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DNA methylation of tumor suppressor genes in hepatocellular carcinoma

Masumeh Sanaei MSc [1], Fraidoon Kavoosi PhD [1,*], Farzan Modaresi PhD[2]

1. Research center for non-communicable diseases, Jahrom University of medical sciences, Jahrom, Iran
2. Department of Microbiology, School of Medicine; Jahrom University of Medical Sciences, Jahrom, Iran
*Corresponding author: Fraidoon Kavoosi, PhD. Research center for non-communicable diseases, Jahrom University of medical sciences, Jahrom, Iran. Email: kavoosifraidoon@gmail.com. ORCID ID: 0000-0002-3328-4746

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Abstract
The basic unit of chromatin is a nucleosome included an octamer of the four core histones and 147 base pairs of DNA. Posttranslational histones modifications affect chromatin structure resulting in gene expression changes. CpG islands hypermethylation within the gene promoter regions and the deacetylation of histone proteins are the most common epigenetic modifications. The aberrant patterns of methylation localized in normally unmethylated CPG islands mediate chromatin compaction resulting in gene silencing and cancer induction. The current review article aimed to assess and analyze the available literature on the tumor suppressor genes (TSGs) hypermethylation in hepatocellular carcinoma (HCC). For this review article, the suitable studies were obtained by searching PubMed, SCOPUS, NCBI, and Ovid database from 1995 up to September 2018 with the MeSH terms combined with free terms. A total 1483 Items were identified in SCOPUS (n = 459), PubMed (n = 832), Ovid (n = 118), and other reference sources (n = 74). After the assessment, 73 manuscripts were included in the current study. In total, 13 genes were found to have the most effect on HCC. Therefore, we selected them to evaluate as candidate genes in this cancer. TSGs can affect cell cycle during various stages of the cycle an at the cell cycle checkpoints. The hypermethylation of these genes results in chromatin compaction and TSGs silencing which induces HCC.
Keywords: Carcinoma, Genes, Methylation, Tumor Suppressor

Introduction

The reported total cell number of a human body is ranged between 10^{12} and 10^{16} cells. The cellular genomic DNA (deoxyribonucleic acid) is organized into the nucleus which is visible under a light microscope and known as chromatin (1). The basic unit of chromatin is a nucleosome included an octamer of the four core histones and 147 base pairs of DNA. At least eight distinct types of modifications have been found on histones (Table I) (2). Posttranslational histones modifications affect the structure of chromatin and its function, resulting in gene expression changes. CpG islands hypermethylation within the gene promoter regions and the deacetylation of histone proteins are the most common epigenetic modifications (3). The most common epigenetic modification of eukaryotic genomes is cytosine methylation. Mammalian DNA methylation results in the formation of 5-methylcytosine (m5C) (4, 5). Recent in vitro studies have shown that aberrant patterns of methylation localized in normally unmethylated CPG islands mediate chromatin compaction resulting in gene silencing and cancer induction. Mammalian cytosine methylation patterns are established by a family of DNA methyltransferases (DNMTs), including DNMT1, 2, 3a, and 3b (6).

Tumor suppressor genes (TSGs) play significant roles in regulating cell-cycle checkpoints, apoptotic induction, and metabolic regulation. Indeed, hypermethylation of CpG islands of TSGs located in the promoter regions is now established as an important pathway for gene inactivation. Generally, TSGs refers

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to a group of cancer genes responsible for genomic stability. At the epigenetic level, TSGs hypermethylation prevents normal cell-cycle progression. Using high-throughput technologies, an increased number of TSGs have been demonstrated in numerous human cancers, more than 716 genes in humans, 628 genes in mouse, and 576 genes in the rat (7). Finally, hypermethylation of TSGs has been shown in several cancers such as hepatocellular carcinoma (HCC). A variety of HCC-related TSGs is known to be altered by epigenetic pathways.

Previously, we evaluated the effect of several histone deacetylase inhibitors and DNA demethylating agents on HCC (8-12). In this review, we will discuss promoter-CpG islands methylation of several TSGs that may involve in HCC. The genes are shown in Table II.

Material and methods

Search strategy

A systemic literature search was performed to identify studies regarding TSGs in HCC. The suitable studies were provided by searching PubMed, SCOPUS, NCBI, and Ovid database from 1995 up to September 2018 with the search terms indicated in Table 1. The included criteria were as follows: (2) the association between DNMTs activity and tumorigenesis; (2) various TSGs involved in HCC; and (3) the association between hypermethylation and the hepatocellular carcinoma. To increase the search quality, both authors (S.M. and K.F.) independently searched and selected suitable articles according to the inclusion and exclusion criteria. To avoid bias, no methodological filters were applied.

Selection

As a basis for the selection of the articles, the PRISMA guidelines were used. The articles were downloaded into EndNote and selected through the following process (Figure 1). The first step study was the identification of the studies by reviewing the title of each article. The second step involved removing any duplicates and obvious false selections. The third step was performed to select the manuscript by focusing on HCC. The un-related articles were omitted if they did not have one of our criteria listed in Table III.

