International Journal of Biomedicine 12(4) (2022) 506-514
http://dx.doi.org/10.21103/Article12(4)_RA2

REVIEW ARTICLE

INTERNATIONAL JOURNAL OF BIOMEDICINE

Manipulation of Epigenome: Opportunities and Pitfalls in Fighting Autoimmune Diseases

Hassan Higazi[1*], Faheem Ahmed Khan[2,3], Sara Ali[1], Salma Mohamed[1], Nuruliarizki Shinta Pandupuspitasari[4], Ashraf S. Yousif[5], Praveen Kumar Kandakurti[6]

[1]Department of Medical Laboratory Science, College of Health Science, Gulf Medical University, Ajman, United Arab Emirates
[2]Laboratory of Molecular Biology and Genomics, Faculty of Science and Technology, University of Central Punjab, Lahore, Pakistan
[3]Research Center for Animal Husbandry, National Research and Innovation Agency, Indonesia
[4]Laboratory of Animal Nutrition and Feed Science, Animal Science Department, Faculty of Animal and Agricultural Sciences, Universitas Diponegoro, Semarang, Central Java, Indonesia
[5]Drugs Farm USA LLC, Massachusetts, USA
[6]Department of Physiotherapy, College of Health Sciences, Gulf Medical University, Ajman, United Arab Emirates

Abstract

Many recent studies have focused on the manipulation of the epigenome to understand the mechanistic programming in health and some disease phenotypes. These studies are designed to provide suitable drug targets to cure and/or prevent the outcome of a disease condition. Autoimmune diseases, including obesity and diabetes, are of major health concern nowadays and are the root cause of several diseases of the heart, lungs, and liver. There are several epigenetic mechanisms underlying the manifestation of autoimmune disorders. The recent advances in today's sequencing technology and genome editing have uncovered the role of epigenetic modifications in autoimmune diseases. In this review, we will cover the recent discoveries and their possible application in the control of autoimmune diseases by improving the long-term use of such technologies. The potential drawbacks will also be discussed so that future experiments may be designed to reduce or eliminate the risk factors associated with the use of recent discoveries in the field of medicine. (**International Journal of Biomedicine. 2022;12(4):506-514.**).

Keywords: autoimmune diseases • epigenome • DNA methylation

For citation: Higazi H, Khan FA, Ali S, Mohamed S, Pandupuspitasari NS, Yousif AS, Kandakurti PK. Manipulation of Epigenome: Opportunities and Pitfalls in Fighting Autoimmune Diseases. International Journal of Biomedicine. 2022;12(4):506-514. doi:10.21103/Article12(4)_RA2

Abbreviations

ADs, autoimmune diseases; **A-FABP**, adipose-fatty acid binding protein; **BMI**, body mass index; **GIT**, gastrointestinal tract; **IBD**, inflammatory bowel disease; **LSG**, labial salivary gland; **MS**, multiple sclerosis; **MeCP2**, methyl cap binding protein-2; **NAWM**, normal appearing white matter; **pSS**, primary Sjögren's syndrome; **PBMCs**, peripheral blood mononuclear cells; **RA**, rheumatoid arthritis; **SSc**, systemic sclerosis; **SLE**, systemic lupus erythematosus; **T1DM**, type 1 diabetes; **T2D,** type 2 diabetes; **WAT**, white adipose tissue.

Introduction

History has witnessed numerous famines, which cause malnutrition in the human population, thereby leading to several diseases, including anorexia; however, recently, obesity has taken the world by surprise and has become one of the leading causes of life-threatening diseases.[(1)] This long history of starved conditions has resulted in the evolution of an

organ termed adipose tissue to provide necessary nutrition in times of need.[1] This event has resulted in better regulation of energy via the central nervous system through a set of defined signaling pathways, as well as a self-system for recognizing energy demand and supply requirements.[2] Over time, the human lifestyle has changed significantly, so that now the fat tissues stored in the body cause overweight and obesity.[3] The function of adipose tissue in the era of under-nutrition and over-nutrition is distinct and requires special attention before it causes damage to other organs and tissues.

