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TOPIC HIGHLIGHT

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Histone modifications and alcohol-induced liver disease: Are altered nutrients the missing link?

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Abstract

Alcoholism is a major health problem in the United States and worldwide, and alcohol remains the single most significant cause of liver-related diseases and deaths. Alcohol is known to influence nutritional status at many levels including nutrient intake, absorption, utilization, and excretion, and can lead to many nutritional disturbances and deficiencies. Nutrients can dramatically affect gene expression and alcohol-induced nutrient imbalance may be a major contributor to pathogenic gene expression in alcohol-induced liver disease (ALD). There is growing interest regarding epigenetic changes, including histone modifications that regulate gene expression during disease pathogenesis. Notably, modifications of core histones in the nucleosome regulate chromatin structure and DNA methylation, and control gene transcription. This review highlights the role of nutrient disturbances brought about during alcohol metabolism and their impact on epigenetic histone modifications that may contribute to ALD. The review is focused on four critical metabolites, namely, acetate, S-adenosylmethionine, nicotinamide adenine dinucleotide and zinc that are particularly relevant to alcohol metabolism and ALD.

Key words: Alcohol; Liver disease; Nutrients; Metabolism; Histone; Epigenetic modifications; S-adenosylmethionine; Acetate; Zinc; Nicotinamide adenine dinucleotide

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INTRODUCTION

Alcoholism is a growing health problem worldwide. In the United States, alcoholism is a major cause of liver-related disease and deaths. Recent statistics reveal 52% of US adults to be "current regular" drinkers (Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2009) and the death rate for alcohol-

induced causes to be on the rise (National Vital Statistics Reports, May 2010). As a result, alcohol-induced liver disease (ALD) continues to be studied, with the objectives of elucidating the underlying mechanisms and discovering potential therapeutic targets.

ALD consists of the spectrum of pathological changes including fatty liver, alcoholic hepatitis and alcoholic cirrhosis. The clinical manifestations of these changes and the pathogenesis of this disease have been extensively studied and described. There is a growing body of evidence supporting the involvement of epigenetic mechanisms in response to environmental inputs in the development of human disease. Accordingly, in recent years, there has been increasing interest in understanding the role of epigenetic mechanisms in the initiation and/or progression of ALD.

Nutrient fluctuations can impact transcriptional activity and expression of selective genes by modulating epigenetic parameters including histone modifications, DNA methylation, and nucleosome positioning. In ALD, especially in chronic alcoholics, the combined effect of alcohol metabolism and compromised nutrition causes major nutrient disturbances that are likely to influence epigenetic mechanisms, gene expression and disease pathogenesis. Covalent modifications of the amino termini of the core histones in nucleosomes play a key role in regulating chromatin structure as well as DNA methylation status. This review interrelates alcohol-mediated nutrient disturbances and consequent histone modifications that may have a contributory role in ALD (Figure 1). Specifically, the review is focused on fluctuations in four critical metabolites, namely, acetate, S-adenosylmethionine (SAM, also known as SAMe or AdoMet), nicotinamide adenine dinucleotide (NAD^+) and zinc that are relevant to alcohol metabolism and ALD.

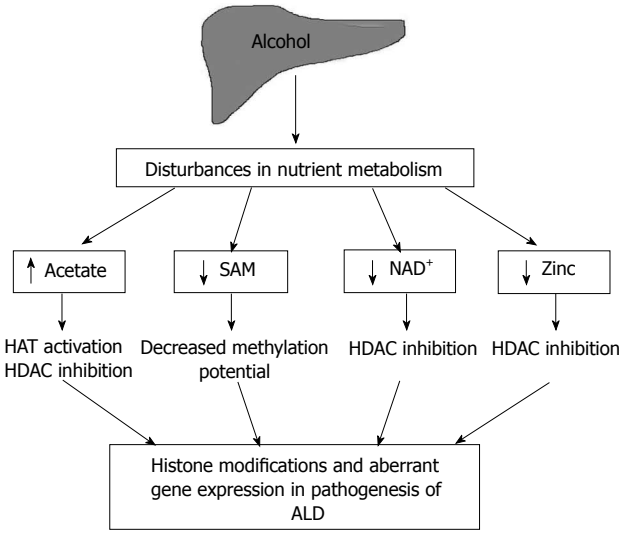

Figure 1 Nutrient disturbances, a potential link between alcohol metabolism and histone modifications in alcohol-induced liver disease. SAM: S-adenosylmethionine; NAD^+: Nicotinamide adenine dinucleotide; HAT: Histone acetyltransferase; HDAC: Histone deacetylase; ALD: Alcohol-induced liver disease.