Results

Using search terms mentioned in the section “Materials and Methods”, a total 1483 items were identified in SCOPUS (n = 459), PubMed (n = 832), Ovid (n = 118), and other reference sources (n = 74). After exclusion of the duplicated articles (n = 53), additional manuscripts were excluded for not meeting inclusion criteria (n = 932). Full manuscript screening contained 498 items, and 425 were excluded according to quality assessment (Figure1). Finally, 73 manuscripts were included in the current study. In total, 13 genes were found to have the most effect on HCC. Therefore, we selected them to evaluate as candidate genes in this cancer.

DNMTs and their roles in tumorigenesis

Epigenetic modifications, such as DNA methylations, and histone modifications have a significant role in the gene expression regulation in mammalian cells.

Methylation of mammalian genomic DNA is catalyzed by DNMTs that responsible for catalyzing the transfer of a methyl group to cytosine nucleotides (Figure 2) (13, 14). The mammalian DNMTs family is subdivided into four active members, including DNMT1, DNMT2, DNMT3A, and DNMT3B. The most abundant DNMT involved in the maintenance of DNA methylation is DNMT1. As mentioned, DNA methylation plays an important role in chromatin stability, gene expression, and genetic imprinting. Epigenetic disruptions caused by DNMTs are associated with cancer induction and progression (15). DNMTs overexpression results in hypermethylation of several TSGs, resulting in gene silencing and tumorigenesis (16).

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Mammalian cyclins, CDK s**, and** CDKIs

Cyclins are defined as proteins that are degraded at every mitosis phase (Figure 3) (17) and the activating partners of a family of protein kinases named the CDK s, most cyclins promote CDK activity.

During the cell cycle, four cyclins are produced comprising D, E, A, and B, which activate CDKs (Figure 4) (18). They require the presence of a CDK to do their regulatory function and they can't act alone (Figure 5) (19). Both CDKs and cyclins have significant roles in the eukaryotic cell cycle regulation. Initially, A pair of cyclins, A, and B were discovered which were associated with a single kinase subunit including CDK1, and then this group had been expanded to multiple CDKs and cyclins involved in the cell cycle processes, differentiation, and transcription. As mentioned, CDKs include a catalytic core and they partner with cyclins, regulatory subunits, which control kinase activity. Each cyclin has one or two CDKs and each CDK has one or two cyclins.

Cyclins in combination with their partner CDK are responsible for phosphorylating other cell cycle regulatory proteins. Most CDKs contain one or two cyclins. In the cell cycle processes, cyclin D is associated with the G1 phase, cyclins A and E are associated with the S phase, and cyclins A and B with the mitosis phase (20, 21). In mammals, the CDK family includes five transcriptional subfamilies (CDK7, CDK8, CDK9, CDK11, and CDK20) and three cell-cycle-related subfamilies (CDK1, CDK4, and CDK5) (22). Cyclins and CDKs are the main regulators of cell cycle progression and are frequently altered in human cancers. They regulate cell-cycle progression, transcription, differentiation, apoptosis, and they are essential for cell cycle phases progression (23). CDKIs, the common negative regulators of the cell cycle, play a key role in controlling the cell cycle progression (Figure 6) (24). To date, at least 2 groups of CDKIs are known in mammalian cells one of which inhibits cyclin D-related kinase activity by binding to CDK4 or CDK6 known as CDK4 (INK4) inhibitor, including p16INK4A, p15INK4B, p18INK4C, p19INK4D, and the other known as the p21 family, comprising p21CIP/WAF1, p27KIP1, and p57KIP2 which inhibit the G1 to S transition. CDKIs inactivation is associated with the neoplastic transformation (Figure 7) (18, 25).

1. CDKs **as** TSGs

1-1. P16^{INK4A}

The p16^{INK4A} gene encodes a critical negative regulator of cell cycle progression, p16 protein, and is a major target for inactivation in HCC. Its location is on chromosome 9p21. DNA methylation of the p16^{INK4A} gene and Down-regulation of the p16 protein has been shown in human HCC cell lines (26). It has been demonstrated that multiple risk factors, including exogenous factors, like vinyl chloride exposure and viral infections, and endogenous factors, like female gender and aging, may be involved in the generation and maintenance of p16^{INK4A} hypermethylation in hepatocarcinogenesis (27).

1-2.P15^{INK4b}

p15^{INK4b}, a cyclin-dependent kinase inhibitor gene, is another TSG with similar chromosomal location and function of p14^{ARF} (28). Hypermethylation of the p15 gene and aberrant alteration of mRNA expression is not only associated with HCC but also with its progression. Higher expression of two methyltransferases, Dnmt1 and Dnmt3b has been indicated with methylation of p16 and p15 genes in human HCC, which could be a biomarker for monitoring of this cancer (29). It has been reported that the hypermethylation of the p15^{INK4b} and p16 can induce HCC, suggesting a unique role for this gene (30).

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1-3.P14^{ARF}

As a TSG, P14^{ARF} located at human chromosome 9p21 is one of the most frequently altered genomic regions in various cancers. The promoter regions of P14^{ARF} are highly abundant with CpG islands that are susceptible to methylation, one of the important mechanisms by which TSGs are inactivated in human cancers (31). This process alters the readability of the DNA and does not change the genetic information.

