Systematic Review
The Emerging Spectrum of Early Life Exposure-Related Inflammation and Epigenetic Therapy
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INTRODUCTION
Inflammation is part of the biological response of body tissues and defense mechanism to harmful stimuli. The immune system recognizes damaged cells, irritants, and pathogens, and the body is attempted to remove harmful stimuli and begin the healing process.1 During the development, the environmental disruptors create prolonged inflammation status, and increase the risk of genomic instability and the introduction of novel mutations. Several signaling pathways involved in the regulation of inflammatory response have been described under the control of epigenetics. Therefore, inflammation is well recognized as a hallmark feature linked to the development of many diseases including cardiovascular disease, diabetes, mental health dysfunction, and certain types of cancer.12,13 Several perinatal environmental factors including nutrition, stress, air pollution, antibiotics can cause and increase the risk of adult diseases via inflammation (Figure 1). An association between early life inflammation and later life diseases has been reported in many literatures.14,18 Epidemiological studies have highlighted the link between perinatal factors (such as breastfeeding-
ing, cesarean delivery, and antibiotic use) and an increased risk for inflammatory bowel disease and/or celiac disease. Perinatal environment determines susceptibility to intestinal inflammatory disorders. Although the mechanisms underlying joint effects remain unclear, one hypothesis is that toxic social and environmental exposures have synergistic effects on inflammatory processes that underlie the development of chronic disease. During maternal obesity along with increased inflammatory markers in the maternal circulation, increased placental production of pro-inflammatory mediators can be found, suggesting that the resulting inflammatory milieu where the fetus develops may have critical consequences for later diseases such as obesity. The association between prenatal undernutrition and later-life metabolic disorders has been well established in multiple animal studies. For instance, placentas from protein-restricted rats exhibit a marked reduction of 11-β-hydroxysteroid dehydrogenase 2 enzyme (11-β-HSD2), which leads to fetal exposure to abnormally high glucocorticoid levels during gestation and later hypertension in the adult offspring. During this process, pro-inflammatory cytokines can cause decreased activity of 11-β-HSD2, and thus may play a role in programming by maternal diet. Similarly, prenatal cytokine exposure is sufficient to induce obesity later in life.

**PRO-INFLAMMATORY PHENOTYPE AND EPGENOMIC REGULATION**

Epigenetics refers to changes in phenotype mediated by altered gene expression. These changes do not occur as a result of the alteration in DNA sequencing. DNA methylation and histone modification are the two major epigenetic mechanisms, which collaborate to package genes in euchromatinor heterochromatin, a packaging that determines whether a gene is activated or silenced. DNA methylation refers to the covalent addition of a methyl group to a cytosine residue in a CpG dinucleotide. Histone modification is a covalent post-translational modification (PTM) to histone proteins, which includes methylation, acetylation, phosphorylation, ubiquitination, and sumoylation. The histones with varied PTMs can impact gene expression pattern by changing chromatin structure or recruiting histone modifiers. Hypermethylation of promoter CpG islands is linked with repressive transcriptional activity because of loss of affinity for transcriptional factors and accessibility by the transcriptional machinery. The crosstalk between DNA methylation and histone modification has also been discovered. The heterochromatin has increased affinity for methylated DNA-binding proteins (MBPs), which further recruit other transcriptional corepressors including histone deacetyltransferases (HDACs), DNA methylases (DNMTs), etc. Hypermethylation of promoter regions is associated with repressive histone marks, while unmethylated promoters are associated with active histone marks. Under latter circumstance, the gene expression is activated, since affinity for MBPs is reduced, and enrichment for active histone marks is increased.

An increased body of evidence shows that a variety of pro-inflammatory mediators is regulated via epigenetic mechanism, which contributes to pathogenesis of diseases. A recent study by Li et al demonstrates that epigenetic regulation of key cytokinocytes can contribute to chronic skin inflammation. Actin polymerizing molecule N-WASP is capable of modulating interleukin IL-23 expression in keratinocytes by regulating the degradation of the histone methyltransferases G9a and GLP, as well as H3K9 dimethylation level of the IL-23 promoter. This mechanism mediates the induction of IL-23 by tumor necrosis factor (TNF-α), a known inducer of IL-23 in psoriasis.

