Chapter 10
Epigenetic Alterations due to Trichloroethylene

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Abstract Trichloroethylene (TCE) is a volatile, water soluble, chlorinated hydrocarbon used as an intermediate in chemical synthesis. Wider use in the past and inappropriate disposal has resulted in large amounts of TCE in soil and water pollution including in hundreds of Superfund hazardous waste sites. Most TCE in human exposure comes through inhalation and drinking water where the main sources are occupational as well as contaminated ground water and soil.

As heritable modifications of DNA and chromatin, epigenetic changes can occur near the time of toxic exposure and remain for years, eventually contributing to overt disease such as cancer or autoimmunity. TCE could affect epigenetics through effects on metabolism, mitochondrial function, cellular signaling and formation of protein adducts. In this chapter, we mainly consider the epigenetic modifications of DNA and histone methylation and histone acetylation.

TCE can be toxic to many different organ systems in humans and animal models. Epigenetic effects have been demonstrated in animal models of TCE induced cancer, autoimmunity, neuropathy and congenital heart defects. TCE causes DNA hypomethylation in rodent models of liver cancer and interventions that restore methylation can also prevent the cancer. We showed that TCE exposure in a mouse model of autoimmune hepatitis causes increased expression of endogenous retrovirus-like sequences, changed expression of DNA methyltransferases and global DNA hypomethylation in CD4+ cells. Findings in this mouse model are discussed in light of the long-established activation of endogenous retrovirus expression in autoimmune diseases. We also studied the effects of TCE on behavior, gene

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expression, metabolism and epigenetics in the plasma and brains of mice. TCE caused a more oxidized cellular environment, compromised methyl metabolism and lower DNA methylation.

Parallel analyses in multiple tissues and the development of biomarkers of TCE exposure are just some of the approaches that will help us understand the long-term health risks of TCE. This should also assist the development of effective interventions to reverse the epigenetic effects of TCE exposure with the goal of preventing diseases such as cancer and autoimmunity.

Keywords Trichloroethylene • Epigenetics • Methylation • Acetylation • Cancer • Autoimmunity • Heart defects • Neuropathy • S-adenosylmethionine • Acetyl coenzyme A • Endogenous retrovirus • Ethanol • Bisphenol A

Abbreviations

5MC	5-methylcytosine
Ac	Acetyl group
AcCoA	Acetyl-coenzyme A
AIH	Autoimmune hepatitis
ATSDR	Agency for Toxic Substances and Disease Registry
B6C3F1	C57B6 strain x C3H strain F1 generation mice
BHMT	Betaine-homocysteine methyltransferase
BPA	Bisphenol A
BPS	Bisphenol S
CH3	Methyl group
DCA	Dichloroacetate
DNMT	DNA methyltransferase
EPA	Environmental Protection Agency (US)
ERV	Endogenous retrovirus
FAS	Fetal alcohol syndrome
GSH	Glutathione (reduced)
GSSG	Glutathione (oxidized)
H4K12	Histone H4 lysine 12
HAT	Histone acetyltransferase
HCY	Homocysteine
HDAC	Histone deacetylase
HERV-K	Human endogenous retrovirus virus K
IAP	Intracisternal A particle
MPTP	N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MuERV	Murine endogenous retrovirus
NTP	National Toxicology Program
PD	Parkinson's Disease

RT-PCR	Real time PCR
SAH	*S*-adenosylhomocysteine
SAM	*S*-adenosylmethionine
TaClo	1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline
TCA	Trichloroacetate
TCE	Trichloroethylene

Trichloroethylene (TCE) is a volatile, water soluble, chlorinated hydrocarbon now used primarily as an intermediate chemical for the production of refrigerants. In the past, TCE was used for a wide variety of additional purposes including industrial degreasing, anesthesia, dry cleaning and food processing (including coffee decaffeination) (Doherty, Chap. 1). Despite its declining use, TCE is still widely used as a metal degreaser and in some other applications. The US Environmental Protection Agency (EPA) estimated that 2.7 million pounds of TCE were disposed of, or released, in the United States in 2011 (http://iaspub.epa.gov/triexplorer/tri_release.chemical). According to the Agency for Toxic Substances and Disease Registry (ATSDR), large amounts of TCE remain in soil and water pollution including in over 800 National Priorities List (Superfund) hazardous waste sites (ATSDR 1997 and 2013).

Aside from occupational exposures, most current human exposure comes from contaminated ground water used for drinking, from inhaling TCE while using contaminated water (e.g. showering) or from contaminated indoor air caused by soil vapor intrusion (Forand et al. 2012). Many United States military personnel and their families have been exposed to TCE through drinking water at Camp Lejeune, North Carolina and elsewhere (ATSDR 1997 and 2013, http://www.atsdr.cdc.gov/sites/lejeune/tce_pce.html).

Remediation of TCE-contaminated soil and ground water is costly and time consuming. Thus, existing pollution and the continued production and use of TCE-containing consumer products means that human exposure to this chemical will continue, at least at low levels, for the foreseeable future. This makes understanding the long-term health effects of chronic TCE exposure particularly important. As described in other chapters in this book, TCE has many adverse health effects in humans. These include cancer and probably also neuropathy, heart defects and autoimmunity. Some of these effects are most obvious in animal models where the effects of controlled, intentional exposure can be quantified (Chiu et al. 2013). The effects of toxic compounds on long-term health can include epigenetic changes which occur near the time of toxic exposure but remain for years and contribute to the later overt presentation of disease (Poirier 2002; Waalkes et al. 2004; Cooney 2007; Cooney and Gilbert 2012; Ray and Richardson 2012; Blusztajn and Mellott 2013). Toxicant exposures just before and during gestation are of particular concern since the embryo and fetus are especially sensitive to epigenetic alterations (Wolff et al. 1998; Waalkes et al. 2004; Cropley et al. 2006; Cooney 2009; Davison et al. 2009; Downing et al. 2011).