Epigenetic silenced p14^{ARF} gene is involved in the important molecular pathway of carcinogenesis, cell cycle regulation. In addition to HCC, CpG island hypermethylation of p14^{ARF} is seen in premalignant conditions such as cirrhotic liver or dysplastic nodules (32).

1-4.P19 ^{INK4d}

The human p19^{INK4d} gene has been located in chromosome l9pl3.2, belongs to the CDKIs that target the CDKs, and inhibits their catalytic activity (33). It has been reported that the loss or downregulation of p19^{INK4D} is frequently detected in HCC suggesting that p19^{INK4D} plays a role in the differentiation of HCC (34). We could not find any article reporting p19INK4D methylation in HCC.

1-5.P21$^{WAF1/CIP1}$

p21, as a cell cycle inhibitor, is expressed in numerous cancer cell lines and is regulated by two molecular mechanisms, including p53-dependent and p53-independent molecular mechanisms. It is an important regulator of hepatocyte cell cycle and differentiation. It has been demonstrated that p21$^{WAF1/Cip1}$ is expressed in HCC HepG2 cell line (35). It is encoded by a gene located on chromosome 6p21.2 (36). Hypermethylation of CpG island acts as a molecular mechanism of the gene inactivation, and it is a recognized mechanism during liver cancer initiation and progression. P21$^{WAF1/CIP1}$ regulates the G1/S checkpoint of the cell cycle by control of CDKs activity. Many factors, including IFN-a, IFN-b, IFN-g, TGF-b, and IL-67, have been shown to upregulate p21$^{WAF1/CIP1}$ throw JAK-STAT, and a p53-independent manner (37). The methylation status of P21is significantly associated with HCC (38). Just the opposite, unchanged the protein level of G0/G1-phase regulators p21 $^{Waf1/cip1}$ has been reported in HCC HCT116 cells (39).

1-6. P27^{kip1}

p27^{kip1}, located on chromosome 12p13, is a TSG and the mammalian cell cycle regulator. Disruption of cell cycle regulation pathway plays an important role in hepatocarcinogenesis. The reduction of p27^{kip1} protein expression has been reported in HCC. The p27 protein is expressed in normal liver and significantly decreased in HCC. Significant hypermethylation of p27 resulted in the loss of p27mRNA transcription has been shown in HCC (40). The frequency of P21^{WAF1}gene silencing by promoter methylation is significantly higher in HCC with a poorer prognosis than HCC with a better prognosis (41).

1-7.P57^{KIP2}

Decreased expression of p57 has been shown in a variety of human cancers such as HCC (42). This gene with 11p15 chromosomal location serves as a TSG. Aberrant methylation of the current gene which has been shown around the transcription start site is closely associated with silencing the gene expression. Methylation of this gene has been demonstrated in various cell lines of HCC including CHC4, CHC20, HLE, CHC32, and HUH7 (43). A few studies have been reported that the p57^{KIP2} gene is moderately hypermethylated in HCC, the expression of which may not be significantly affected by this methylation (44).

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2. Other TSGs

2-1. P53

P53 protein plays an important role in cellular responses such as cell death and cell-cycle arrest. Protein p53 is the product of a 20-Kb gene localized on chromosome 17, 17pl3.1. The methylation of p53 is associated with low expression levels of the gene which plays an important role in several human neoplasms, such as ovarian cancer (45). P53 is regulated via protein methylation/ demethylation. Many studies have been reported that histone lysine methyltransferases KMT3C, KMT5, and KMT5A methylate p53 at specific C-terminal lysines. By this means, they suppress or enhance the transcriptional activity of this gene depending on the methylation status (46). Cell cycle and apoptosis are two key determinants of cell fate controlled by the p53 gene. Cell cycle arrest in G1 and G2 (Figure 8) allows the process of DNA repair and prevent genetic changes to be transmitted to the next cellular generation. Upon DNA damage, the p53 gene is activated and plays its regulatory functions through p21- arresting the cell cycle, and Bax and Bcl-2 proteins leading to apoptosis (47).

Although the methylation of this gene has been reported in several cancers, we could not find any article which reports p53 methylation in HCC.

2-2. P73

p73, a p53 family member, is a TSG mapped to the 1p36.33 region that contains two promoters at the N-terminus (48). TAp73 acts as a tumor suppressor gene and induces cell cycle arrest and cell death; whereas; ΔNp73 has oncogenic properties that inhibit TAp73 and p53 functions. It has been demonstrated that the overproduction of p73 protein activates the transcription of p53-responsive genes and induces cell growth inhibition in a p53-like manner by inducing apoptosis (49). An elevated p73 transcription has been shown in the HCC by in situ hybridization. A decreased level of p73 mRNA expression has been detected in non-neoplastic hepatocyte cells. Because of the ability of p73 to induce the expression of $p21^{WAF1/CIP1}$, suggests that p73 plays its role as a transcription factor (50). An increased p73 expression and p21 induction have been reported in HCC Hep3B cells (51). However, p73 has not yet been found to be methylated in HCC.

2-3. P63

P63 is known as p53 family members and is located on chromosomes 3q27-29.