During a plastic interval of the prenatal and neonatal segments of life, a stable reprogramming of gene expression can occur and may predispose the individuals to adult disease. At a molecular level, epigenetic processes including DNA methylation and histone modifications constitute a major mechanism by which environmental factors may establish a new phenotypic trait during this plastic interval. A recent study demonstrates that preterm infant outcomes are associated with modulation of host immune and inflammatory responses, which are impaired by acute intrauterine and microbiota factors. The latter one plays a pivotal role in maturation of the immune system and in the prevention or development of diseases occurring during lifetime. Concomitantly, prenatal inflammatory exposure results in hypermethylation of promoter regions for TLR-signaling pathways, which play a role in the innate immune response.

Several clinical studies have shown that epigenetics may be involved in the pathogenesis of chronic inflammatory diseases. In the intestinal mucosa of celiac disease patients, DNA methylation play a role in regulating the NF-kB pathway, associated with dysregulation of the inflammatory response. Activation of NF-kB has been shown to elevate the expression of genes encoding for cytokines, chemokines, and other pro-inflammatory mediators such as IL-6, IL-8. In addition, early-life stress has been associated with modification of hypothalamic-pituitary-adrenal
Uterine fibroids (UFs) are hormonally-regulated benign smooth muscle myometrial tumors that severely affect female reproductive health, although their unknown etiology limits effective care. An increasing body of evidence supports the hypothesis that UFs originate from stem cells in the myometrium, although the specific cell of origin for these tumors has remained elusive. Myometrial stem/progenitor cells (MMSCs) and UF stem/progenitor cells (UFSCs) have been identified. MMSCs are a subset of cells residing in the uterine myometrium, that remain their capacity to self-renew through asymmetric division rates as well as producing differentiated cells, which play an important role in tissue regeneration. MMSCs represent a subgroup of cells with a tumor cell population, which also retain the ability to reconstitute tumors. Notably, the difference between MMSCs and UFSCs at DNA level is that MED12 mutations were found only in UFSCs, but not MMSCs. In addition, the defect of DNA repair response was recently observed in UFSCs. In UFs, a recent study shows that higher numbers of macrophages are inside and close to UFs as compared to the more distant myometrium. Notably, several key pro-inflammatory mediators including IL-11, IL-13 and TGF-β are overexpressed in UFs. The latter one in particular is a potent chemoattractant factor for macrophages. Another group has reported that many pro-inflammatory mediators that trigger or enhance specific aspects of inflammation are upregulated in UF tumors as compared to adjacent myometrium tissues. In addition, the levels of tumor necrosis factor TNF-α, a cell-signaling protein involved in systemic inflammation, is elevated in Caucasian women with clinically symptomatic UFs. A recent study also shows that UF progenitor cells secrete higher levels of Th2 pathway cytokines (IL4, IL-5, IL-10, and IL-13), and significantly lower levels of Th1/Th17 cytokines (IL-6, IL-12, IL-17A, INF-γ, G-CSF, and TGF-β1), suggesting that the altered pattern of cytokine expression and secretion may enhance UF development via chronic inflammation with the involvement of infiltrating immune cells.

The link between UF development and early life exposure to xenoestrogens via inflammation has been recently identified in Eker rat animal model. The adult Eker rats developmentally exposed to diethylstilbestrol (DES) exhibits significantly higher expression of pro-inflammatory markers (TNF-α, NF-κB and IL1β) in myometrium. Combinantly, the macrophage number is also significantly increased in DES-exposed myometrium in adult stage. Flow cytometry analysis demonstrates that the production of several inflammatory cytokines is increased in DES-MMSCs versus vehicle exposed (VEH)-MMSCs. By RNA-sequencing analysis, some of key pro-inflammatory genes including Pcdh7, Pdpn, Cxcl10, Cd40, Ptgser2, and Eregr, exhibits upregulation in MMSCs from myometrium early-life exposed to DES versus control (VEH). Subsequently, gene set enrichment analysis on the ChIP-sequencing data demonstrates that an enrichment of H3K4me3 (an active mark for gene transcription) at the promoters of inflammation responsive genes (IRGs) is observed in DES-MMSCs as compared to VEH-MMSCs. Furthermore, the increased expression of IRGs in DES-MMSCs is positively correlated with the elevated H3K4me3 epigenetic mark. In addition, the mRNA expression of reprogrammed key cytokine genes encoding CCL-2, CCL-7, CSF-1, which contribute to the recruitment of monocytes/macrophage, exhibits a significant upregulation in DES-MMSCs versus VEH-MMSCs. These studies suggest that developmental exposure to xenoestrogens such as DES alters the inflammatory microenvironment in the myometrium and increases the risk of adult onset of UFs by permanently reprogramming pro-inflammatory genes in MMSCs towards a pro-fibroid epigenomic landscape.

