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Systematic Review

The Emerging Spectrum of Early Life Exposure-Related Inflammation and Epigenetic Therapy

Qiwei Yang, PhD[1*]; Mohamed Ali, BPharm, MSc[1,2]; Abdeljabar El Andaloussi, PhD[1]; Ayman Al-Hendy, MD, PhD[1]

[1]*Department of Obstetrics and Gynecology, University of Illinois at Chicago, Chicago, IL, USA*
[2]*Clinical Pharmacy Department, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt*

[*]***Corresponding author***
Qiwei Yang, PhD
Research Associate Professor, Department of Obstetrics and Gynecology, University of Illinois at Chicago, Chicago, IL 60612, USA; E-mail: qiwei@uic.edu

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ABSTRACT

Early life exposure to a variety of insults during sensitive windows of development can reprogram normal physiological responses and alter disease susceptibility later in life. During this process, inflammation triggered by a variety of adverse exposures plays an important role in the initiation and development of many types of diseases including tumorigenesis. This systematic review article summaries the current knowledge about the role and mechanism of inflammation in development of diseases. In addition, epigenome alteration related to inflammation and treatment options using epigenetic modifiers are highlighted and discussed.

Keywords
Early life exposure; Environmental factors; Inflammation; Uterine fibroids; Epigenetic modifiers.

INTRODUCTION

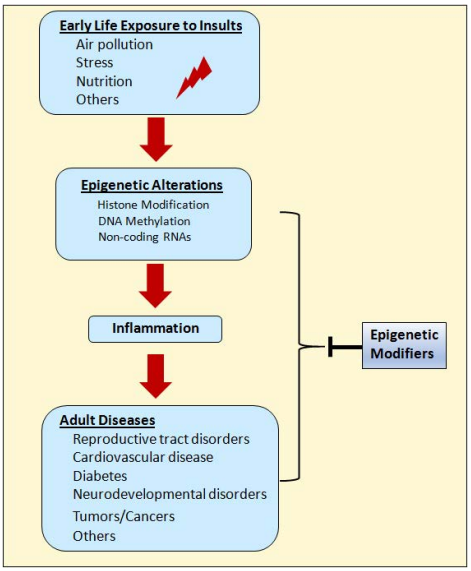
Inflammation is part of the biological response of body tissues and defense mechanism to harmful stimuli. The immune system recognizes damaged cells, irritants, and pathogens, and the body is attempted to remove harmful stimuli and begin the healing process.[1] During the development, the environmental 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 varied types of tumors.[2-10] Inflammatory cells and cytokines in the local tissue microenvironment promote a pro-inflammatory milieu, which can act in an autocrine and/or paracrine manner on the infiltrating immune cells and modified malignant cells. Thus the composition of the inflammatory microenvironment has a pivotal influence on risk of disease development and progression.[2] In the case of tumors, inflammation switches to immunosuppression due to tumor evasion from anti-tumor immune response. A promising approach for reversing the tumor immune evasion phenotype is epigenetic therapy, which exhibit efficacy in patients with refractory advanced non-small cell lung cancer. In this study, the epigenetic therapy was able to increases the numbers of activated immune cells in a mouse model of ovarian cancer.[11] The goal of this systematic review is to summarize the available information on the therapeutic effect of epigenetic agents, which are able to reverse pro-inflammatory phenotype of diseases.

DEVELOPMENTAL ENVIRONMENTAL FACTORS INDUCE INFLAMMATION RESPONSE

Inflammation plays an important role in the initiation and development of much type of 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 breastfeed-

ing, cesarean delivery, and antibiotic use) and an increased risk for inflammatory bowel disease and/or celiac disease.[19] 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.[20] 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.[21] The association between prenatal undernutrition and later-life metabolic disorders has been well established in multiple animal studies.[22,23] 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.[23] 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.[24] Similarly, prenatal cytokine exposure is sufficient to induce obesity later in life.[24,25]

Figure 1. *Early Life Exposure to a Variety of Insults Increases the Risk and Development of Diseases in Later Life via Inflammatory Pathway by Reprogramming the Epigenome. Epigenetic Modifiers Targeting Inflammatory Pathways are Capable of Inhibiting the Pro-inflammatory Phenotype, Therefore Leading to Suppressing/Preventing the Development of Diseases.*