This gene with other p53 family members, TP53 and TP73 genes, encode proteins with similar domain structures. Similar mechanisms regulate p53, p63, and p73 genes expression and the abnormal expression of these genes contributes to carcinogenesis

(52). P63 exhibits a tissue-specific role and does not function as classical TSGs and is rarely mutated in human cancers. It contributes to many human cancers via both p53-dependent and p53-independent pathways (53). P63 shares some p53 functions, such as apoptosis and cell cycle arrest. Reduced expression of p63 has been reported in HCC Hep3B (54).

2-4. $P18^{INK4c}$ gene

The human *$p18^{INK4c}$* gene is located on chromosome 1p32, a region frequently altered in numerous cancers (55). To date, very little reports are available regarding $p18^{INK4C}$ methylation in HCC. Previous experimental works have demonstrated the methylation of the $p18^{INK4C}$ gene and the expression of the $p18^{INK4C}$ protein in HCC, but the methylation of this gene is not yet known (56, 57).

2-5. Estrogen Receptor as TSGs

Nuclear estrogen receptors (ERs), as TSGs, contain two subtypes, including ERα and ERβ encoded ESR1 and ESR2 located on chromosomes 6q25.1 and 14q22-24 respectively (58). These

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receptors exist in hepatocytes in healthy, cirrhotic, or HCC and mediate estrogen-responsive biological effects through DNA dependent or independent manner (59). As a tumor suppressor gene, ESR1 encodes ERα, a ligand-activated transcription factor with several hormone-binding domains. The relation between this gene and malignant disease has been reported in a variety of tissues such as HCC, colon, breast, and bladder cancer. One of the mechanisms by which the ESR1 induces HCC is promoter hypermethylation, resulting in a silenced gene (60). ERα is transcribed from two promoters; the two transcripts share similar sequences. The 5′ region of both transcripts includes upstream open reading frames encoding potential peptides of 20 and 18 amino acids (59). Previously, we reported ERα hypermethylation in HCC (61). The relation between ERβ hypermethylation and HCC has not yet been reported.

2-6. DLC-1

The gene deleted in liver cancer-1 (DLC-1), mapped to 8p21.3–22, has been identified as a TSG and attractive candidate promoter methylation in cancer (62). The inhibitory and antiproliferative effect of the gene has been shown in HCC. Indeed, transcriptional silencing of the gene by hypermethylation contributes to the DLC-1 gene activation. It has been shown that the COOH terminus of DLC-1 includes a highly conserved RhoGAP domain, which acts to catalyze the intrinsic GTPase activity of Rho family proteins (63). DLC-1 possesses GAP activity, which is specific for CDC42 and RhoA. Besides, DLC-2, a novel DLC-1 homology, located on chromosome 13q12.3 (64), has been demonstrated that shares a high identity with DLC-1 in amino acid sequence and also contains similar functional domains that have been reported in DLC-1 (SAM, RhoGAP, and START domain). RhoGAP domain is the most conserved region between DLC-1 and DLC-2. Indeed, both DLC-1 and DLC-2 exert RhoGAP activity toward RhoA and CDC42. Finally, DLC-1 acts as a TSG by negative regulation on the CDC42- and RhoA- mediated transformation. Epigenetic DLC-1 promoter hypermethylation decreases DLC-1 mRNA expression in hepatoma cell lines and primary HCCs (65).

2-7. GSTP1 (Glutathione S-transferase P1)

The GSTP1 gene, located on chromosome 11q13, encodes glutathione S-transferase π which protects the normal liver cell against cytotoxic and carcinogenic influences (66). Somatic GSTP1 DNA hypermethylation has been indicated in several human cancers, including HCC. Epigenetic silencing of GSTP1 by CpG island hypermethylation is common in human HCC (Hep3B, HepG2) (67, 68). In addition to premalignant conditions such as cirrhotic liver or dysplastic nodules, promoter hypermethylation of the GSTP1 has been shown in HCC). The promoter methylation of the GSTP1 gene has been associated with hepatocarcinogenesis (69). Hypermethylation of this gene has been demonstrated as a biomarker of HCC (70).

2-8. E-cadherin

E-cadherin, a single transmembrane domain glycoprotein, known as a TSG, plays a significant role in Wnt signaling and tumorigenesis.

This gene is located on chromosome 16q22.1 (71). E-cadherin contains two domains including the N-terminal ectodomain that play a major role in the maintenance of epithelial tissues and the cytoplasmic domain which interacts with β-catenin or plakoglobin. The cadherin-catenin complex alteration leads to the change of cell polarity, proliferation, motility, and differentiation. Besides, the effect of E-cadherin on cellular suppression, cell growth inhibition, transformation, and invasiveness has been demonstrated in different model systems. Decreased expression of E-cadherin has

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been associated with the disruption of cell-cell contacts, metastatic potential, invasiveness, and epithelial-mesenchymal transition. E-cadherin has been known as a TSG by the finding of genetic mutations in combination with LOH at the E-cadherin gene (CDH1) locus in various cancers. The epigenetic mechanisms which can down-regulate E-cadherin gene expression include promoter hypermethylation and binding of transcriptional repressors, such as Sip1 and Snail, that are up-regulated in dedifferentiated cancer cells (72, 73). However, the E-cadherin gene expression is fundamental for invasiveness and intraepithelial expansion, and the growth of intrahepatic metastases HCC progression (74).