The obesity epidemic is currently posing a significant threat because it affects children and young adults, compromising their life expectancy by nearly one-half due to an increase in obesity-related disease burden.[4] Obesity can be defined in terms of BMI, where >30 kg/m^2 is considered obese, whereas >25 kg/m^2 is taken as overweight.[5] In the evolutionary context, the genotypes that support energy storage are more suited to survive in the age of famine and low food availability; however, recent developments in agriculture and the food industry have resulted in an epidemic of obesity that is strongly associated with an increase in the incidence of several diseases, including T2D, hypertension, heart ischemia, and other metabolic diseases.[4] Such genotypes termed as "thrifty genotypes"[6] became un-adaptive in recent times of low energy expenditures and are strongly associated with T2D. It was Neel who correlated obesity to sickle cell anemia, of which allele was beneficial to carry at certain times of adaptation and survival.[7] While Neel's hypothesis is partially acceptable, Hales and Barker later showed that malnutrition in the uterus actually causes a disturbance in glucose tolerance and other metabolic syndromes, which is supported by epidemiological data.[8] However, more recently, both hypotheses are being challenged with predator theory, which relates obesity to a genetic drift because of the absence of predators in the recent era.

The epigenetic changes in relation to ADs, obesity, and diabetes have been recently studied, and several target proteins have been recommended for anti-obesity and anti-diabetic targets. This review will go through the major findings and recent biological questions in the context of autoimmunity, obesity, and diabetes and pose it to the scientific community for further research and development.

Countering Obesity and Diabetes

Obesity is one of the major public health issues of the current era,[9] associated with several major diseases of vital organs, such as the heart, lungs, and kidneys, and affecting life-sustaining systems such as circulation, breathing, and excretion, causing mortality and morbidity.[10] Obesity is strongly associated with cancers; however, its molecular mechanism was vague until Hao et al.[11] discovered that circulating adipose fatty acid binding protein (A-FABP) is the cause of promoting breast cancer by direct interaction with tumor cells and activates the IL-6/STAT3/ALDH1pathway. According to the WHO, 1.9 billion adults of age 18 and above are overweight, out of which 650 million are obese. The problem continues in children, and 41 million children under age 5 are reported to be overweight or obese.[12] Much of the world's population is at risk of developing T2D because of easily available high caloric foods, which are now the routine diet of many. This includes children and adolescents, exposing them to the future threat of energy intake and expenditure imbalance.[13] Advanced research in understanding the mechanism and pathways associated with obesity and its cure is a very important need of the moment. Several labs are demonstrating obesity's linkage to epigenetic modulation, and its interaction with diets and environmental factors is becoming clearer.

Gene expression is considered at the core of the obesity problem, which is controlled by several epigenetic mechanisms, including DNA methylation, histone acetylation, and phosphorylation, affecting key pathways responsible for maintaining energy homeostasis. Today basic and advanced molecular, immunological and biotechnological procedures help diagnose several important mechanistic insights into previously unknown phenomena.[14] The following will illustrate the recent advancements in obesity research with a focus on the epigenome.

The major cause of obesity is insulin resistance, which leads to an imbalance in energy homeostasis and has been the target focus of research. It is well established that chronic inflammation of the adipose tissue, skeletal muscles, and liver is the major cause of obesity,[15] with a critical role played by miRNAs and exosomes.[16] Exosomes are the micro-vesicles that have the capability to carry miRNAs, of which the adipose tissue secreting exosomes are shown to carry miR155,[17] of which PPAR-γ is the target gene, and of which miR155 KO mice are shown to have high insulin sensitivity and glucose tolerance[16] It also demonstrates the ability of exosomes to carry the miRNAs of choice to target cells and tissues to therapeutically treat insulin sensitivity and glucose tolerance. WAT browning via activation of the AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1) pathways or increasing the number of brown adipocytes that can dissipate energy is another approach to overcoming obesity outbreaks and is a major area of diabetes and obesity research.[15] Recently, in mouse inguinal WAT, researchers observed neural arborizations at the single-fiber level and uncovered how the sympathetic nervous system and CNS play a role in the architecture of adipose tissue.[18] The efficient induction of begging in humans remains a problem, where a recent study showed how intermittent fasting can induce beiging of WAT and help improve diabetes.[19]