**PRECLINICAL STUDIES OF EPIGENETIC AGENTS**

Epigenetic modifiers/agents targeting DNMTs and histone modified enzymes have been widely investigated in preclinical studies of many diseases. Moreover, a variety of studies demonstrate that these epigenetic modifiers suppress and ameliorate varied diseases including immunopathogenesis, tissue damage, pain, bone and cartilage destruction, and cancers, etc. via inflammation.

The zinc-dependent mammalian histone deacetylase (HDAC) family comprises over 10 enzymes, which have specific and critical functions in development and tissue homeostasis. Increased evidence points to a link between misregulated HDAC activity and many oncologic and non-oncologic diseases. Thus, the development and usage of HDAC inhibitors provide a promising option for therapeutic treatment. Currently, the effect of HDAC inhibitors on suppression of diseases via anti-inflammatory pathway has been widely investigated both in vitro and in vivo. As shown in table 1, most of the epigenetic modifiers targets inflammatory pathway by inhibition of HDAC activity, therefore leading to suppression of diseases via inflammatory pathway. HDAC inhibitors effect that contributes largely to their therapeutic benefits, is achieved through histone deacetylation, chromatin remodeling and transcriptional reprogramming, as well as other unknown or not fully characterized mechanisms.
Table 1. The Anti-Inflammatory Effect of Epigenetic Agents