2-9. Cytokine and suppressors of cytokine signaling

Cytokines are secreted proteins that regulate various biological processes and cellular responses by binding to their receptors by which activate intracellular complex signal transduction pathways comprising the Janus kinase signal transducer and activator of transcription (JAK-STAT) pathway. Cytokine signaling is dependent on the JAKs and STATs. They induce receptor aggregation resulting in members of the JAK family of cytoplasmic tyrosine kinases activation and phosphorylation/dimerization of the STAT family of transcription factors, leading to the transcription of genes with STAT recognition sites in their promoters. (75). Three families of proteins inhibit cytokine signal transduction, including the suppressors of cytokine signaling (SOCS), the protein inhibitors of activated STATs (PIAS), and the SH2-containing phosphatases (SHP) (76, 77). The SOCS proteins are small molecules containing a C-terminal SOCS box and a central src homology 2 domains (78). To date, the eight SOCS family members have been identified, comprising SOCS1-7 and CIS that the most studied family members include SOCS1, SOCS2, and SOCS3 (Figure 9) (79). The principal cytokine signaling transduction pathway, the JAK/STAT signaling pathway, is negatively regulated by the SOCS-1 gene, dysregulation of the pathway is involved in the malignant transformation for several cancers, such as HCC. SOCS-1 switches cytokine signaling 'off' using its interaction with JAK. This gene is frequently silenced by methylation of the CpG islands in human HCC (80). The SOCS2 gene is located on chromosome 12q21.3–q23 (81) and induced by several kinds of cytokines that activate STAT5. The most important ones include IL-1, IL-2, IL-3, IL-4, IL-6 IL-15, GH, EPO, PRL, GM-CSF, CNTF, G-CSF, IFN-alpha, IFN-gamma, LIF, and insulin. SOCS2 is associated with growth hormone (GH) signaling and is involved in cell growth. Methylation of the SOCS2 gene promoter region is one possible mechanism that explains SOCS proteins down-regulation in cancer (82). We couldn't find any article which reports SOCS2 methylation in HCC.

SOCS3 gene is located on chromosome 17q25.3. The SOCS3 expression is induced by several cytokines, including interleukin (IL) - 6 and IL-10 (83). SOCS3 plays a crucial role in the JAK/STAT signaling pathway inhibition in HCC. Aberrant methylation of SOCS3 has been reported in HCC HuH2, Hep3B, and HT17 cell lines (84). Besides, it has been demonstrated that SOCS3 methylation is associated with the major clinical features of HCC (85).

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Table I. Various classes of histone modifications

Chromatin Modifications	Residues Modified	Functions Regulated
Proline Isomerization	P-cis > P-trans	Transcription
Methylation (arginines)	R-me1, R-me2a, R-me2s	
Deimination	R > Cit	
Sumoylation	K-su	
ADP ribosylation	E-ar	
Ubiquitylation	K-ub	Repair and Transcription
Phosphorylation	S-ph, T-ph S-ph, T-ph	
Methylation (lysines)	K-me1, K-me2, K-me3	
Acetylation	K-ac	

Table II. The TSGs discussed in the current study.

Gene	Location
p16^{INK4A}	9p21
p15^{INK4b}	9p21
P14^{ARF}	9p21
p19^{INK4d}	l9pl3.2
p21$^{WAF1/Cip1}$	6p21.2
p27^{kip1}	12p13
p57^{KIP2}	11p15
P53	17pl3.1.
p73	1p36.33
P63	3q27-29
P18^{INK4c}	1p32
ERα	6q25.1
ERβ	14q22-24
DLC-1	8p21.3–22
GSTP1	11q13
E-cadherin	16q22.1
SOCS1	16p12-p13.1
SOCS2	12q21.3–q23
SOCS3	17q25.3

Table III. All search terms used in this systematic review

Number	Search term
1	Chromatin Modifications
2	Methylation
3	Acetylation
4	TSGs
5	Methyltransferases
6	Tumorigenesis
7	Cyclins
8	Cyclin-dependent kinases (CDKs)
9	CDK inhibitors (CDKIs)
10	Cytokine
11	Cancer
12	HCC