The induction of beiging, however, requires activation of β-adrenergic receptors mostly by cold induction, which is why no successful therapeutic agent could be introduced until now as the β-adrenergic signaling pathway is involved in several functions of tissues and raises safety concerns. Thus what is required is a safe way to induce thermogenic fat cells that can burn fat to reduce weight without causing harm to the body. To this end, Chen et al.[20] discovered fat cells that burn only glucose and termed them glycolytic beige cells. This discovery opens a new avenue to combat obesity as it follows a previously uncharacterized pathway. If such cells are found in humans, they can help develop new therapeutic avenues.

Epigenetics of Systemic Sclerosis

A major autoimmune disease of connective tissues is SSc where skin and internal organs manifest varied clinical features of heterogeneous nature having more prevalence in females than in males.[21] The pathological outcome of SSc is

extensive fibrosis of the skin, blood vessels, lungs, and GIT.[22] The researchers are of the view that anomalous production of IL-1a in SSc patient's skin lesional fibroblasts induces IL-6 and procollagen, which has an epigenetic component that is causing fibrosis.[23] Before it is secreted, such a mechanism can operate at three different levels: gene transcriptional regulation, RNA stability control, and degradation of collagen molecules.[24]

Earlier in 2013, a study published in The Journal of Investigative Dermatology reported the upregulation of p300, an acetyl-transferase that has a predominant role in SSc and that is controlled by TGF-β.[25] The etiology of SSc is reportedly connected to dysregulation in the epigenetic landscape of certain genes. DNA methylation at the promotor region remains at the core of such research. Several important targets in this connection are reported. The hypomethylated genes in SSc are ITGA9, COL23A, ADAM12, COL4A2, and MYO1E, including transcription factors such as RUNX1, RUNX2, and RUNX3 in both diffuse cutaneous SSc and limited cutaneous SSc.[26] The hypermethylation in the promotor region of Foxp3 in SSc patients is determined as one of the other factors in the development of SSc.[27] The defective angiogenesis and micro vasculopathy in SSc patients are linked to lower expression of NRP1 that disturbs VEGF-A/VEGFR-2.[28] Recently, MeCP-2 has been shown to have a predominant role in systemic fibrosis.[29] Mechanistically, TGF-B regulates the expression of MeCP-2 in SSc fibroblasts, which regulates the expression of the extracellular matrix that epigenetically represses sFRP-1 antagonist of the Wnt signaling pathway. This in turn enhances Wnt signaling, which favors fibrosis through glycolysis. MeCP-2 can be targeted as a key regulator in SSc fibrosis.[29] Vasculopathy is one of the hallmarks of SSc and has been recently linked to trappin-2, which upregulates in absence of Fli1 to cause pathological conditions in vessels.[30] Emerging data provides a strong connection of the long noncoding RNA in driving the response of IFNs and its functional relevance in SSc.[31] Several epigenetic therapies at present are considered to cure SSc, which targets include, but are not limited to, histone modifications[32] and methylation regulation.[29] Tables 1 and 2 illustrate ADs, their epigenetic cause, and targeted genes and cells.

Epigenetics of Inflammatory Bowel Disease

IBD is a chronic condition that accompanies patients throughout their whole life. It has been widely accepted that IBD is caused by the dysregulation of cell/cell junction, causing defective barrier activity, resulting in enhanced severity of the disease.[70] It has been classified into two major classes as inflammatory ulcerative colitis and Crohn's disease.[71] Moreover, Crohn's disease affects the entire GIT, whereas ulcerative colitis only affects the large bowel.[72] Recent studies are focused on investigating the role of tight junction dynamics and factors responsible for microtubule organization. One such factor identified is ACF7,[70] the ablation of which demonstrates poor wound healing and tight junction dynamics.