PRO-INFLAMMATORY PHENOTYPE AND EPIGENETIC 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.[26] 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, ubiquitylation, 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 activate 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.[27-33] A recent study by Li et al demonstrates that epigenetic regulation of ke ratinocytes can contribute to chronic skin inflammation.[34] 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.[34]

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.[35-37] 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.[38] 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.[39,40] Concomitantly, prenatal inflammatory exposure results in hypermethylation of promoter regions for TLR-signaling pathways, which play a role in the innate immune response.[35]

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.[19] 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.[20,41] In addition, early-life stress has been associated with modification of hypothalamic-pituitary-adrenal

(HPA) axis- and neuroplasticity-related methylations. Changes in DNA methylation status of glucocorticoid receptor (GR) gene, a key regulator of inflammatory activity and others, was observed in response to early life stress.[42]

In addition to DNA methylation, histone modification has been reported to be associated with regulation of pro-inflammatory phenotype and adult disease due to early life insults. For example, an animal study demonstrates that the promoter of gene (GR/NR3C1) that encodes the GR, which play an important role in creating a pro-inflammatory environment, exhibits differential levels of histone acetylation as well as DNA methylation in the hippocampus of offspring of high *versus* low licking and grooming (LG) and arched-back nursing (ABN) mothers. Importantly, central infusion of the HDAC inhibitor (TSA) is capable of elevating H3K9 acetylation and hypermethylation of GR promoter with increased NGF1-A binding, GR expression as well as HPA response to stress in the offspring of the low-LG-ABN mothers.[42]

PRO-INFLAMMATORY PHENOTYPE OF UTERINE FIBROIDS

Uterine fibroids (UFs) are hormonally-regulated benign smooth muscle myometrial tumors that severely affect female reproductive health, although their unknown etiology limits effective care.[43,44] 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.[45] Myometrial stem/progenitor cells (MMSCs) and UF stem/progenitor cells (UFSCs) have been identified.[46-49] 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. UFSCs represent a subgroup of cells with a tumor cell population, which also retain the ability to reconstitute tumors.[50] Notably, the difference between MMSCs and UFSCs at DNA level is that *MED12* mutations were found only in UFSCs, but not MMSCs.[46] In addition, the defect of DNA repair response was recently observed in UFSCs.[51] In UFs, a recent study shows that higher numbers of macrophages are present inside and close to UFs as compared to the more distant myometrium.[52] 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.[50] 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.[53] 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.[54]

The link between UF development and early life exposure to xenoestrogen *via* inflammation has been recently identified in Eker rat animal model.[55] The adult Eker rats developmentally exposed to diethylstilbestrol (DES) exhibits significantly higher expression of pro-inflammatory markers (TNF-α, NF-kB and IL1β) in myometrium. Concomitantly, 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 *verse* vehicle exposed (VEH)-MMSCs. By RNA- sequencing analysis, some of key pro-inflammatory genes including Pcdh7, Pdpn, Cxcl10, Cd40, Ptger2, and Ereg, exhibits upregulation in MMSCs from myometrium early-life exposed to (DES) verse 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-MSCs 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 verse 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.[55]

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[32,56-61] (Table 1).