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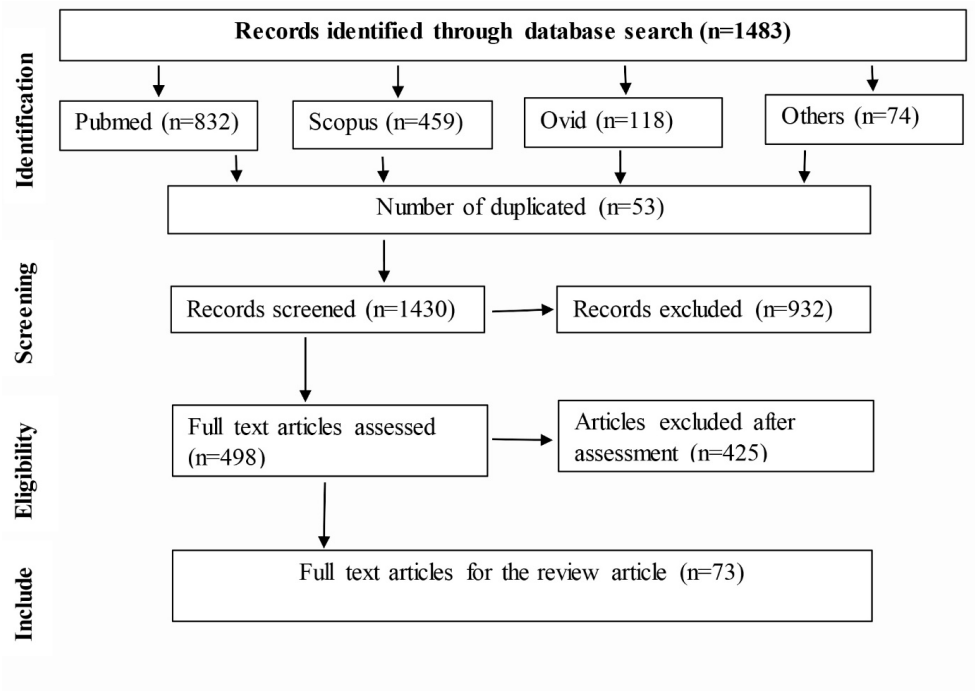

Figure 1. The methodological quality assessment and PRISMA flow diagram

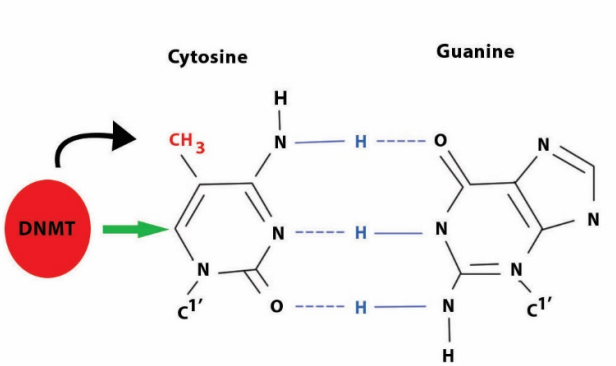

Figure 2. Cytosine methylation in the DNA strand. The addition of a methyl group to the cytosine, CH3 (red color), at the five positions of the cytosine pyrimidine ring does not sterically interfere with GC base pairing (blue lines).

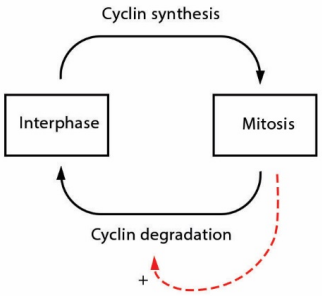

Figure 3. A simple possible model for the synthesis and degradation of the cyclin in the cell cycle

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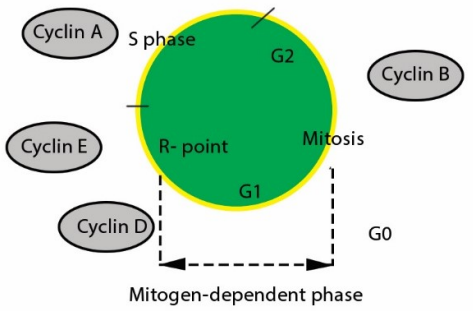

Figure 4. Cyclins and cell cycle progress. Four major cyclins are produced in the cell cycle which activates CDKs. G0: gap 0 phase; G1: gap 1 phase; S: synthesis phase; G2: gap2 phase.