Other studies have demonstrated the role of DNA methylation in the onset and prevalence of IBD influenced by the microbiome. The study by Harris et al.[73] in 2016 revealed a close relationship between the epigenome of the colon and microbiome in adolescents and children, demonstrating several differentially methylated regions having a number of possible therapeutic targets for treating IBD. Intestinal epithelial cell methylation and transcription patterns in child IBD patients define further subtypes and disease associations.[74] Another study demonstrates that a catalytic subunit PRC2, the EZH2 in epithelial cells, is responsible for keeping the epithelial cell barrier integrity.[75]

Gene regulation is a key factor in developing a certain phenotype, which is regulated by DNA methylation. Genome-wide DNA methylation studies have the potential to provide therapeutic targets, which can be used to improve disease phenotypes. A whole genome DNA methylation study performed on naïve ulcerative colitis patients determined several hypo- and hyper-methylated regions of the genome that in the future can be used as potential therapeutic targets in ulcerative colitis patients.[76] There are 577 differential DNA methylation sites with 210 target genes, which a study showed to be responsible for chronic inflammation of the colon in epithelial cells.[77] In a study by McDermott et al.,[78] the top-ranked, IBD-associated PBMC differentially methylated region (promoter region of TRIM39-RPP2) was also significantly hypomethylated in colonic mucosa from pediatric patients with ulcerative colitis; in addition, the authors confirmed TRAF6 hypermethylation using pyrosequencing and found reduced TRAF6 gene expression in PBMCs of IBD patients. Another important gene, Na_/H_exchanger-3 (NHE3), which is responsible for Na absorption and is associated with IBD, is regulated by epigenetic modulation of DNA methylation.[79]

Microbiota diversity and its response is strongly related to IBD, and recently a mechanism by which it can interact has been dissected. A study by Kelly et al. illustrated a new insight into H3K4me3 involved in key pathways of immunoglobulin, cell survival, metabolism, and cell-to-cell signaling. They identified some unexplored key targets in epithelial cells that can be influenced by commensal microbiota in infant IBD patients.[80] There are several genetic markers identified that are associated with IBD and IgG: IKZF1, LAMB1, and MGAT3. Recently, methylation in the promotor region of MGAT3 in CD3+ T cells from patients with ulcerative colitis has been detected.[81] All such targets provide an opportunity to look for further details of its involvement in disease prognosis and cure. The recent technologies of genome editing, including CRISPR-Cas9,[82] can be applied to rewrite the epigenome to its normal state, eliminating the drastic effects of environmental and other burdens on the genome. It is important to keep a full follow-up record of such experiments to eliminate the unwanted outcomes of such applications and to keep the safety concerns associated with each manipulation in mind, and do compulsory experimentation before taking any drug or therapeutic agent for clinical trials.

The Mechanistic Insights into Systemic Lupus Erythematosus

The immune system's capability to recognize self from non-self is essential to conducting defense against foreign antigens and is accomplished during the early developmental stage.[83] Females are more prone to ADs than males,[84] as is the case of SLE, a multisystem, chronic autoimmune disease[85] resulting from T cell hypomethylation, because of lower expression and activity of DNMT1 in Lupus T cells,[86] characterized by a defective ERK signaling pathway, which is reported nine times higher in females of reproductive age.[84]

Table 1.
Epigenetic alterations in autoimmune diseases at the level of DNA methylation.