ALCOHOL AND ACETATE

The principal route of ethanol oxidation is through the enzyme liver alcohol dehydrogenase, which converts alcohol to aldehyde with the reduction of NAD^+ to NADH[1]. Acetaldehyde is then further oxidized by acetaldehyde dehydrogenase to acetate. The other major route of oxidation is through the microsomal ethanol oxidizing system (MEOS), in which the chief enzyme catalyzing alcohol oxidation is the cytochrome P450 mixed-function oxidase isoenzyme CYP2E1[1]. This route is engaged when alcohol is ingested in large quantities or in chronic alcoholics, who upregulate CYP2E1 expression. Thus, the end-product of both pathways of ethanol metabolism in the liver is free acetate[1]. This free acetate is then incorporated into acetyl-coenzyme A (acetyl-coA), by the catalytic action of the cytosolic and mitochondrial enzymes acetyl-coA synthetases[2]. Acetyl-coA is the substrate for histone acetylation, in addition to being utilized in the Krebs cycle, fatty acid synthesis and acetylation of other proteins[3].

Alcohol increases acetate production

Ethanol consumption has been shown to increase blood acetate levels significantly in several studies, dating back to the 1980s. Short-term ethanol administration in humans led to a sustained steady state concentration of 0.4 to 0.6 mmol acetate within 2 to 5 h following ingestion in a study consisting of healthy male and female volunteers[4]. Although this phenomenon was also seen in alcoholics, there were variations in the kinetics of acetate production, with chronic alcoholics eliminating alcohol faster and producing more acetate[5,6]. Acetate levels were significantly higher both in the hepatic vein (1.79 and 1.15 mmol) and peripherally (0.91 and 0.52 mmol) in alcoholics than in non-alcoholics respectively[6]. In another study employing an enzymic acetate detection method, acetate concentration in peripheral human blood increased to about 20 times the normal level with ethanol consumption, whereas neither fasting nor the intake of a fatty meal significantly influenced acetate concentration[7].

Acetate and histone modifications

Amongst the various modifications documented at the tails of histone proteins in humans, acetylation and methylation are the best characterized[8]. Generally, acetylation at the lysine residues of histones depicts a transcriptionally permissive state, allowing opening up of the chromatin structure and access to transcriptional machinery[8]. Hyperacetylation of histones has been observed after alcohol administration in both, cell culture and animal studies[9-13]. In a 2003 study by Park *et al*[12], ethanol increased acetylation at lysine 9 on histone 3 (H3K9Ac) in a dose- and time-dependent manner in isolated rat hepatocytes. There was a remarkable 8-fold increase in the amount of H3K9Ac at 24 h by 100 mmol ethanol without an increase in histone 3 protein expression[12]. Also, inhibition of the metabolism of ethanol to acetate largely abolished this effect, suggesting that production of the ethanol metabolite, acetate, was critical to the process of acetylation[12]. Similar experiments in rat hepatic stellate cells (HSCs) demonstrated an increase in H3K9Ac levels with

no changes at lysines 14 or 18[9]. An *in vivo* study of the effect of acute ethanol (binge drinking) in rats concluded that the ethanol-induced increase in H3K9Ac was largely restricted to the liver, lung and spleen, with the liver showing a maximal increase of ~6-fold in a 12 h period[10].