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*

Epigenetic-based Agents	Family	Target	Diseases	Model	Effect	Route /Concentration	Reference
Dihydrocaffeic acid (DHCA) -Malvidin-3'-O-glucoside (Mal-gluc)	Phytochemicals	Plasma pro-inflammatory interleukin 6 (IL-6) level	Chronic stress/ depression	Mouse model of systemic inflammation	DHCA inhibited DNA methylation at the CpG-rich IL-6 sequences introns 1 and 3. -Mal-gluc increased histone acetylation of the regulatory sequences of the Rac1 gene.	Orally -Mal-gluc (0.5μg/kg/ day) -DHCA (5 mg/kg/day) for 24 days	82
JIB-04	Pan-selective KDM inhibitor	Human macrophages	Atherosclerosis	RAW264.7 cells	JIB-04 induced apoptosis of macrophages in a dose-dependent manner.	1 μM JIB-04 for 24 hours	83
CBP30	Selective inhibitor of the bromodomains of CBP (CREB binding protein)/ p300	Human Th17 cells	Human type-17–mediated diseases such as ankylosing spondylitis and psoriatic arthritis	Th17 cells from healthy donors and patients with ankylosing spondylitis and psoriatic arthritis	CBP30 reduced secretion of IL-17A and other pro-inflammatory cytokines.	2 μM CBP30 for 24 hours	84
GSK151 -JQ1	Bromodomainex-traterminal (BET) inhibitors	Th17 cells	Intraocular inflammatory disease: Posterior uveitis	Mouse model of Experimental autoimmune uveitis (EAU)	Both abrogated the uveitogenic capacity of Th17 cells to transfer EAU.	oral gavage for 5 days 20 mg/kg	72
GSK151 -JQ1	Bromodomainex-traterminal (BET) inhibitors	Human Th17 cells	Intraocular inflammatory disease: Posterior uveitis	Human CD4+ T- cells	Both significantly downregulated Th17-associated genes IL-17A, IL-22, and retinoic acid–related orphan receptor γt.	JQ1 (30, 300 nM) or GSK151 (30, 300 nM) for 5 days	72
MS402	BD1-selective BET bromodomain inhibitor	Mouse naive CD4+ T cells	Inflammatory bowel diseases	Mouse model	MS402 blocked Th17 maturation and ameliorates T-cell transfer-induced colitis.	10 mg/kg twice a week starting either at week 0, or week 5 for 7 or 3 weeks, respectively	73
Trichostatin A (TSA)	Histone deacetylase (HDAC) inhibitor	T-cells	Systemic lupus erythematosus (SLE)	Cultured Human peripheral blood mononuclear cells	TSA Downregulated CD40L and IL-10. -TSA reversed the skewed expression of multiple genes implicated in the immunopathogenesis of SLE.	0-1000 ng/ml for 18 hours	59
Trichostatin A (TSA)	HDAC inhibitor	macrophages	Acute lung injury (ALI)	Lipopolysaccharide (LPS)-induced mouse of ALI	TSA caused substantial attenuation of adverse lung histopathological changes and inflammationdue to substantial macrophage phenotypic changes.	1 μg/g body weight for 2 weeks	85
Trichostatin A (TSA)	HDAC inhibitor	peripheral blood mononuclear cells (PBMC)	pathogenic microorganisms induced inflammation	LPS-stimulated from PBMC healthy broilers	TSA down-regulated mRNA expression of IL-1 β, IL-6 and tumor necrosis factor alpha (TNF-α).	5 μM for 4 hours	86
Trichostatin A (TSA) -Nicotinamide (NIC)	HDAC inhibitors	Macrophages	Rheumatoid arthritis	Macrophages derived from the inflamed joints of patients with RA	Both Blocked the production of IL-6 and TNF-alpha by macrophages.	TSA (2 μM) NIC (20 mM) for 4 hours	87
ITF2357 (Givinostat)	HDAC inhibitor	Streptococcus pyogenes cell wall arthritis	Acute arthritis	Injection of 25 μg SCW fragments into the right knee joint of C57/Bl6 mice	ITF2357 reduced the production of pro-inflammatory cytokines by synovial tissue.	Oral administration of 1 and 10 mg/kg ITF2357 at 2 hours, 6 hours, day 1 and day 2	88
ITF2357 (Givinostat)	HDAC inhibitor	PBMCs	Concanavalin-A-induced hepatitis	Mouse model	ITF2357 significantly reduced liver damage. -ITF2357 reduced LPS-induced serum TNF-alpha and interferon gamma (IFN-γ) by more than 50%.	Oral 1 or 5 mg/kg one time	89
Suberoylanilide-hydroxamic acid (SAHA) (Vorinostat)	HDAC inhibitor	Mouse macrophages	Inflammatory diseases	-In vivo animal model -In vitro.	- Both reduced the production of pro-inflammatory cytokines TNF-alpha, IL-1-beta, IL-6, and IFN-γ.	-50 mg/kg single oral or IV administration of SAHA to mice -200 nM for 1 hour	90
MI192	HDAC3 selective inhibitor	PBMCs	Rheumatoid arthritis(RA)	RA patients by spectrophotometric assay, prior to and after 12 weeks of Etanercept therapy.	MI192 inhibited TNF production at high concentrations and dose-dependently inhibited IL-6 in RA.	Dose range of 10 μM-5 nM for 18 hours.	91