Cell Type	Diseases	Genes alteration	Epigenetic alteration (DNA)		Pathological site	References
			Hyper-methylation	Hypo-methylation		
Peripheral blood CD4+ T cell	SLE, RA, SSc	CD40LG		√	CD40L (B cell costimulatory molecule encoded on the X chromosome)	(33) (34, 35)
	SLE, SSc, pSS	CD70		√	CD70, B cell costimulatory molecule associated with overproduction of IgG	(36-38)
	SSc, T1DM, RA	FOXP3	√		Forkhead box protein 3, involved in quantitative defects of regulatory T cells	(27, 39, 40)
	MS	HLA-DRB1		√	HLA class II beta chain	(41)
	SLE	IL10, IL13		√	Involved in autoantibody production and tissue damage	(42, 43)
	SLE	IRF5, IFIT2		√	Involved in type I interferon pathway	(44)
	SLE	ITGAL		√	Integrin α-L, associated with cell-cell adhesion	(45)
	SLE	PRF1		√	Perforin 1, involved in autoreactive killing	(46)
Naïve CD4+ T cell	SLE, pSS	STAT1, IFI44L, USP18		√	Involved in type I interferon pathway	(47, 48)
	pSS	LTA		√	Lymphotoxin-α	(47)
	pSS	RUNX1	√		Transcription factor associated to lymphoma	(47)
B cell	SLE	CD5		√	CD5, involved in activation and expansion of autoreactive B cells	(49)
	SLE	HRES-1		√	Human endogenous retroviruses proteins, involved in induction of cross-reactive autoantibodies	(50)
PBMC	RA	IL-6		√	IL-6, involved in B cell response	(51)
	SLE	IFNGR2, MMP14		√	IFN-γ receptor 1, Matrix metalloproteinase-14, involved in inflammation	(52)
	SLE	LCN2		√	Neutrophil gelatinase-associated lipocalin, iron transporter and marker for SLE	(52)
	MS	SHP-1	√		A negative regulator of cytokine signaling through NF-κB and STATs	(53)
CD14+ monocyte	T1DM	HLA-DQB1		√	HLA class II	(54)
	T1DM	RFXAP		√	HLA class II regulating element	(54)
	T1DM	NFKB1A		√	Regulator of apoptosis and inflammation	(54)
	T1DM	GAD2		√	GAD65, a major autoantigen involved in T1D	(54)
	T1DM	TNF	√		Key inflammatory cytokine	(54)
	T1DM	CD6	√		Involved in lymphocyte activation and differentiation	(54)
Fibroblast	SSc	FLI1	√		Involved in type I collagen expression	(55)
Fibroblast, PBMC	SSc	DKK1, SFRP1	√		Wnt signaling antagonists	(56)
Synovial fibroblast	RA	SFRP1, SFRP4	√		Wnt signaling antagonists	(57, 58)
	RA	DR3	√		Death receptor 3, associated with cell apoptosis	(59)
NAWM	MS	PAD2		√	Peptidyl argininedeiminase type II, responsible for the increased citrullinated myelin basic protein	(60)
LSG	pSS	DST	√		BP230, bullous pemphigoid antigen 1 protein	(61)

SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; MS, multiple sclerosis; SSc, systemic sclerosis; T1DM, type 1 diabetes; pSS, primary Sjögren's syndrome; PBMC, peripheral blood mononuclear cell; NAWM, normal appearing white matter; LSG, labial salivary gland.

Table 2. Epigenetic alterations in autoimmune diseases at the level of histone modification.

Cell type	Disease	Epigenetic alteration	Affected gene	Dysregulation		References
				upregulation	downregulation	
T cell	SLE	H3 and H4 hypoacetylation, H3K9 hypomethylation	ND			(62)
		Increased histone H3 acetylation at lysine 18 (H3K18ac)	IL10	√		(29)
		Increased H3 acetylation, dimethylated H3 lysine4 (H3K4me2)	CD70	√		(63)
	T1DM	Increased H3K9me2	CTLA4		√	(64)
B cell	SSc	H4 hyperacetylation, decreased HDAC2 and HDAC7; H3K9 hypomethylation, decreased SUV39H2 (member of HMT), increased JHDM2A (member of HDM)	ND			(6)
Monocyte	T1DM	Increased H3K9 acetylation (H3K9Ac)	HLA-DRB1, HLA-DQB1	√		(65)
	SLE	Global H4 hyperacetylation	IRF1, RFX1, BLIMP1	√		(66)
Fibroblast	SSc	Increased H3 and H4 deacetylation	FLI1		√	(55)
		Inhibition of H3K27me3	FOSL2	√		(67)
Synovial fibroblast	RA	Increased zeste homologue 2 (EZH2, member of HMT)	SFRP1		√	(57)
		Increased sirtuin 1 (Sirt1, member of HDAC)	ND			(68)
Oligodendrocyte	MS	Increased histone H3 deacetylation	ND			(69)