<table>
<thead>
<tr>
<th>Epigenetic-based Agents</th>
<th>Family</th>
<th>Target</th>
<th>Diseases</th>
<th>Model</th>
<th>Effect</th>
<th>Route/Concentration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHCA (Mal-gluc)</td>
<td>Phytochemicals</td>
<td>Plasma pro-inflammatory interleukin 6 (IL-6) level</td>
<td>Chronic stress/ depression</td>
<td>Mouse model of systemic inflammation</td>
<td>DHCA inhibited DNA methylation as the CpG-rich IL-6 sequences</td>
<td>Orally</td>
<td>82</td>
</tr>
<tr>
<td>Mal-gluc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mal-gluc (0.5μg/kg/ day)</td>
<td>dhca (5 μg/kg/ day) for 24 days</td>
</tr>
<tr>
<td>NIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>JIB-04 induced apoptosis of macrophages in a dose-dependent manner</td>
<td>1 μM JIB-04 for 24 hours</td>
</tr>
<tr>
<td>TSA</td>
<td></td>
<td>Human macrophages</td>
<td>Atherosclerosis</td>
<td>RAW264.7 cells</td>
<td>JIB-04 induced apoptosis of macrophages in a dose-dependent manner</td>
<td>1 μM JIB-04 for 24 hours</td>
<td>82</td>
</tr>
<tr>
<td>TSA</td>
<td></td>
<td>Human Th17 cells</td>
<td>Human type-17-mediated diseases such as ankylosing spondylitis and psoriatic arthritis</td>
<td>Th17 cells from healthy donors and patients with ankylosing spondylitis and psoriatic arthritis</td>
<td>TSA Downregulated CD40L and IL-23 and reduced pro-inflammatory cytokines.</td>
<td>2 μM CBP30 for 24 hours</td>
<td>84</td>
</tr>
<tr>
<td>TSA</td>
<td></td>
<td>Human Th17 cells</td>
<td>Intracellular inflammatory disease: Posterior uveitis</td>
<td>Mouse model of experimental autoimmune uveitis (EAU)</td>
<td>Both abrogated the uveotoxic capacity of Th17 cells to transfer EAU.</td>
<td>Oral gavage for 5 days 20 μg/kg</td>
<td>72</td>
</tr>
<tr>
<td>DHS</td>
<td></td>
<td>Human Th17 cells</td>
<td>Intracellular inflammatory disease: Posterior uveitis</td>
<td>Human CD4+ T cells</td>
<td>Both significantly downregulated Th17-associated genes IL-17A, IL-22, and retinoic acid-related orphan receptor γt.</td>
<td>JQ1 (30.300 nM) or GSK151 (30.300 nM) for 5 days</td>
<td>72</td>
</tr>
<tr>
<td>CBP30</td>
<td></td>
<td>Mouse naive CD4+ T cells</td>
<td>Inflammatory bowel diseases</td>
<td>Mouse model</td>
<td>MS402 blocked Th17 maturation and ameliorates T-cell transfer-induced colitis.</td>
<td>10 μg/ml twice a week starting either at week 0, or week 5 for 7 or 3 weeks, respectively</td>
<td>73</td>
</tr>
<tr>
<td>CBP30</td>
<td></td>
<td>T-cells</td>
<td>Systemic lupus erythematosus (SLE)</td>
<td>Cultured Human peripheral blood mononuclear cells</td>
<td>TSA Downregulated CD40L and IL-10.</td>
<td>0-1000 ng/ml for 18 hours</td>
<td>79</td>
</tr>
<tr>
<td>TSA</td>
<td></td>
<td>Macrophages</td>
<td>Acute lung injury (ALI)</td>
<td>Lipopolysaccharide (LPS)-induced mouse of ALI</td>
<td>TSA caused substantial attenuation of adverse lung histopathological changes and inflammation due to substantial macrophage phenotypic changes.</td>
<td>1 μg/g body weight for 2 weeks</td>
<td>85</td>
</tr>
<tr>
<td>TSA</td>
<td></td>
<td>Macrophages</td>
<td>Pathogenic microorganisms induced inflammation</td>
<td>LPS-stimulated from PBMC healthy broilers</td>
<td>TSA down-regulated mRNA expression of IL-1, IL-6, and tumor necrosis factor alpha (TNF-α).</td>
<td>5 μM for 4 hours</td>
<td>86</td>
</tr>
<tr>
<td>TSA</td>
<td></td>
<td>Macrophages</td>
<td>Rheumatoid arthritis</td>
<td>Macrophages derived from the inflamed joints of patients with RA</td>
<td>Both blocked the production of IL-6 and TNF-alpha by macrophages.</td>
<td>TSA (2 μM) NIC (20 μM) for 4 hours</td>
<td>87</td>
</tr>
<tr>
<td>NIC</td>
<td></td>
<td>Macrophages</td>
<td>Streptococcus pyogenes cell wall arthritis</td>
<td>Acute arthritis</td>
<td>Injection of 25 μg SCW fragments into the right knee joint of C57Bl/6 mice</td>
<td>ITF2357 decreased the production of pro-inflammatory cytokines by synovial tissue.</td>
<td>Oral administration of 1 and 10 mg/kg ITF2357 at 2 hours, 6 hours, day 1 and day 2</td>
</tr>
<tr>
<td>NIC</td>
<td></td>
<td>PBMCs</td>
<td>Concavalin-A-induced hepatitis</td>
<td>Mouse model</td>
<td>ITF2357 significantly reduced liver damage.</td>
<td>Oral 1 or 5 mg/kg one time</td>
<td>89</td>
</tr>
<tr>
<td>NIC</td>
<td></td>
<td>Mouse macrophages</td>
<td>Inflammatory diseases</td>
<td>In vivo animal model</td>
<td>- Both reduced the production of pro-inflammatory cytokines TNF-α, IL-1-beta, IL-6, and IFN-γ.</td>
<td>-50 mg/kg single oral or IV administration of SAHA to mice</td>
<td>-200 nM for 1 hour</td>
</tr>
<tr>
<td>MI192</td>
<td></td>
<td>PBMCs</td>
<td>Rheumatoid arthritis (RA)</td>
<td>RA patients by spectrophotometric assay, prior to and after 12 weeks of Etanercept therapy.</td>
<td>MI192 inhibited TNF production at high concentrations and dose-dependently inhibited IL-6 in RA.</td>
<td>Dose range of 10 μM-5 μM for 18 hours.</td>
<td>91</td>
</tr>
</tbody>
</table>