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Valproic acid (VPA)	HDAC inhibitor	regulatory T cell (Tregs)	Rheumatoid arthritis.	Collagen-induced arthritis (CIA) mouse model	VPA treatment increased both the suppressive function of CD4(+), CD25(+)Tregs and the numbers of CD25(+),FOXP3(+)Tregs in vivo.	400 mg/kg daily starting on day 21 of the study till day 60	92
Curcumin	Naturalpolyphenol extracted from turmeric, pan-HDAC inhibitor	Hepatocellular carcinoma cell line	Hepatocellular carcinoma	Cancer stem cells (CSCs)	Curcumin had CSC-depleting activity attributed to a NF-κB-mediated HDAC inhibition.	25 μM for 3 days	93
Curcumin	HDAC and p300/CBP-specific inhibitor	Human lymphoma cell line (Raji)	Lymphoma	Human cancer cell line	Curcumin prevented degradation of I-kappaB alpha and inhibits nuclear translocation of the NF-kappaB/p65 subunit, as well as expression of Notch 1, induced by tumor necrosis factor-alpha.	12.5 μmol/L for 24 hours	94
Curcumin	Natural polyphenol extracted from turmeric, pan-HDAC inhibitor	covalently closed circular DNA (cccDNA)	Hepatitis B virus infection	HepG2.2.15 cell line	Curcumin inhibited HBV gene replication via down-regulation of cccDNA-bound histone acetylation.	20 μmol/L for 2 days	95
-Minocycline -Garcinol	Histone acetylation (HAT) inhibitor	cultured retinal Müller glia	Diabetic retinopathy	Diabetic rats	- 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.	-10 mg/kg, i.p. injection, 5× per week for 10 weeks - 20 μm Garcinol for 24 hours, 20 nM Minocycline for 4 days	96
-Theophylline -Resveratrol	Activators of histone deacetylase	cultured retinal Müller glia	Diabetic retinopathy	Diabetic rats	Both significantly inhibited the acetylation and induction of the inflammatory proteins in elevated glucose levels.	-10 μm for 4 days. -50 μm for 24 hours	96
-MS-275 (Entinostat) -MGCD0103 (Mocetinostat)	class I HDAC inhibitors	persistent spontaneous nociception (PSN)	Peripheral inflammatory pain	rats inflamed by subcutaneous injection of bee venom (BV)	Both prevented peripheral inflammatory pain.	Intrathecal single dose of 60 nmol/20 μL	60
-Indole-3-carbinol (I3C) -3,3'-diindolylmethane (DIM)	Natural indoles-found in cruciferous vegetables, inhibitors of HDAC class I	Vβ8(+) T cells	Staphylococcal enterotoxin B (SEB)induced inflammation	In vivo animal model	Both significantly decreased SEB-induced T cell activation and cytokine production.	40 mg/kg, i.p. every other day for up to 5 days	97
Depsipeptide (FK228)	HDAC inhibitor	Synovial tissues	Rheumatoid arthritis	Animal model of autoantibody-mediated arthritis	-FK228 inhibited joint swelling, synovial inflammation, and subsequent bone and cartilage destruction in mice with AMA. - FK228 decreased the levels of tumor necrosis factor alpha and interleukin-1beta.	2.5 mg/kg single intravenous dose on day 4	98
MS-275	HDAC inhibitor	-Prostate tissue Macrophages	Chronic prostatitis	-Experimental autoimmune prostatitisrats -Macrophage cell line	- MS-275 reduced the local accumulation of immune cells and mRNA levels of representative pro-inflammatory molecules. - MS-275 switched macrophages from classic M1 to anti-inflammatory M2 phenotype	5 mg/kg, i.p. daily from day 0 to day 14	99
Panobinostat (LBH589)	HDAC inhibitor	PBMCs	HIV-associated inflammation	HIV-infected adults	- LBH589 reduced multiple established plasma markers of inflammation as high-sensitivity C-reactive protein, matrix metalloproteinase 9, soluble CD40 ligand and IL-6. - LBH589 reduced the proportions of intermediate monocytes and tissue factor-positive monocytes.	20 mg three times per week, every other week, for 8 weeks	100
Sulforaphane (SFN)	HDAC inhibitor	Monocyte-derived dendritic cells	Systemic inflammation	Porcine cells	-SFN regulated the TLR4-induced activity of transcription factor NF-κB and TBP -SFN suppressed the IRF6 and TGF-ß1 production -SFN impaired the pro-inflammatory cytokine TNF-α and IL-1ß secretion into the cell culture supernatants.	10 μM for 24 hours	101