SLE, systemic lupus erythematosus; T1DM, type 1 diabetes; SSc, systemic sclerosis; RA, rheumatoid arthritis; MS, multiple sclerosis; HMT, histone methyltransferases; HDAC, histone deacetylase; HDM, histone demethylase; ND, not determined.

The predominant adaptive immune cells, B lymphocytes and T lymphocytes, are both involved in the development of SLE.[83] Methylation of certain genes is one of the major reasons for ADs, and it has been found that B cell promoter hypermethylation is associated with SLE pathogenesis.[88] CD4+T cells from SLE patients with lower expression of TNFAIP3, because of hypermethylation of histone H3K4, resulting in overproduction of pro-inflammatory cytokines, appears to be a probable cause of SLE.[89] Wang et al.[6] showed that Talen(transcription activation-like effector nuclease)-mediated enhancer knockout influences TNFAIP3 gene expression and mimics a molecular phenotype associated with SLE.

Genome-wide association studies in SLE [90] identified more than 50 risk genes or loci to higher heritability of SLE. Recent genome sequencing technologies have uncovered unprecedented information regarding the development of ADs. The perturb-ATAC sequencing, for example, has shown enrichment of NF-κB binding sites near the causative variations of SLE and SSc,[91] and these sites show altered accessibility at chromatin level when NFKB1 or RELA are depleted.[92]

A shift in DNA methylation status in naïve CD4+ T cells was observed in favor of T cell activation in SLE patients with a significant increase in EZH2 binding enrichment near high methylation activity in lupus patients.[93] Furthermore, it was determined that EZH2 has a predominant role in T cell adhesion by upregulating JAM-A, hence providing a therapeutic target for lupus treatment by either blocking expression of EZH2 or JAM-A to limit T cell migration or adhesion.[94] The lupus patients demonstrated demethylated CD4+CD28+KIR+CD11a^{hi} T cells characterized by epigenetic modulation, resulting in pro-inflammatory cytokines, providing another therapeutic avenue to treat lupus by either eliminating these cells or blocking them to produce pro-inflammatory cytokines.[84]

Mechanistic Insight of Protein Acetylation and Deacetylation

Epigenetic modifications control the expression of genes that become the focus of basic and medical research to find suitable drug targets for the prevention and cure of ADs. ADs in particular are prone to histone acetylation and deacetylation, which demands a detailed investigation of the mechanistic understanding of these modifications.[95] The interaction of negatively charged DNA backbone is possible because of the positively charged histones N-terminal, which is neutralized by histone acetylation, hence weakening DNA binding and making the chromatin accessible to transcription.[96] HATs and HDACs are the two enzyme classes responsible for acetylation and deacetylation respectively. The chromatin is closed when de-acetylation takes place, consequently resulting in decreased gene expression due to no access by transcription factors. The environmental effects and diseases affect the life expectancy and living quality of an individual (Figure 1).

Currently, more than 2000 proteins are identified to be acetylated in mammalian cells, which enhance the canvas of acetylation comparable to other major post-translational mechanisms such as phosphorylation and ubiquitination.[97] A wide range of proteins involved in different cellular processes undergo acetylation, making it one of the important events to be studied in detail. Almost all enzymes involved in gluconeogenesis, glycolysis, TCA cycle, urea cycle, fatty acid oxidation, and glycogen and nitrogen metabolism are acetylated.[43] There are several mechanisms by which acetylation regulates substrate availability, one of which is by blocking the enzyme binding to a substrate; another is by blocking the binding of metabolites. Acetylation can also modulate the localization of proteins.[98]