10.1 Epigenetics

Epigenetics consists of heritable chromatin modifications that affect gene expression and help guide the development and health of plants and animals throughout their lifecycles. A broad range of factors affect epigenetics. These include exposure to certain toxicants such as TCE. However, there are few data on the effects of TCE on DNA methylation and fewer yet on some other epigenetic modifications such as histone methylation and histone acetylation. The available data will be discussed later in this chapter. Epigenetics has been extensively reviewed (Cooney 2007, 2010; Cooney and Gilbert 2012; Dawson and Kouzarides 2012), so only a few general points will be discussed here. Epigenetics has been much studied in cancer and the knowledge and many of the approaches from that work can be applied to toxicology research.

For vertebrates, CG dinucleotides (called CpGs) are the principal targets of DNA methyltransferases (DNMTs) which use the methyl group donor S-adenosylmethionine (SAM) to methylate DNA at the five position of cytosines to form 5-methylcytosine (5MC, Ooi et al. 2009). This reaction also yields the metabolite S-adenosylhomocysteine (SAH) which is often recycled back to SAM by methyl metabolism. Because the CpG sequence is a palindrome, methylation patterns on parental DNA strands can be copied onto daughter strands during cell division by DNMT1. This process is sometimes called maintenance methylation. DNA is also sometimes *de novo* methylated by DNMT1 and by the dedicated *de novo* DNMTs, DNMT3a and DNMT3b. These heritable DNA methylation patterns can propagate long-term changes in gene expression in generations of daughter cells and sometimes in generations of animals (Cropley et al. 2006; Cooney 2007; Champagne and Curley 2009; Li et al. 2011). 5MC near transcription start sites and other nearby regulatory regions tends to silence gene expression (Weaver et al. 2005; Ooi et al. 2009). This works in part by preventing transcription factor access and attracting methylated DNA binding proteins. Silence is maintained by protein complexes that also modify histones to reinforce transcriptional silence in some cases or "poise" a region for activation in other cases (Dawson and Kouzarides 2012). DNA demethylation can occur when 5MC is removed by base excision repair and/or oxidation of the methyl group. A series of increasingly oxidized products of 5MC, namely 5-hydroxymethylcytosine, 5-formylcytosine and 5-carboxycytosine are all found in mammalian DNA (Seisenberger et al. 2013). Demethylation is especially prominent post-fertilization and in primordial germ cells, both times when DNA methylation patterns are extensively rewritten (Hackett et al. 2013; Seisenberger et al. 2013).

Some of the major DNA binding proteins of chromatin, the histones, are also enzymatically methylated using SAM (Kooistra and Helin 2012; Dawson and Kouzarides 2012). Whether histone methylation promotes or silences gene activity depends on the specific methylation site(s). Most histone methyltransferases, demethylases and histone binding proteins are site and methylation specific. There are greater varieties and specificities of histone methyltransferases, histone

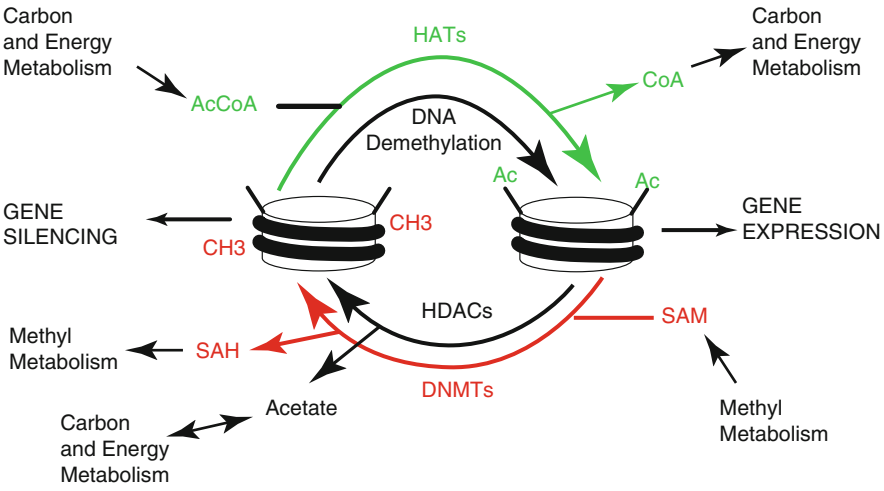

Fig. 10.1 Histone acetylation and DNA methylation: two major epigenetic factors affecting gene expression. Histones in chromatin (nucleosomes) are shown as short cylinders with histone H3 and H4 tails projecting up. Acetyl groups from acetylCoA are used by histone acetyltransferases (*HATs*) to acetylate these histone tails and promote gene expression. This process is reversed by HDACs that remove the acetyl groups. DNA in chromatin (nucleosomes) is shown looping around the histones. Methyl groups from SAM are used to by DNMTs to methylate DNA and silence gene expression. This process is reversed by DNA demethylation processes that result in unmethylated cytosine (Adapted from Cooney (2010))

demethylases and methylated histone binding domains than there are for corresponding enzymes and binding domains for histone acetylation or methylation of DNA.

Gene activity can also be regulated by histone acetylation which depends on histone acetyltransferases (HATs), histone deacetylases (HDACs) and the acetyl donor acetyl-coenzyme A (AcCoA, Cooney 2010). Gene activity is nearly always promoted by histone acetylation. Figure 10.1 shows the dependence of DNA methylation on methyl metabolism and of histone acetylation on carbon and energy metabolism and illustrates how DNA methylation and histone acetylation have largely opposite roles in regulating gene expression.