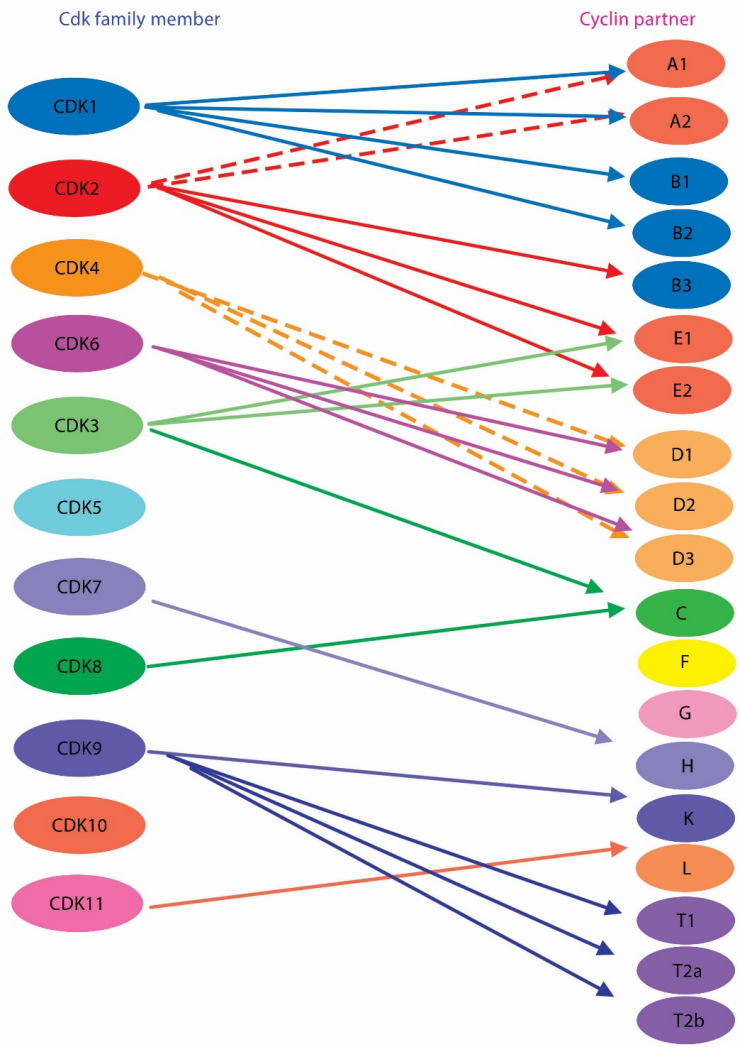

Figure 5. The common mammalian cyclin-dependent kinase (CDK) family members and their interacting cyclin partners.

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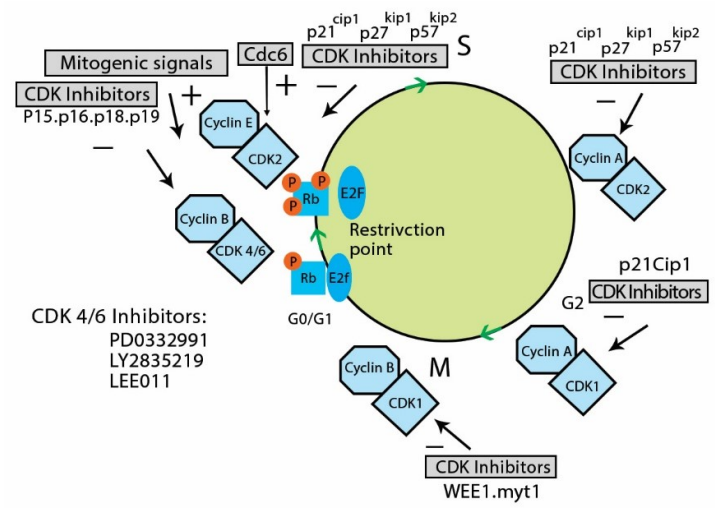

Figure 6. Key regulators of the mammalian cell cycle. The positive regulators of cell cycle progression are shown by green plus signs and the cell cycle inhibitory proteins are shown by the red minus sign. The phosphorylation events on the Rb are indicated by the yellow P. CDK: cyclin-dependent kinase; Rb: retinoblastoma protein.

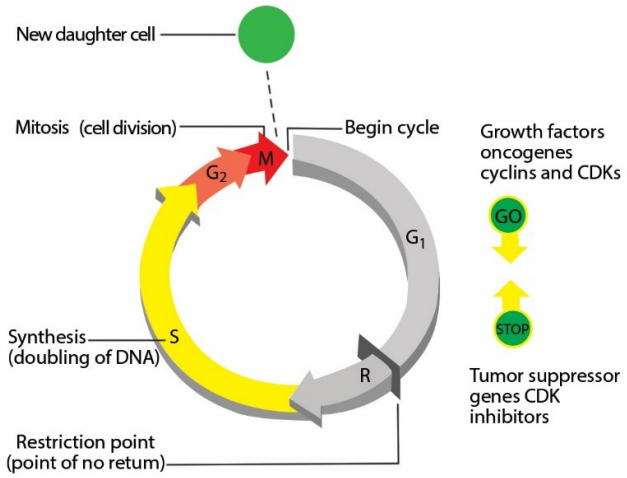

Figure 7. Cell cycle phases. Loss of the cell cycle checkpoint controls results in genomic instability, uncontrolled proliferation, and cancer induction. G0: gap 0 phase; G1: gap 1 phase; S: synthesis phase; G2: gap2 phase; M: mitosis phase.

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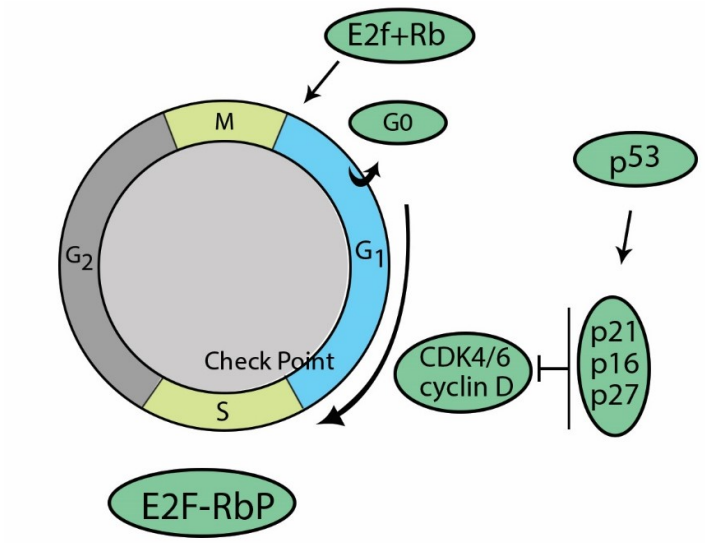