An increase in the acetylation of histones in response to ethanol may be brought about by an orchestration of events that (1) increase the substrate for the reaction, acetyl-coA, (2) and/or modulate the enzymes controlling histone acetylation (HATs, HDACs). A study by Shukla's group in 2005 demonstrated that ethanol increased histone 3 acetylation at lysine 9 by specifically modulating HAT(s) targeting lysine 9 in rat hepatocytes[13]. However, it was not determined whether ethanol induced this effect by increasing transcriptional expression of HAT(s) or by specifically augmenting their activity. Accordingly, H3K9Ac and HAT activity was also increased by acetate in these cells, again indicating it as the likely mediator of ethanol-induced histone acetylation[13]. Interestingly, signaling pathway analysis showed that mitogen-activated protein kinase kinase (MEK) and c-Jun N-terminal kinase (JNK) inhibitors reduced ethanol-induced acetylation without affecting ethanol-induced HAT activity. This suggests a role for MEK and JNK in histone 3 acetylation induced by ethanol; however, the mitogen-activated protein kinase (MAPK) cascades may influence histone 3 acetylation without involving HAT activity. In similar experiments, acetate-induced acetylation was not affected by MEK or JNK inhibitors further indicating that the MAPK pathway was not downstream of acetate in the process of acetylation. The precise role of MAPKs in ethanol-induced histone acetylation needs further investigation[13]. Another study in which rats were fed ethanol intragastrically demonstrated that levels of P300, a histone acetyltransferase, increased corresponding to the peaks in urinary alcohol levels, and this correlated with an increase in histone 3 acetylation at lysine 9[14].

A recent study by Day's group very elegantly demonstrated that the formation of acetate from alcohol is key to the process of alcohol-induced inflammatory gene expression by promoter histone acetylation in acute alcoholic hepatitis[15]. Treatment of Monomac6 cells (human macrophage cell line modeling Kupffer cell responses in ethanol) with ethanol increased global H3 and H4 acetylation and reduced HDAC activity significantly. Ethanol also induced the expression of acetyl-coA synthetases (ACSS1 and 2), the enzymes required for conversion of acetate to acetyl-coA, the substrate for acetylation reactions. Corresponding to this effect, increased acetylation was observed at the promoters of inflammatory cytokines IL-6 and tumor necrosis factor (TNF)-α, with an increase in their mRNA expression. Notably, when these experiments were performed using acetate, these effects could be reproduced. What underscores the critical role of acetate in these ethanol-induced effects is that inhibition of ethanol metabolism to acetate using 4-methylpyrazole (4-MP) completely abrogated the effects and histone acetylation remained at baseline[15]. This confirms that acetate is indeed, the mediator of alcohol-induced histone acetylation.

Although there are no published reports regarding the exact mechanisms by which acetate formed by ethanol metabolism may affect histone acetylation, some hypotheses have been suggested. Acetate may increase HAT activity simply by increasing substrate availability for the reaction. Since acetate is also the product of deacetylation reaction, free acetate may cause feedback inhibition of HDACs[15]. It should also be noted that most of the studies done with regard to ethanol-induced acetylation measure global acetylation and studies focusing on specific genes affected by alcohol metabolism are only beginning to be performed. One such gene examined in hepatocytes is ADH1 (Class 1 alcohol dehydrogenase)[13], while TNFα and IL-6 have been examined in Monomac6 cells[15] in response to alcohol. Also of interest are the findings that alcohol seems to have an effect on the acetylation at certain lysine residue, such as lysine 9 on H3 (H3K9), but not others (H3K14, H3K18)[9,12]. Further research is required to explore the significance and relevance of these findings.