Epigenetic alterations are primarily mediated by covalent modifying enzymes that add or remove methyl groups, acetyl groups and other groups from chromatin in combination with enzymes and other proteins that recognize these modified sites and recruit protein complexes that then facilitate transcription or silencing. The known epigenetic modifications of DNA are 5MC and its methyl oxidized forms, as described above. In contrast, there are many histone modifications in addition to methylation and acetylation (Dawson and Kouzarides 2012) and some RNAs have prominent roles in epigenetics (Kurokawa et al. 2009; Collins et al. 2010; Lee 2012). Although histone methylation has high specificity and is often thought to lead in epigenetic processes, gene expression is often linked to DNA methylation

and/or histone acetylation, and gene expression can often be changed by metabolites or drugs targeting DNA methylation or histone acetylation (Weaver et al. 2005; Eilertsen et al. 2008; Champagne and Curley 2009; Peleg et al. 2010; Cooney 2010).

Many genes will have DNA and histone modifications consistent with their transcriptional activities; however some "bivalent" genes have modifications or complexes with silencing and activating features at the same time (Dawson and Kouzarides 2012). These "bivalent" genes are poised to become transcriptionally active. As discussed in the rest of this article, most epigenetics work to date on TCE has been done on DNA methylation and histone methylation and acetylation.

10.2 Effects of TCE on Metabolism and Other Mechanisms for Epigenetic Change

The likelihood that TCE impacts DNA methylation is bolstered by its previously identified effects on pathways that regulate epigenetic alterations. For example, TCE has been shown to affect methyl metabolism which in turn regulates SAM levels and is important for epigenetics (Gilbert et al. 2009; Blossom et al. 2012, 2013).

TCE affects antioxidant defenses where it depletes reduced glutathione (GSH) and cysteine and causes other changes all consistent with TCE producing oxidative stress (Blossom et al. 2012, 2013, discussed below in Sect. 10.6). Oxidative stress can compromise methyl metabolism when homocysteine (and indirectly methionine via SAM and SAH) is drawn through the transsulfuration pathway to make cysteine for glutathione synthesis and antioxidant defenses. Examples of this have been described in liver (Mosharov et al. 2000), brain (Vitvitsky et al. 2006) and plasma (Melnyk et al. 2012). Compromise of methyl metabolism occurs because production of cysteine for glutathione synthesis depletes levels of SAM and its precursors methionine, homocysteine (HCY) and SAH. This leaves less SAM available for cellular methylation reactions such as DNA and histone methylation.

TCE also affects mitochondrial function including oxidative phosphorylation (Lash et al. 2001; Gash et al. 2008; Sauerbeck et al. 2011) which would be expected to affect overall energy metabolism. Energy metabolism and mitochondrial function could also have effects on epigenetics by, for example, affecting the levels of AcCoA available for histone and transcription factor acetylation and gene activity (Cooney 2008, 2010; Wallace et al. 2010). Zeisel (2013) discusses numerous connections between energy metabolism and methyl metabolism and potential effects on epigenetics. Thus, there are multiple pathways by which TCE could impact the pathways that affect epigenetics. Significant effects of TCE on a variety of normal, endogenous metabolites measured in plasma, serum and urine (Blossom et al. 2012; Fang et al. 2013b) suggest that TCE's effects are systemic and likely affect multiple organs.

When evaluating the effects of TCE on epigenetic pathways, TCE metabolites must also be considered (Lash et al. 2000; Kim et al. 2009; Chiu et al. 2013, Gilbert, Chap. 2). TCE metabolism is complex and has multiple steps including oxidation (by cytochrome P450 enzymes and alcohol dehydrogenase),

glucuronidation (by UDP-glucuronosyltransferases) and glutathione conjugation (by glutathione S-transferases) (Lash et al. 2000). Major metabolites include trichloroacetate (TCA), trichloroethanol and chloral hydrate (Lash et al. 2000). However metabolism and therefore metabolite levels differ with routes of exposure, tissue, species, sex and other factors (Abbas and Fisher 1997; Lash et al. 2000; Clewell et al. 2000; Kim et al. 2009). Just a few TCE metabolites are discussed in this chapter because they relate to diseases caused by TCE (such as cancer and Parkinson's disease).

For example, the TCE metabolite dichloroacetate (DCA) has important effects on energy metabolism, mitochondrial function and apoptosis (Bonnet et al. 2007) and tends to activate mitochondria in cancer cells. Because of this, DCA is studied as an anticancer agent (Sun et al. 2010; Strum et al. 2013). Because DCA activates mitochondria and opens the pathway to burn AcCoA (Bonnet et al. 2007) it may well affect epigenetics (especially histone acetylation, Cooney 2008). On the other hand, when given to healthy mice, DCA is a liver carcinogen (Bull et al. 1990; Herren-Freund et al. 1987; Pereira et al. 1997, as discussed below in the Sect. 10.3). Thus the actions of DCA deserve attention so that we can understand its toxic effects as well as its therapeutic potential.

There are many ways that toxicants can interfere with epigenetics. These include alterations in metabolism, cell signaling, mitochondrial function, enzyme activities, and endogenous retrovirus (ERV) activity (Cooney and Gilbert 2012). TCE could affect epigenetics in these ways and through changes in the expression of genes involved in epigenetic control and direct modification of proteins causing changes in their enzymatic or other activities.

The effects of toxicants such as TCE on the various pathways that regulate epigenetics are just beginning to be identified. Once obtained, this important mechanistic information will help predict long-term effects of toxicant exposure, which may lead to the development of interventions. Many clues concerning possible TCE-induced epigenetic alterations come from cancer studies which will be discussed next.

