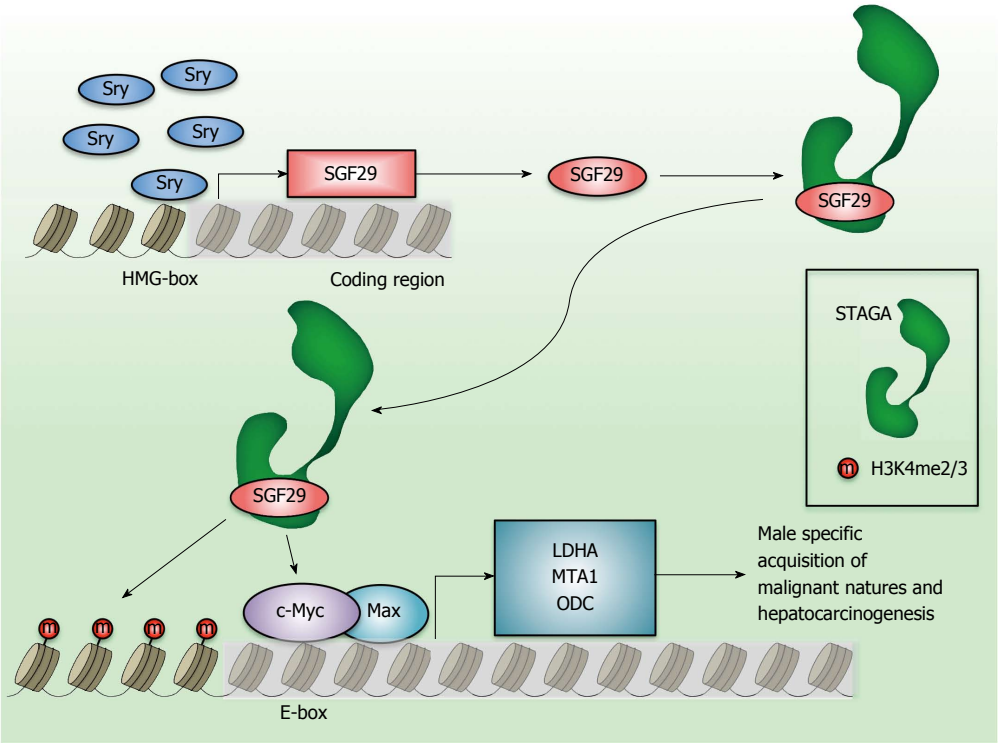

Figure 1 SAGA-associated factor 29 and Sry pathway in hepatocarcinogenesis. Deregulated c-Myc expression is a hallmark of many human cancers. The transcriptionally active marker of histone H3, H3K4me3/2 (red small circles depicted in left bottom of the figure), is frequently observed in the active promoter region of the E-box sequences in the c-Myc target genes. SGF29, a component of STAGA complex, which can interact with H3K4me2/3 induce the acetylation of histone at the sites of c-Myc loaded E-box leading to histone unwinding and significant induction of downstream target gene transcription. The upstream regulation of SGF29 elicited by male specific transcription factor, Sry, is also deregulated in HCC. Eventually, c-Myc target genes such as LDHA, ODC and MTA1 expression are induced, which could account for a molecular insight into the male specific acquisition of human HCC driven by the deregulated Sry and SGF29 pathway. SGF29: SAGA-associated factor 29; STAGA: SPT3-TAF9-GCN5-acetyltransferase; Sry: Sex-determining region Y; HCC: Hepatocellular carcinoma; LDH-A: Lactate dehydrogenase-A; ODC: Ornithine decarboxylase; MTA1: Metastasis-associated protein 1.

the DNA-binding and transactivation domains, but most of Sry proteins from different species except for mouse and rat do not have an obvious transactivation domain[145]. Although many Sry-binding partner proteins are reported to bind to the non-conserved region of Sry[146-149], physiological relevance between these interactions and testis differentiation remains obscure[150,151]. Although Sry expression is limited in brain, thymus and testis in adulthood, some HCC cell lines such as K2 cells overexpress this gene[134]. Moreover, the copy number gain or amplification of this gene locus occur in 11.8% (8/68) of human male HCC cases, which may reflect the fact that Sry is deregulated in some human HCC[152]. The deletion of Sry expression causes the lowered SGF29 expression in K2 cells together with the decreased level of LDHA and MTA1[134]. Like SGF29, the reduced Sry expression leads to the diminished colony forming ability in soft agar and tumorigenicity *in vivo*. The Sry expression solely does not bypath the malignant phenotype when SGF29 is deleted, which reveal that the induction of SGF29 brought by Sry is necessary for the acquisition of c-Myc-dependent transformation activity. Taken together, these findings suggest a hypothetical model of Sry and SGF29 pathway in male specific malignancy of HCC (Figure 1). The aberrant expression of Sry causes the elevation of SGF29, which is integrated into STAGA complex to augment the c-Myc target genes' expression. Because Sry is expressed only in male, this scheme may be the explanation of male-specific acquisition of malignancy and hepatocarcinogenesis.

CONCLUSION

STAGA is one of the histone acetyltransferase complex and crucial for malignant transformation activity of c-Myc. STAGA complex can bind to c-Myc, and the deletion of key components of STAGA suppress the c-Myc target genes' transcription. Thus, uncovering the regulatory mechanism of STAGA complex can sheds light on the oncogenesis driven by c-Myc. As a component of STAGA, SGF29 physically interact with transcriptionally active histone marker H3K4me2/3. Whether SGF29 simultaneously associates with both STAGA complex and histone H3K4me2/3 is unclear, SGF29 might facilitate the efficient recruitment of Pol Ⅱ to the promoter region of c-Myc target genes. We have shown that SGF29 expression is deregulated in some rodent HCCs and is important for tumorigenic activity of c-Myc. Furthermore, because Sry is shown to be directly upregulate the SGF29 transcription and the amplification of *Sry* gene is observed in human

male HCCs, Sry may be an attractive target for c-Myc-involved HCCs as well as SGF29. Given that c-Myc is deregulated in many human cancer types, the Sry-SGF29-c-Myc axis might be implicated in the onset of these cancers. However, not having any information about the expression level of SGF29 in cancers other than HCC, more detailed survey for this point will be required. On the other hand, in addition to Sry, c-Myc, AML-1a and GATA-1 may also bind the promoter region of *SGF29* gene in *in silico* data analysis. Whether these factors will be the real upstream regulator(s) of *SGF29* gene or not should be revealed. Although there are several protein complexes which are recruited to c-Myc, implications of these complexes in malignant transformations are unclear. Moreover, because the relationships between c-Myc and STAGA components other than SGF29, GCN5, and TRRAP are unknown, deubiquitination or TBP recruiting activities of STAGA toward c-Myc should be also clarified.

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