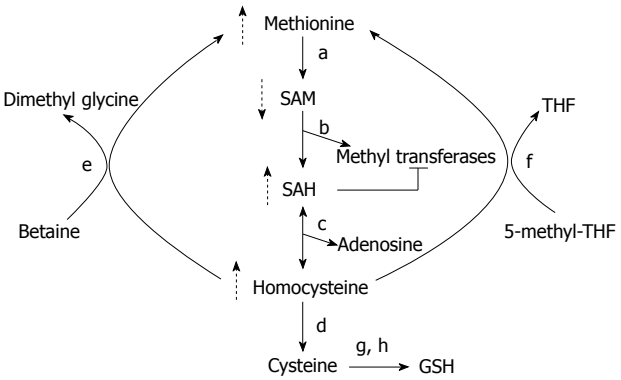

Figure 2 S-adenosylmethionine metabolism in alcohol-induced liver disease. Effects of alcohol are indicated by dotted arrows; a: Methionine adenosyltransferase; b: Enzymes involved in transmethylation reactions; c: S-adenosylhomocysteine (SAH) hydrolase; d: Cystathionine-β-synthase; e: Betaine homecysteine methyltransferase; f: Methionine synthase; g: glutamate-cysteine synthetase; h: Glutathione (GSH) synthetase. SAM: S-adenosylmethionine; THF: Tetrahydrofolate.

ALCOHOL AND SAM

SAM is the one of the most widely used cofactors in nature, probably second only to ATP[16]. The liver is the main source of SAM in humans, and is also largely the site where SAM is metabolized by methyltransferases to S-adenosylhomocysteine (SAH)[17,18] (Figure 2). SAH is a potent inhibitor of all methyltransferases, and needs to be promptly eliminated by the body by a reaction catalyzed by SAH hydrolase[19]. SAM is an essential molecule that is vital to numerous cellular processes and is the principal biological methyl donor required for methylation of histones; as also other proteins, DNA, RNA, biogenic amines and phospholipids. It gives away its high energy methyl group to methyltransferases in transmethylation reactions, and thus, plays a central role in the epigenetic regulation of genes that are controlled by histone or DNA methylation[19]. The ratio of SAM to SAH is a critical determinant of the efficiency of transmethylation reactions and hence this ratio is referred to as the cellular

methylation potential[20]. SAM dependent methyltransferases is a broad class of enzymes that contains over a hundred genes[21,22]. Besides, SAM also contributes to gene regulation by methylation of non-histone proteins such as tumor suppressor p53, transcriptional factor TAF10 and the receptor for angiogenic factor VEGF, VEGFR1[23].

Alcohol causes SAM deficiency

SAM deficiency in alcohol-induced liver disease was first described in the early 1980s[24]. Hepatic MAT activity was found to be subnormal in alcohol-dependent individuals, blocking the conversion of methionine to SAM and resulting in hypermethioninemia[25-27]. Alcohol-dependent individuals often display glutathione (GSH) deficiency because GSH synthesis requires SAM[27,28]. Hepatic SAM depletion in response to chronic alcohol consumption has been studied both in humans and in animal models. SAM deficiency has been associated with hepatitis in humans[29], and different stages of alcohol-induced liver injury in rats[30], baboons[31] and micropigs[32].

Ethanol may deplete hepatic SAM by more than one mechanism (Figure 2). Ethanol administration reduces hepatic MAT activity by the oxidation or nitrosylation of the cysteine residue at position 121 and this may be affected by the reactive oxygen and nitrogen species generated during ethanol metabolism[33,34]. MAT activity has also been shown to be reduced due to decreased gene expression of MAT1 (liver specific MAT) in alcoholic hepatitis patients[29] and ethanol-fed micropigs[35]. In another study in rats, chronic ethanol administration decreased SAM levels and glutathione concentration without affecting MAT and it was proposed that SAM consumption was increased to fuel glutathione synthesis[36]. In addition to increased consumption, SAM deficiency may occur because its synthesis may be inhibited by the unavailability of methionine, the endogenous precursor of SAM. Chronic ethanol administration can influence methionine synthesis by decreasing methionine synthase (MS) activity, and the hepatic levels of folate and betaine[35,37-39]. Thus, alcohol consumption can affect aspects of SAM production and metabolism at multiple levels to result in hepatic SAM deficiency in ALD.

SAM and histone modifications

Unlike histone acetylation, which is generally a transcriptionally permissive modification, histone methylation is known to exhibit differential effects that depend on the position of the particular residue that is modified. Methylation of the lysine at position 9 on H3 (H3K9) is a silencing event[40,41], and opposes the transcription-activating acetylation (H3K9Ac) of the same residue. On the other hand, methylation of lysine 4 on H3 (H3K4) activates transcription, and trimethylation at this residue (H3K4Me3) is strongly correlated with active transcription[42]. Also, in contrast to histone acetylation, histone methylation appears to be a more permanent mark and is relatively irreversible[43,44].