10.3 Cancer

The EPA considers TCE a known carcinogen (USEPA 2011). Numerous studies indicate that occupational exposure to TCE causes cancer including kidney cancer (Jollow et al. 2009; Karami et al. 2012; Hansen et al. 2013, Wartenberg, Chap. 9). Studies, including those of the National Toxicology Program (NTP), show that TCE causes hepatocarcinoma in mice but not in rats (NTP 1988 and 1990; Bull 2000). For example, in a 2 year study of B6C3F1 mice given 1,000 mg/kg TCE by corn oil gavage, hepatocellular carcinoma rates for males were 8/48 in controls and 31/50 in TCE dosed ($P<0.001$) and for females 2/48 in controls and 13/49 in TCE dosed ($P<0.005$) (NTP 1990). Cytomegaly of the kidney (toxic nephrosis) was seen in nearly all TCE dosed B6C3F1 mice and Fischer 344 rats (both sexes) but in none of the controls. Some kidney cancer was seen Fischer 344 rats but its incidence was too

low to prove carcinogenicity of TCE (NTP 1990). Some other studies report TCE as a cause of cancer in rats (NTP 2011).

TCE's identification as carcinogenic but not mutagenic is important since in general, all cancers studied in humans and rodents have extensive epigenetic changes (Cooney 2008; Fernandez et al. 2012). Cancers typically also have extensive metabolic, genetic and chromosomal rearrangements (Bonnet et al. 2007; Cooney 2010; Wallace et al. 2010; Vogelstein et al. 2013). Few data are available on the epigenetics of human cancers that likely arose from TCE exposure (Brauch et al. 1999; Banks et al. 2006). However, promising approaches are being developed to address this. For example, Ellsworth et al. (2012) used mutational profiling to find significant differences between brain cancers in human subjects exposed to chlorinated solvents and subjects judged to have sporadic brain cancers.

However, our greater interest is in early epigenetic changes due to TCE that may later lead to cancer. Identifying these changes gives us the opportunity to reverse them early on and prevent the cancer. Mice have been used for such studies because, as discussed above, chronic TCE exposure causes hepatocarcinoma (NTP 1990). To address early events that may lead to cancer, mouse models have been used to look at acute effects of TCE. Several genes that promote cell proliferation, often called oncogenes, tend to be highly expressed in cancers and, importantly, in precancerous lesions. In two of these genes, *c-jun* and *c-myc*, TCE in acute high-doses (1,000 mg/kg/day), given to female B6C3F1 mice for 5 days, decreased DNA methylation of *c-jun* and *c-myc* promoters in the liver. This correlated with increased *c-jun* and *c-myc* gene expression in the liver (Tao et al. 2000a). When mice were given methionine (to increase their SAM levels, Wang et al. 2001) just after TCE dosing, they did not show this *c-jun* and *c-myc* hypomethylation. Similar results were seen when giving mice either DCA or TCA, both metabolites of TCE. In related (but not identical) study designs, TCE and TCA increased DNMT activity in liver when female B6C3F1 mice were first treated with the tumor initiator *N*-methyl-*N*-nitrosourea (Tao et al. 2000b). Overall, this indicates that in the female B6C3F1 mouse model of hepatocarcinoma, short-term effects can be reversed with methionine. Because many human exposures to TCE are in the past, it would be practical to know what treatments would reverse TCE's effects in this mouse model in the weeks and months after TCE exposure.

TCE metabolites DCA and TCA are also liver carcinogens in mice (Bull et al. 1990; Herren-Freund et al. 1987; Pereira et al. 1997). Methionine supplementation prevented most DCA induced cancer and hypomethylation (Pereira et al. 2004). This pattern of oncogene hypomethylation, oncogene overexpression, compromised methyl metabolism and increased DNMT enzyme activity (although sometimes lower expression of *Dnmt* genes) have been shown for liver cancer in rodent models treated with toxicants or methyl deficient diets (Wainfan and Poirier 1992, Pascale et al. 2002; Phillips et al. 2009; Pogribny et al. 2012; Frau et al. 2013). Often early effects predisposing to cancer can be prevented or reversed by methyl donors, folate or similar treatments which often, but not always, reduce cancer incidence (Tao et al. 2000a; Pascale et al. 2002; Sie et al. 2011; Gonda et al. 2012; Fang et al. 2013a; Frau et al. 2013).

One of several hallmarks of cancers is extensive genome rearrangement (Vogelstein et al. 2013) which may be promoted by several factors including transcriptional activation and transposition of ERVs and other interspersed DNA repeats (Romanish et al. 2010). This activation of ERVs probably results from loss of epigenetic silencing normally found on most ERVs and interspersed DNA repeats (Cherkasova et al. 2011). However in most cases it is unknown whether this deregulation occurs prior to cancer, or during cancer development and progression. Of course, the timing of deregulation will help determine whether ERV activation causes some cancers or is mainly involved in later processes such as progression or metastasis (Downey et al. 2012). Although data is not available on ERV activation in TCE induced cancers, when investigating the causes of autoimmunity, we found ERV activation in the T-cells of TCE-treated mice (Gilbert et al. 2012). The activation of ERVs by TCE in tissues prone to TCE-induced cancer has yet to be reported.

Starting from these data, interventions (methionine, folate and other model epigenetic effectors) should be designed and tested in animal models to prevent long-term adverse effects of TCE, including cancer, and to quantify likely effectors and markers (*c-jun*, *c-myc*, *Dnmt1* and *Dnmt3a&b* gene expression, ERV expression and others) to provide guidance for testing similar interventions in people exposed to TCE.