Cont...
<table>
<thead>
<tr>
<th>Compound</th>
<th>HDAC Class/Target</th>
<th>IC50/ID50/ED50</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid (VPA)</td>
<td>HDAC inhibitor</td>
<td></td>
<td>VPA treatment increased both the suppressive function of CD4(+) and CD25(+) Tregs and the numbers of CD25(+)FoxP3(+) Tregs in vivo.</td>
</tr>
<tr>
<td>Curcumin (Natural polyphenol extracted from turmeric, pan-HDAC inhibitor)</td>
<td>HDAC and p300/ CBP-specific inhibitor</td>
<td></td>
<td>Curcumin had CSC-depleting activity attributed to a NF-κB-mediated HDAC inhibition.</td>
</tr>
<tr>
<td>Curcumin (Natural polyphenol extracted from turmeric, pan-HDAC inhibitor)</td>
<td>HDAC and p300/ CBP-specific inhibitor</td>
<td></td>
<td>Curcumin prevented degradation of I-kappaB alpha and inhibited nuclear translocation of the NF-kappaBp65 subunit, as well as expression of Notch 1, induced by tumor necrosis factor-alpha.</td>
</tr>
<tr>
<td>Curcumin (Natural polyphenol extracted from turmeric, pan-HDAC inhibitor)</td>
<td>HDAC and p300/ CBP-specific inhibitor</td>
<td></td>
<td>Curcumin inhibited HBV gene replication via down-regulation of cccDNA-bound histone acetylation.</td>
</tr>
<tr>
<td>-Minocycline</td>
<td>Activators of histone deacetylase</td>
<td></td>
<td>Both inhibited early diabetic retinopathy via decreased expression of inflammatory proteins. Both significantly inhibited the acetylation and induction of the inflammatory proteins in elevated glucose levels.</td>
</tr>
<tr>
<td>-Garcinol</td>
<td>Activators of histone deacetylase</td>
<td></td>
<td>Both significantly inhibited the acetylation and induction of the inflammatory proteins in elevated glucose levels. Both prevented peripheral inflammatory pain.</td>
</tr>
<tr>
<td>-Theophylline</td>
<td>Activators of histone deacetylase</td>
<td></td>
<td>Intraarticular single dose of 60 nmol/20 μL</td>
</tr>
<tr>
<td>-Indole-3-carbinol (I3C)</td>
<td>Activators of histone deacetylase</td>
<td></td>
<td>Both significantly decreased SEB-induced T cell activation and cytokine production.</td>
</tr>
<tr>
<td>-3,3’-dindolylmethane (DIM)</td>
<td>Activators of histone deacetylase</td>
<td></td>
<td>Both significantly decreased SEB-induced T cell activation and cytokine production.</td>
</tr>
<tr>
<td>Depsipeptide (FK228)</td>
<td>HDAC inhibitor</td>
<td></td>
<td>Both significantly decreased SEB-induced T cell activation and cytokine production.</td>
</tr>
<tr>
<td>MS-275 (Entinostat)</td>
<td>HDAC inhibitor</td>
<td></td>
<td>Both significantly decreased SEB-induced T cell activation and cytokine production.</td>
</tr>
<tr>
<td>Panobinostat (LBH589)</td>
<td>HDAC inhibitor</td>
<td></td>
<td>Both significantly decreased SEB-induced T cell activation and cytokine production.</td>
</tr>
<tr>
<td>Sulforaphane (SFN)</td>
<td>HDAC inhibitor</td>
<td></td>
<td>Both significantly decreased SEB-induced T cell activation and cytokine production.</td>
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</tbody>
</table>
The Bromodomain and Extra-Terminal Domain (BET) family proteins play a crucial role in regulating gene transcription through epigenetic interactions between bromodomains and acetylated histones during cellular proliferation and differentiation processes.63 Bromodomains that can specifically bind acetylated lysine residues in histones serve as chromatin-targeting modules that decipher the histone acetylation code. BET inhibitors are capable of inhibiting retinal inflammatory disease and inflammatory bowel diseases.62,71

In addition to targeting HDACs and BET proteins, the inhibitors of DNMTs have been widely used in many pre-clinical studies for a variety of diseases, as well as in some clinical application.63-70 Notably, emerging evidence suggests that BET proteins are involved in pathogenesis of inflammatory diseases62 and BET inhibitors exhibit potent anti-inflammatory effects in several types of diseases. In the brain of the Alzheimer’s disease animal model, the BET inhibitor JQ1 decreases neuroinflammation with a reduction in the expression of the pro-inflammatory modulators IL-1β, IL-6, TNF-α, CCL-2, NOS-2 and PTGS-2 in the brain of mice.71 In addition, BET inhibitors are capable of inhibiting retinal inflammatory disease and inflammatory bowel diseases.62,73

**FUTURE DIRECTIONS AND CONCLUSION**

Tumor initiation and disease development via inflammatory pathway are linked with early life exposure to a variety of adverse insults via epigenetic reprogramming, which play an important role in alteration of pro-inflammatory profiling and phenotype. Much
more attention is needed to identify epigenetic agents, which exhibit potent anti-inflammatory effect with minimum of side effects. In addition, more studies are needed to evaluate the role of epigenetic-based drugs alone or in combination with other chemical agents in suppressing inflammation as a means of prevention and management of many diseases including UF.

CONFLICT OF INTEREST

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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