The effect of ethanol on histone and DNA methylation has been studied in cell culture and animal studies[9,10,45,46]. However, in comparison to histone acetylation, studies involving methylation changes with ethanol are only beginning to be documented. Pal-Bhadra *et al*[45] examined the effect of ethanol on H3 methylation in primary rat hepatocytes, and reported contrasting methylation patterns at H3K9 and H3K4 following ethanol treatment. H3K9 dimethylation was decreased whereas H3K4 dimethylation was increased. Further analysis showed that K9 methylation was associated with the promoters of ethanol-downregulated genes [L-serine dehydratase (Lsdh) and Cytochrome P450 2C11 (CYP2C11)] and K4 methylation with those of ethanol-upregulated genes [Alcohol dehydrogenase-1 (Adh-1) and Glutathione S-transferase Yc2 (GST-Yc2)] in these cells[45]. In earlier studies in rat liver and rat hepatic stellate cells, ethanol had been shown to increase acetylation at H3K9 with little, if any, change in methylation at the same residue[9,10]. In another recent study using a chronic rat model for ethanol (intragastric feeding model), a significant increase was noted in dimethyl histone 3 lysine 4 (H3K4Me2). Trimethylation of histone 3 lysine 27 (H3K27Me3), a transcriptionally silencing modification, also increased significantly after chronic ethanol feeding[46]. Similarly, the effect of SAM treatment on histone methylation[47,48] and gene expression[49] has been documented in some studies. When SAM was administered along with ethanol intragastrically to rats for a month (chronic model), SAM remarkably attenuated the ethanol-induced liver injury[48]. Histone 3 trimethylation at lysine 27 (H3K27Me3) was significantly increased with SAM treatment, irrespective of ethanol feeding. SAM also prevented most of the changes in gene expression caused by ethanol feeding. Since H3K27 trimethylation correlates with gene repression, it was postulated that SAM stabilized global gene expression and prevented the blood alcohol level (BAL) cycle through this epigenetic modification[48]. Other experiments in RAW and Kupffer cells show that SAM can inhibit the LPS-stimulated expression of pro-inflammatory genes such as TNF-α and i-NOS at the transcriptional level. In these studies, it was found that LPS increased the trimethylation of H3K4 at the promoters of these genes, and treatment with SAM reversed this effect[47]. Overall, research thus far indicates that SAM deficiency may be an important mediator of histone modifications in ethanol-induced liver disease.

ALCOHOL AND NAD$^+$

The ubiquitous biological molecule, NAD$^+$, was first discovered in 1906, and since then, has been widely studied for its ever-expanding repertoire of cellular functions. NAD$^+$ is best known for its role in oxidation-reduction reactions in cell metabolism[50]. NAD$^+$ is also the precursor of the important second messenger cyclic ADP-ribose[51], and more recently, has been found to be absolutely essential for the protein deacetylase activity of sirtuins[52,53]. Sirtuins or Sir2 proteins are a class of histone deacetylases and in addition to their role in gene transcription, are also involved in the regulation of ageing and metabolic processes[54]. Thus, from being a coenzyme in redox reactions, NAD$^+$ has come a long way, now being called

a critical metabolic regulator of transcription, longevity, calorie-restriction mediated life-span extension and several age-associated diseases, including diabetes, cancer and Alzheimer's disease[55].