10.4 Immune Disease

Some forms of immune disease including those associated with autoimmunity have been studied for their epigenetic alterations (reviewed by Cooney and Gilbert 2012). In particular, lupus, whether idiopathic or drug-induced, has been well studied in this regard. In pioneering work, Bruce Richardson and colleagues have shown a range of epigenetic effects from global DNA hypomethylation to gene specific DNA hypomethylation in lupus (Gorelik and Richardson 2010). Further, they reproduced similar effects in mouse models of lupus (Quddus et al. 1993; Yung et al. 1996). Some recent studies have used massively parallel surveys to look for DNA methylation changes in humans with autoimmune disease (Fernandez et al. 2012). These show that, unlike cancer and aging which cause mainly gene-specific hypermethylation, autoimmunity causes a preponderance of gene-specific *hypo*methylation.

TCE exposure has been associated with autoimmune disease in both humans and mouse models (Gilbert, Chap. 2). However, the mechanism by which TCE causes immune disease and other long-term health effects has not been determined and only a few studies have addressed the metabolic and epigenetic effects with TCE induced autoimmunity.

Gilbert et al. (2009) studied autoimmune hepatitis (AIH) in female MRL+/+ mice exposed to TCE (0.5 mg/ml in drinking water). AIH in this mouse model is observable at 26 weeks of TCE exposure and resembles idiopathic AIH in humans. Gilbert et al. measured liver gene expression, endogenous metabolite levels, oxidized proteins, liver microsomal protein specific antibodies and histopathology. Gene array results showed that of 200 genes whose expression was significantly

altered by TCE, 85 % of these showed increases in gene expression. Genes whose expression was increased included several for the metabolism and detoxification of TCE including alcohol dehydrogenases, cytochrome oxidases and glutathione *S*-transferases. At least one of each of these enzyme types was confirmed by real-time PCR (RT-PCR). They also found that betaine-homocysteine methyltransferase (BHMT) gene expression was increased in the array data but this did not reach significance with RT-PCR data. Interestingly however, metabolite analysis showed that SAH levels were significantly decreased and *N*,*N*-dimethylglycine levels were significantly increased, both of which would be an expected outcome of increased BHMT activity. They found no evidence of increased oxidative stress in the livers of TCE treated animals. Overall these results suggest that chronic TCE may improve methyl metabolism in the liver.

Using this same mouse model of AIH, we recently compared control mice with mice treated with TCE (Gilbert et al. 2012). Among other endpoints, we studied expression of *Dnmt* genes and the murine endogenous retrovirus (MuERV) and the related, ERV-like intracisternal A particle (IAP) repeats. ERVs are often overexpressed in autoimmunity (Perl et al. 2010) and their expression is controlled by epigenetics including 5MC (Walsh et al. 1998; Gaudet et al. 2004; Kato et al. 2007). We compared splenic CD4+ T cells from control mice with those from mice that we treated for 12 weeks with 0.5 mg/ml TCE in drinking water. After stimulating both groups of cells for 24 h we observed IAP expression that was over 8-fold higher and MuERV expression that was over 2.5-fold higher in TCE treated mice ($p<0.05$). *Dnmt1* expression was significantly higher and *Dnmt3a* expression several fold lower with TCE treatment. In some tissues and some developmental stages of mouse, DNMT1 and DNMTs 3a and 3b are needed for IAP methylation (Gaudet et al. 2004; Kato et al. 2007). This indicates that changes in the epigenetic machinery and in the expression of ERVs may be important in murine AIH. ERV expression may contribute to the disease process in autoimmunity and specific mechanisms have been proposed for this (Perl et al. 2010). However, of these numerous possible mechanisms, definitive experiments have not been done to identify one or more specific mechanisms as causal. It is possible that the decline in Dnmt3a expression contributes to the activation of IAPs following TCE dosing, however additional research is needed to understand how TCE affects IAP and MuERV expression.

To look at epigenetic alterations directly, we compared total DNA methylation in splenic CD4+ T cells from control mice with those from TCE treated mice (in this case after 17 weeks of TCE exposure). After stimulation, total DNA methylation was lower in the cells from TCE treated mice. In other words, TCE caused global hypomethylation in mouse CD4+ T cells (Gilbert et al. 2012). This occurred after treatment with either 0.01 or 0.1 mg/ml TCE-containing drinking water. Consistent with hypomethylation, we observed a nearly 3-fold increase ($p<0.05$) in IAP expression in these same cells for mice treated at the 0.1 mg/ml TCE level.

Compared to earlier studies of female mice with possibly improved liver methyl metabolism on TCE exposue (Gilbert et al. 2009), our recent studies (Blossom et al. 2012 and 2013) of metabolite levels in plasma and brain of male mice showed impaired methyl metabolism in response to chronic TCE. These more recent studies

were done in male MRL+/+ mice so that we cannot make a comparison of TCE's effects on multiple organs (liver, brain, plasma). Future studies are needed to study metabolism, gene expression and epigenetics in the liver, brain, T-cells, plasma, urine etc. from MRL+/+ mice of the same TCE exposures, same time points and same sex.

These various effects show that epigenetic alterations occur in TCE-treated mice, however the mechanisms are unclear. Effects on methyl metabolism could explain some or all of these effects as could effects on the expression of Dnmts. Further work is needed to determine how TCE causes these metabolic, gene expression and epigenetic changes and which changes come first. A better understanding of these effects may contribute to deciphering the mechanisms for other TCE induced diseases (in general, methyl metabolism affects cancer, heart defects and neuropathies (Tao et al. 2000a; Pascale et al. 2002; Hobbs et al. 2005a, b). Mechanisms will then allow us to design interventions that may reverse or ameliorate the long-term effects of TCE as has been done for some other toxic exposures (Tao et al. 2000a; Pascale et al. 2002; Downing et al. 2011, Otero et al. 2012, Bekdash et al. 2013).