Figure 8. Cell cycle process and the control of G0-G1 checkpoint, cyclin-dependent kinase inhibitor function of p53, p21, p16, and p27. G0: gap 0 phase; G1: gap 1 phase; S: synthesis phase; G2: gap2 phase; M: mitosis phase. Rb: retinoblastoma protein. E2F, E2F transcription factor: A link between the Rb and viral oncoproteins

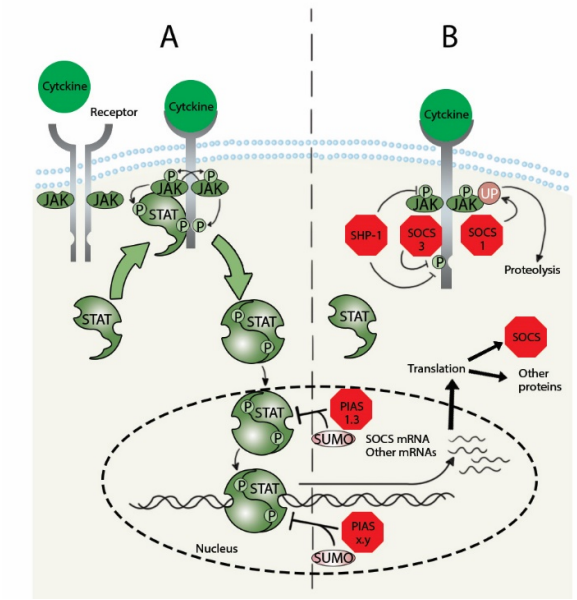

Figure 9. Regulation of signal transduction, the JAK-STAT pathway. A. The JAK-STAT pathway is activated when a cytokine binds to its receptor at the cell surface. Activated JAK creates binding sites for STATs which are also phosphorylated by JAK. The STAT proteins can transport into the cellular nucleus and induce the transcription of the genes. B. The signaling pathway and transduction are repressed by three pathways. SHP-1, which can dephosphorylate JAKs or receptors. PIAS proteins, which modulate the activities of STATs leads to the inhibition of transcriptional activation. SOCS proteins induced in response to cytokine signaling can inhibit JAK activity. SOCS: suppressor of cytokine signaling; Jak/STAT

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Discussion

Main findings

Promoter epigenetic instability reported by promoter DNA methylation of multiple tumor-related genes is characterized as a key molecular pathway of TSGs silencing in many cancers, including HCC. In the current study, we performed a detailed analysis of a large number of promoter DNA methylation in HCC. Our review has included several studies that evaluated the contribution of promoter methylation resulting in HCC. We mainly focused on the 19 TSGs involved in HCC as shown in Table II. The relationship between these genes hypermethylation and the incidence of HCC has been indicated by other works assessed these genes mRNA expression and their promoter CpG island methylation. Using high-throughput technologies, an increased number of TSGs have been identified in various cancers, more than 716 genes in humans, 628 genes in mouse, and 576 genes in the rat (7). Our investigation identified several TSGs and their proteins involved in tumorigenesis, cell growth, and apoptosis in HCC as shown in Table II. The reactivation of these genes has a clear correlation with cell growth inhibition and apoptosis induction in HCC. As indicated in Figures 5, 7, and 8, TSGs use various pathways and molecular mechanisms to play their roles. Additionally, most TSGs act duration cell cycle phases especially cell cycle checkpoint controls (Figures 7 and 8). Epigenetic disruptions caused by DNMTs are associated with cancer induction and progression (15). DNMTs overexpression results in hypermethylation of several TSGs, resulting in gene silencing and tumorigenesis (16). The mammalian DNMTs family is subdivided into four active members including DNMT1, DNMT2, DNMT3A, and DNMT3B. The most abundant DNMT is DNMT1 which involves the maintenance of methylation. These findings highlighted a potential novel for these regulatory genes during cell cycle phases and cell cycle checkpoints. Besides, this review highlighted a significant effect of the mammalian DNMTs family which their activities induce DNA hypermethylation, resulting in silenced TSGs and tumorigenesis.

Strengths and limitations

This review is the first study that has systematically assessed the experimental works for TSGs-mediated liver protection. We used comprehensive search strategies in a wide range of data sources, had access to the full texts of all identified articles, and assessed a wide range of experimental outcomes. Meanwhile, this study has important limitations. Several included studies had significant methodological limitations and obvious molecular mechanisms of TSGs. Further researches are needed to evaluate the molecular mechanisms of the identified TSGs to provide a further understanding of the protection role of these genes.

Conlusion

TSGs can affect cell cycle during different phases of the cycle and at the cell cycle checkpoints. The hypermethylation of these genes may be one of the causes of chromatin compaction and TSGs silencing which induces HCC.

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Conflicts of interest

There are no conflicts of interest.

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