Alcohol depletes NAD+

Alcohol metabolism utilizes NAD^+ at the very initial steps of breakdown[1]. NAD^+ is used up both when alcohol dehydrogenase converts alcohol to acetaldehyde and when acetaldehyde dehydrogenase further converts it to acetate. In both these reactions, NAD^+ is reduced to NADH. Several acute effects of ethanol are caused by the reduction of the NAD^+/NADH ratio in the liver, as a consequence of ethanol metabolism. An increased NAD^+/NADH ratio in the liver disrupts fatty acid oxidation and can induce ketogenesis, lactic acidosis, hyperuricemia and hypoglycemia[56]. Even after conversion of ethanol to acetate, NAD^+ continues to be consumed. Acetate forms acetyl-coA, which reduces NAD^+ to NADH once it enters the Krebs cycle. Chronic ethanol consumption also recruits the CYP2E1 pathway for metabolism, which adds to the imbalance in the hepatic redox state by reducing NAD^+ and increasing hydroxyl radicals[57]. The oxidative stress and reactive oxygen species (ROS) caused by ethanol consumption are only aggravated by the poor nutritional status in chronic alcoholics, and play a major part in depleting NAD^+ and advancing liver injury[58].

NAD+ and histone modifications

The NAD^+/NADH ratio in the liver likely plays a major role in the regulation of histone modifications and thus, gene transcription/silencing[59]. Histone deacetylases are categorized into three main classes, and class Ⅲ HDACs or sirtuins (SIRT), are activated only in the presence of NAD^+. In sirtuin-mediated deacetylase reactions, NAD^+ is hydrolyzed into nicotinamide and accepts the acetate moiety, O-acetyl-ribose. The nicotinamide formed is a potent inhibitor of sirtuin HDAC activity. Thus, the histone deacetylase activity of sirtuins is intricately controlled by NAD^+ metabolism, requiring NAD^+ for catalysis and being inhibited by nicotinamide. Ethanol, as discussed earlier, increases histone acetylation in the liver. The mechanisms underlying this effect of ethanol are not well characterized; however, there are reports of increased HAT activity[10] and/or decreased HDAC activity[11]. It may then be postulated that ethanol-induced inhibition of HDACs is due to the depletion of NAD^+ caused during its metabolism. Ethanol has already been shown to inhibit sirtuin expression and activity in other studies in the liver[60,61]. Chronic administration of ethanol in mice reduced hepatic SIRT1 protein levels and significantly inhibited its deacetylase activity in a recent study by You *et al*[61]. In an earlier report, ethanol was shown to increase SREBP-1c (Sterol regulatory binding protein-1c) lysine acetylation and transcriptional activity in rat H4IIEC3 cells, and this effect was at least in part, mediated by SIRT1 inhibition[62]. Results from another study reaffirm the link between ethanol consumption and SIRT1 reduction, and in this study ethanol reduced hepatic SIRT1 mRNA expression to half its baseline levels[60]. In addition, independent studies have shown that oxidative stress can inhibit HDACs[63-66].

In light of these findings, it can be hypothesized that the interplay between NAD^+ levels, reactive intermediates and oxidative stress will impact histone modifications and gene expression in ALD.

ALCOHOL AND ZINC

Zinc is an essential trace element and is vital in carbohydrate and protein metabolism, glucose control, wound healing, the immune system, digestion, fertility, and growth[67-69]. Zinc plays an important role in controlling gene expression, antioxidant defense and DNA repair. Abundant changes in gene expression in dietary zinc deficiency have been profiled in several tissues, including the liver[70,71], although the mechanisms have not been investigated. Zinc is an essential cofactor for over 300 enzymes; of particular relevance to this review are the zinc-requiring enzymes, namely (1) histone deacetylases (HDACs) that catalyze the removal of an acetyl group from lysines on histones protein tails, thereby increasing the accessibility of nucleosomal DNA and resulting in transcriptionally active chromatin; and (2) histone demethylases that demethylate Lys residues on histones and modulate gene expression.

Alcohol causes zinc deficiency

Zinc deficiency is often observed in chronic alcoholics and approximately 30%-50% of alcoholics are thought to have low zinc status[67,69], possibly due to decreases in intestinal absorption, increased urinary excretion and/or inadequate dietary zinc intake. Clinical studies have demonstrated that zinc concentrations in both serum and liver were significantly reduced in patients with alcoholic steatosis, hepatitis, and cirrhosis[72-75]. Indeed, zinc insufficiency is one of the most commonly observed nutritional manifestations of alcoholic liver disease[76]. Zinc depletion in the liver has also been documented in animal models of ethanol-induced liver injury[77-82]. Investigations of zinc metabolism in alcoholics has demonstrated that ethanol consumption leads to increased Zn excretion in urine[83] and decreased Zn absorption from intestine[84,85]; the latter is also seen in a chronic ethanol feeding animal model[86].