10.5 Heart Defects

TCE exposure during gestation causes heart defects in the offspring of rodents (Caldwell et al. 2010; Palbykin et al. 2011) and birds (Loeber et al. 1988; Rufer et al. 2010; Makwana et al. 2010) and probably in humans (Yauck et al. 2004; Forand et al. 2012, Selmin, Chap. 8). Yauck et al. (2004) compared infants with congenital heart defects with infants without congenital heart defects for whether or not their mothers lived near TCE-emitting sites. They also compared other factors including maternal age, alcohol use, chronic hypertension, and preexisting diabetes. After adjusting for other factors, they found that, in older women (>37 years of age), the proximity of residence to TCE-emitting sites was associated with a three-fold increased risk of offspring congenital heart defects. In a more recent study, Forand et al. (2012) also found offspring cardiac defects more prevalent when mothers were exposed by soil vapor intrusion of TCE which contaminated their indoor air.

In rat studies, TCE reduced expression of the cardiac gene *Serca2a* in association with hypermethylation of its promoter in embryonic heart after maternal exposure to low concentrations (10 ppb) of TCE in drinking water (Palbykin et al. 2011). In this same study, SAM concentrations were lower in embryos whose mothers were exposed to TCE. In an earlier study by this same group, mouse embryonic heart gene expression was surveyed with DNA microarrays to show broad effects of TCE on cardiac gene expression (Caldwell et al. 2010). They further showed that maternal folate supplementation had its own pattern of altered gene expression and did not reverse the broad effects on embryonic gene expression caused by maternal TCE exposure. Thus while methyl metabolism is changed by TCE, specific gene methylation is not necessarily altered in the same direction as metabolism.

Although much TCE metabolism occurs in the livers of adults, in early bird embryos the liver and brain are not yet developed and the heart must metabolize TCE directly (Makwana et al. 2013). This may begin to explain the adverse cardiac effects of TCE in early development (Selmin, Chap. 8).

Several studies show that maternal diets affecting methyl metabolism such as broadly methyl supplemented diets (Wolff et al. 1998) or folate supplemented diets may positively affect health outcomes for offspring who are exposed to toxicants or have specific genetic defects (Downing et al. 2011; Cho et al. 2012; Billington et al. 2013). Folate supplementation alone did not reverse TCEs effects on gene expression in mouse embryos (Caldwell et al. 2010). Additional interventions combined with massively parallel assays (e.g. next generation sequencing for transcription, DNA methylation etc.) may reveal effective interventions. Maternal interventions to ameliorate TCE's effects on the developing heart have yet to be developed.

10.6 Neurological Effects

Acute TCE exposure, usually as occupational inhalation, can cause intoxication including dizziness, confusion, headaches, numbness, loss of consciousness, and in unusual circumstances, even death (ATSDR 1997). In addition, there can be many longer term neurological effects including memory loss and trigeminal nerve neuropathy (ATSDR 1997). Neurological effects of TCE are reviewed in two chapters of this book on neurotoxicity, by Bale (Chap. ___) and Goldman (Chap. 6) and here I select just a few examples to discuss and to emphasize the important role, in general, of epigenetics in memory, behavior, dementia and neurological function.

Epigenetics and especially DNA methylation and histone acetylation have key roles in animal behavior (Weaver et al. 2005; Champagne and Curley 2009), memory (Miller and Sweatt 2007; Sweatt 2012; Feng et al. 2010) and in dementia (Peleg et al. 2010; Pavlopoulos et al. 2013, reviewed by Cooney 2010). In rats, maternal behavior toward pups in the first postnatal week has lifelong effects on pup behavior (Weaver et al. 2005; Champagne and Curley 2009). Because female pups, once grown, will show different nursing behavior toward their pups, these behavioral effects might be passed on to multiple generations (reviewed by Cooney 2007). These behavioral effects can be attributed at least in part to changes in DNA methylation and histone acetylation in the hippocampal glucocorticoid receptor promoter and can be modified by treatments that target these pathways (Weaver et al. 2005; Champagne and Curley 2009).

Miller and Sweatt (2007) showed that epigenetics and especially DNA methylation are essential for normal memory formation. They showed that hippocampal RNA levels for the DNMTs 3a and 3b were increased with fear conditioning in rats and that DNMT inhibitors prevented memory formation (Miller and Sweatt 2007; Sweatt 2012). Subsequent studies knocking out either or both Dnmt1 and Dnmt3a just in forebrain excitatory neurons showed that a single knock out allowed memory formation but the knockout of both Dnmts interfered with synaptic plasticity, learning and memory (Feng et al. 2010).

To study epigenetics and memory in aged animals, Peleg et al. (2010) tested hippocampus-dependent associative learning in mice at various ages up to 16 months of age. In 3 month old mice, learning upregulated histone H4 lysine 12 (H4K12) acetylation and changed expression of over 2,000 genes whereas in 16 month old mice changes in H4K12 acetylation were insignificant and only 6 genes were differentially expressed. Injection of HDAC inhibitors into the hippocampus of 16-month old mice increased H4K12 acetylation and improved learning. This study shows that reversible histone acetylation changes are important parts of age-related memory loss. Recently, RbAp48, a natural histone deacetylase inhibitor protein, has been shown to help regulate both histone acetylation and memory (Pavlopoulos et al. 2013). In young mice, RbAp48 in the dentate gyrus of the hippocampus helped maintain histone acetylation and normal memory. In aged mice, RbAp48 levels are low and correspond to lower histone acetylation and poor memory performance. Experimental manipulations to lower RbAp48 in young mice adversely affected their memories and manipulations to increase RbAp48 in old mice improved their memories.