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Sirtinol	class III HDAC inhibitor	Endothelial cells	skin inflammation	human dermal microvascular endothelial cells	Sirtinol significantly reduced membrane expression of adhesion molecules in TNFα- or IL-1β-stimulated cells.	10 μM for 18 hours	102
5-Aza 2-deoxycytidine (Aza)	DNA methyl transferase (DNMT) inhibitor	Macrophages	Acute lung injury (ALI)	LPS-induced mouse of ALI	Aza caused substantial attenuation of adverse lung histopathological changes and inflammationdue to substantial macrophage phenotypic changes.	1 μg/g body weight for 2 weeks	85
Cambinol	HDAC inhibitor	macrophages	Inflammatory diseases	Bone marrow derived macrophage	Cambinol inhibited the expression of cytokines (TNF, IL-1β, IL-6, IL-12p40, and IFN-γ).	12.5, 50 μM for 1 hour	103
NW-21	Novel HDAC inhibitor	Human monocytes	Rheumatoid arthritis	In vitro	NW-21significantly reduced mRNA expression of monocyte chemotactic protein 1 and macrophage inflammatory protein 1α in monocytes stimulated by lipopolysaccharide or TNF-α.	20 nM for 24 hours	104
NW-21	Novel HDAC inhibitor	Radiocarpal joint	Rheumatoid arthritis	collagen antibody-induced arthritis animal model	NW-21reduced inflammation and bone loss in the arthritis modelusing paw inflammation scoring, histology and live animal micro-CT.	daily oral administration at 5 mg/kg/day till end of study	104
MS-275	Benzamide HDAC inhibitor	Macrophage	Alzheimer disease associated neuroinflammation	Immortalized murine macrophage cell line	MS-275 attenuated inflammatory activation of a mouse macrophage.	20 ng/mL for 24 hours	105
MS-275	HDAC inhibitor	Sciatic nerves and inguinal lymph nodes	Human inflammatory demyelinating polyradiculoneuropathies	Experimental autoimmune neuritis mice	- MS-275 reduced the severity and duration of EAN and attenuated local accumulation of macrophages,T cells and B cells. - MS-275 reduced mRNA levels of pro-inflammatory interleukin-1beta, interferon-gamma and interleukine-17. - MS-275 increased expression of anti-inflammatory cytokine interleukine-10 and anti-inflammatory M2 macrophages in sciatic nerves.	3.5 mg/kg, i.p. once a day from day 10 to day 14	106
Tubastatin	HDAC6 selective inhibitor	macrophages	Rheumatoid Arthritis	THP1 cells Freund's complete adjuvant (FCA) induced animal model of inflammation	-Tubastatin inhibited TNF-α and IL-6 in LPS stimulated human THP-1 macrophages. -Tubastatin significantly inhibited of IL-6 in paw tissues of arthritic mice.	272 nM and 712 nM for 24 hours 30 mg/kg i.p. for 5 days	107

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.[62] Bromodomains that can specifically bind acetylated lysine residues in histones serve as chromatin-targeting modules that decipher the histone acetylation code. BET inhibitors that are capable of targeting BET bromodomains and exhibiting therapeutic effects have been described.[63-70] Notably, emerging evidence suggests that BET proteins are involved in pathogenesis of inflammatory diseases[62] and BET inhibitors exhibit potent anti-inflammatory effectsin 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-1b, 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.[72,73]

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.[74-79] The approved anti-DNMTdrugs 5-azacitidine (5AC) and 5-aza-2'-deoxyazacytidine (DAC) are in clinical use for the treatment of myelodysplastic syndrome of all types and chronic myelomonocytic leukemia.[80] The inflammation related studies in animal model of lung injury demonstrate that inhibition of DNMTs activity, at least in part, augments regulatory T-cells (Tregs) number and function to accelerate repair of experimental lung injury. Mice that received DAC exhibited accelerated resolution of their lung inflammation.[81]

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 UFs.

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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