Zinc and histone modifications

While class Ⅲ HDACs require the cofactor NAD^+ for their deacetylase function, the class Ⅰ, Ⅱ and Ⅳ HDACs are structurally distinct and require zinc for their deacetylase function[87]. A suboptimal zinc concentration, as is observed in alcoholic individuals, is highly likely to significantly decrease the activity of HDACs, leading to altered gene expression. Indeed, the alcohol-induced decrease in HDAC activity observed by others[88] and us [unpublished results] may be attributed, at least in part, to lowered zinc levels. A direct effect of zinc on epigenetic histone changes was demonstrated in a recent study using chromatin immunoprecipitation assays, wherein zinc treatment rapidly decreased Lys4-trimethylated and Lys9-acetylated histone H3 in the metallothionein1 (MT1) promoter and

decreased total histone H3. Also, the micrococcal nuclease sensitivity of the MT1 promoter was also increased by zinc, suggesting that the chromatin structure in the MT1 promoter may be disrupted by zinc-induced nucleosome removal[89]. Another *in vitro* study showed that p21 transcription was downregulated by lowered zinc in HepG2 cells[90]. Zinc deficiency led to a reduction in acetylated histone-H4 on the p21 promoter resulting in reduced p21 promoter accessibility, which contributed to the decrease in p21 promoter activity and the downregulation of p21 mRNA and protein expression in zinc-depleted HepG-2cells. Specifically, the amounts of acetylated histone-4 associated with the proximal and distal p21 promoter regions were decreased in severe zinc-deficient (73% and 64%, respectively) and mild zinc deficient (82% and 77%, respectively) cells compared with zinc-normal (100% and 100%, respectively)[90].

A recently discovered histone lysine demethylase, LSD2, was shown to not only contain a CW-type zinc finger motif, but also to bind zinc with 3:1 molar ratio (zinc: protein), suggesting that zinc maybe important for its activity[91]. Also, a zinc finger motif located at the end of the conventionally defined JmjC domain of histone demethylases, such as jumonji-type JMJD2A, is thought to be essential for enzymatic function[92]. Changes in zinc status as seen with chronic alcohol consumption are expected to cause dramatic alterations in gene expression, leading to phenotypic changes. In addition to direct epigenetic effects, zinc deficiency is also known to reduce the utilization of methyl groups from SAM in rat liver, resulting in genomic DNA hypomethylation and histone hypomethylation[93,94]. This occurs due to the fact that the enzyme betaine-homocysteine S-methyltransferase (BMHT) is a zinc metalloenzyme[95]. Overall, we believe that alcohol consumption-induced zinc deficiency may greatly impact gene expression *via* direct and indirect epigenetic histone modifications and modulation of chromatin structure and gene expression.

In addition to the nutritional alterations mentioned in this review, alcohol is known to cause disturbances in other nutrients, which may also play a role in the epigenetic changes effected by alcohol. Alcohol has also been shown to influence other histone modifications, such as glycation[96] and phosphorylation[97]. The significance of these modifications in relation to gene expression is, however, not clear.

CONCLUSION

Alcohol metabolism is inextricably connected to the regulation of key nutrient metabolites in the liver. There is a growing body of literature suggesting a role for the complex interplay between alcohol-induced nutrient changes, histone modifications and gene expression. It is becoming widely accepted that specific aberrant patterns of histone modifications play a fundamental role in chromatin structure and function contributing to the development of disease processes. Epigenetic histone modifications provide a plausible link between alcohol-mediated nutrient alterations and pathogenic gene expression. However, in ALD, the precise contribution of histone modifications in the alteration of expression of specific genes remains largely unknown. Clearly more advances are needed and will be witnessed in this area that will enhance our knowledge about the epigenetic mechanisms underpinning ALD pathogenesis and lead to the development of relevant therapeutic strategies.

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