TCE and some of its metabolites cause dopaminergic neurodegeneration and may be a cause of Parkinson's Disease (PD, Gash et al. 2008; Liu et al. 2010; Sauerbeck et al. 2012, Goldman, Chap. 6). The TCE metabolite 1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline (TaClo) inhibits mitochondrial complex 1 (Janetzky et al. 1995) diminishing energy production. TaClo is a structural analog of the dopaminergic neurotoxin N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Bringmann et al. 1995; Akundi et al. 2004). MPTP is an established cause of PD in humans and in animal models. This work provides a plausible mechanism by which TCE may cause Parkinson's disease in people and should be sufficient to warrant avoiding TCE and related chlorinated solvents. Additional research is needed to establish a clear cause and effect.

Alpha-synuclein, a main component of Lewy bodies, is overexpressed in PD patients. A range of epigenetic effects have been found affecting the alpha-synuclein gene and other genes *in vitro* and in PD patients including alpha-synuclein gene hypomethylation in PD patients (reviewed by Coppedè 2012). Metabolic changes in PD patients could affect epigenetics as serum HCY is above normal and methylation potential (SAM/SAH ratio) varies with higher SAM/SAH correlating with better cognitive function (Obeid et al. 2009).

These recent studies indicate that factors affecting epigenetics could have important effects on behavior and memory. We studied several effects of TCE on behavior, gene expression, metabolism and epigenetics in the hippocampi and cerebella of male mice (Blossom et al. 2012, 2013). In assays of their hippocampi as well as separate assays of cerebella, TCE treated male mice had decreased GSH, decreased ratio of reduced glutathione/oxidized glutathione (GSH/GSSG), decreased cysteine/cystine and increased cystine (the oxidized form of cysteine) and increased 3-nitrotyrosine (Blossom et al. 2012, 2013). These measures indicate that TCE treated mice have a more oxidized environment in their hippocampi and cerebella.

In blood plasma, TCE-treated male mice had higher HCY and SAH levels and lower methionine and SAM levels and lower SAM/SAH ratios (Blossom et al. 2012).

All of these measures suggest lower methylation capacity. These TCE-treated mice also had lower plasma SAM + SAH and HCY + methionine levels suggesting that more HCY is being converted to cysteine, presumably in response to oxidative stress. These changes are all in the directions that would be expected to compromise cellular methylation reactions including DNA methylation (Cooney 2006)

In cerebella, TCE treated male mice had lower methionine levels and lower total 5MC than untreated controls (Blossom et al. 2013). Overall this data indicates that TCE produces oxidative stress and lower methylation capacity in these brain regions and possibly in many tissues based on the plasma values we observed. Studies in female mice suggest that chronic TCE may increase methylation capacity in the liver (Gilbert et al. 2009), which is the opposite of the direction we observed in the brains and plasma of male mice and the CD4 + T-cells of female mice. Future experiments will measure the responses of several tissues and plasma in the same mice to ascertain the effects of chronic TCE on methyl and antioxidant metabolism. These measures will provide data on which we can base interventions with the aim of ameliorating the adverse health effects of chronic TCE.

10.7 Endogenous Retroviruses (ERVs)

ERVs are endogenous components of our genomes (Walsh et al. 1998; Bannert and Kurth 2004; Perl et al. 2010) which are inherited though the germline (Mendelian inheritance). They are thought to have arisen over evolutionary time from repeated retroviral infections of germline cells (Bannert and Kurth 2004). While retroviral infections often lead to integration of the proviral genome into host DNA, only infection of the germline leads to Mendelian inheritance to subsequent generations. Examples of ERVs in humans include endogenous retrovirus virus K (HERV-K) and, in mice, IAPs and MuERVs. Most ERVs are largely silent in healthy cells and tend to remain in place in the genome for extended times and, apparently, for many generations (Wolff et al. 1998; Morgan et al. 1999). In certain developmental stages and in some diseases, ERVs can become transcriptionally active and sometimes transpose in the genome (Romanish et al. 2010). Activation of ERVs can result in their transcription and cause interference with expression of nearby "host" genes. Effects on nearby "host" genes can be over expression, deregulated expression, silencing and other forms of dysregulation (Wolff et al. 1998; Rakyan et al. 2003; Druker et al. 2004). Following transcription, the expression of ERV-encoded proteins can lead to ERV transposition and the promotion of other aberrant processes that disrupt the genome (e.g. reverse transcription of "host" RNAs) (Romanish et al. 2010).

ERVs are controlled by epigenetic silencing including 5MC (Walsh et al. 1998; Cooney et al. 2002; Gaudet et al. 2004; Schulz et al. 2006; Reiss et al. 2010; Cherkasova et al. 2011). Many nutritional (Cooney et al. 2002), metabolic and genetic factors (Gaudet et al. 2004) can affect ERV expression.

ERV activity is clearly correlated, and may be causal, in some cancers and some forms of autoimmunity. Increased ERV expression is found in several types of autoimmune diseases in both humans and mice (Balada et al. 2010; Baudino et al. 2010).

We find that TCE activates expression of two ERVs in mice after 12 weeks of exposure and long before the development of overt disease (autoimmune hepatitis) (Gilbert et al. 2012). This was the first report of TCE-induced ERV overexpression and the increase of IAP transcripts we observed was the strongest transcript induction we have observed with TCE. Because of their high copy number (e.g. about 1000 IAP copies in the mouse genome), small increases in the expression of individual ERVs could have large overall effects if tens or hundreds of ERVs per genome increase their expression.

Retroviral expression seems to have a direct role in autoimmune pathology (Perl et al. 2010) but its role in TCE-induced pathology remains to be determined. The role of ERV expression in other TCE-induced diseases such as heart defects, cancer and neuropathies should be investigated.

10.8 Potential for Epigenetic Effects from TCE Coexposure with Other Toxicants

Coexposure with TCE and other toxicants could result in broader or additive epigenetic effects in some cases or a cancellation of effects in others. Here I discuss two compounds, ethanol and bisphenol A (BPA), to which people are routinely exposed and thus significant coexposure with TCE is likely.

The use of ethanol is widespread. Ethanol has clear epigenetic effects on the fetus during pregnancy and these epigenetic effects may explain much of fetal alcohol syndrome (FAS, Ramsay 2010). Several studies in mice show that 5MC patterns on imprinted genes (such as *Igf2* and *H19*) are changed by maternal alcohol consumption (Haycock and Ramsay 2009; Stouder et al. 2011; Downing et al. 2011; Veazey et al. 2013; Resendiz et al. 2013). Culture of embryos *in vitro* with alcohol also shows extensive changes in 5MC (Liu et al. 2009). Other fetal alcohol mouse studies, some including genes for neural development, show changes in 5MC and histone modifications (Veazey et al. 2013). Supplementation of maternal diets with a combination dietary methyl supplement (folic acid, vitamin B12, betaine, choline, methionine and zinc, Downing et al. 2011) or a dietary choline supplement (Otero et al. 2012, Bekdash et al. 2013) ameliorated some epigenetic and other effects of maternal alcohol on rodent fetuses.

Chronic alcohol use has been shown to cause hepatocellular carcinoma in mice (Tsuchishima et al. 2013). This occurred without tumor initiation by another carcinogen. Ethanol also affects detoxification pathways (Lu and Cederbaum 2008) which can change the detoxification of xenobiotics including TCE and some other carcinogens (Nakajima et al. 1988; Klotz and Ammon 1998). However, the interactions of ethanol and TCE with respect to epigenetics have not been reported.

In adult human subjects, DNA from peripheral blood shows methylation differences between alcohol dependent and control American subjects (Zhang et al. 2013a) and Chinese subjects (Zhang et al. 2013b). In Americans, two genes, *GABRB3* and *POMC* were differentially methylated in African-American subjects while several other genes were differentially methylated in European-American subjects.

Bisphenols were originally developed as estrogen agonists but found widespread use as the building blocks of plastics (Vogel 2009). A variety of bisphenols are agonists or antagonists for estrogen receptors and other nuclear receptors (Molina-Molina et al. 2013). Bisphenols and other estrogen disrupting chemicals can have effects at low doses that are not revealed by more traditional studies of high exposures (Vandenberg et al. 2012).

Bisphenol-A (BPA) and its analog bisphenol-S (BPS) are widely used as the main component in some plastics and as a component in numerous other consumer products including thermal paper cash register receipts and the inside lining of metal food cans (Biedermann et al. 2010; Liao and Kannan 2011). In some cases, including food can lining, these uses stretch back to the 1960s. Use in receipts leads to contact with paper currency which is then subsequently handled by many individuals (Liao et al. 2012).

Mouse studies of BPA and epigenetics have yielded varying results. Using the yellow-agouti mouse model, some small studies show changes in epigenetically determined coat color with BPA and the naturally occurring soy estrogen, genistein (Dolinoy et al. 2006, 2007). Yellow-agouti mouse studies with well-controlled coat color quantification and scoring, including a recent large study, find no change in epigenetically determined coat color with soy protein isolate (Badger et al. 2008), genistein or BPA (Rosenfeld et al. 2013). Studies using other models show effects of BPA on epigenetics, including effects on imprinting (Susiarjo et al. 2013) and effects in the brain (Kundakovic et al. 2013). The route of BPA dosage is important because realistic exposure models give much different results than models using artificial exposures (Vandenberg et al. 2013). Coat color studies are best using quantitative methods (Badger et al. 2008; Ounpraseuth et al. 2009, Rosenfeld et al. 2013) or where unique phenotypes are produced by the treatment (Wolff et al. 1998; Cooney et al. 2002). Clearly more research is needed to determine if BPA affects mainly specific tissues at specific life stages or if its effects are more pervasive involving most tissues (including the periphery e.g. skin and hair) and most life stages (e.g. fetal exposure and adult exposure at multiple ages).

Alcohol and bisphenols are just a few of the more common compounds affecting epigenetics which are likely coexposures with TCE. Other compounds include genistein (from soy products), sulforaphane (from broccoli, Watson et al. 2013). Several nutrients such as folates, betaine and methionine will be found in all subjects as they are nutrients and metabolites. However, these nutrients will be found in greatly varying levels in diets (Cooney 2006) which will likely affect subjects' responses to TCE.

10.9 Conclusions

TCE remains a widespread environmental pollutant and human exposure will continue for the foreseeable future. TCE has a wide range of health effects covering multiple major organs. These health effects can occur during gestation or in adults following chronic exposure.

By investigating epigenetic alterations we expect to decipher the early molecular effects that lead to later disease. Genome wide analyses are needed using next generation sequencing and similar broad measures to understand the extent of TCE's effects. Likewise, effects in multiple organs and at multiple life stages require study. It is important to find predictive biomarkers for the disease(s) to which TCE-exposed individuals are most susceptible.

Understanding the metabolic and cellular signaling effects of TCE exposure will also help us understand how epigenetic alterations occur in the first place. Knowing metabolic and cellular signaling effects may allow us to design interventions for those still exposed to TCE. Coexposures with other toxicants, with phytochemicals and with varying nutritional states need to be measured, and then appropriately addressed. Various therapeutic strategies have been developed for cancer and aging (Cooney 2010; Dawson and Kouzarides 2012). Some of these, especially nutrients and well-tolerated drugs, may be good candidates for preclinical studies (e.g. animal models) to reverse TCE effects.

Understanding epigenetics of TCE exposure will help us understand a wide range of health problems associated with TCE. Further, this understanding will help us design interventions to reverse epigenetic changes before disease develops.

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