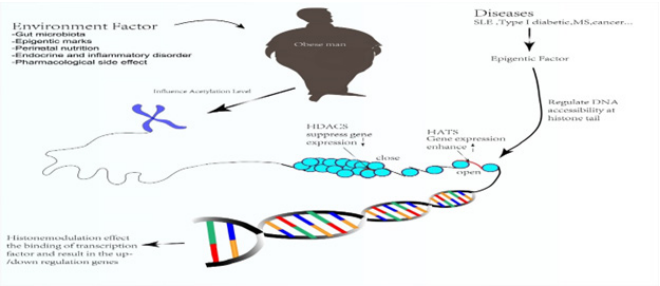

Fig. 1. *Environmental factors induce obesity and disease by affecting acetylation and de-acetylation.*

Conclusion

In summary, epigenetic modifications play a crucial role in autoimmune disease onset, which is monitored and controlled in homeostasis by certain therapies, and therapeutic agents can relieve many of the disease symptoms. DNA methylation and protein acetylation play a very important role in maintaining the epigenome of organisms; hence, more focused studies on the safety concerns of these targets are required before bringing bench research to clinical settings.

Acknowledgements

We thank Nada Jovanovic from MGH IHP for the language proof-reading and editing the manuscript.

Competing Interests

The authors declare that they have no competing interests.

References

1. Li C, Tobi EW, Heijmans BT, Lumey LH. The effect of the Chinese Famine on type 2 diabetes mellitus epidemics. Nat Rev Endocrinol. 2019 Jun;15(6):313-314. doi: 10.1038/s41574-019-0195-5.
2. Lenard NR, Berthoud HR. Central and peripheral regulation of food intake and physical activity: pathways and genes. Obesity (Silver Spring). 2008 Dec;16 Suppl 3(Suppl

***Corresponding author:** Dr. Hassan Higazi. Department of Medical Laboratory Sciences, College of Health Sciences, Gulf Medical University, Ajman, United Arab Emirates. E-mail: hhigazi8@gmail.com*

3):S11-22. doi: 10.1038/oby.2008.511.
3. Stefan N, Schick F, Häring HU. Causes, Characteristics, and Consequences of Metabolically Unhealthy Normal Weight in Humans. Cell Metab. 2017 Aug 1;26(2):292-300. doi: 10.1016/j.cmet.2017.07.008.
4. Thaiss CA, Levy M, Grosheva I, Zheng D, Soffer E, Blacher E, et al. Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection. Science. 2018 Mar 23;359(6382):1376-1383. doi: 10.1126/science.aar3318.
5. Global BMI Mortality Collaboration, Di Angelantonio E, Bhupathiraju ShN, Wormser D, Gao P, Kaptoge S, Berrington de Gonzalez A, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet. 2016 Aug 20;388(10046):776-86. doi: 10.1016/S0140-6736(16)30175-1. Epub 2016 Jul 13. PMID: 27423262; PMCID: PMC4995441.
6. Wang S, Wen F, Tessneer KL, Gaffney PM. TALEN-mediated enhancer knockout influences TNFAIP3 gene expression and mimics a molecular phenotype associated with systemic lupus erythematosus. Genes Immun. 2016 Apr;17(3):165-70. doi: 10.1038/gene.2016.4.
7. NEEL JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? Am J Hum Genet. 1962 Dec;14(4):353-62. PMID: 13937884; PMCID: PMC1932342.
8. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia. 1992 Jul;35(7):595-601. doi: 10.1007/BF00400248. PMID: 1644236.
9. Crossman MK, Kazdin AE, Galbraith K, Eros L, Santos LR. Evaluating the Influence of the Presence of a Dog on Bias toward Individuals with Overweight and Obesity. Anthrozoös. 2018;31(1):77-88.
10. Gurzov EN, Stanley WJ, Pappas EG, Thomas HE, Gough DJ. The JAK/STAT pathway in obesity and diabetes. FEBS J. 2016 Aug;283(16):3002-15. doi: 10.1111/febs.13709.
11. Hao J, Zhang Y, Yan X, Yan F, Sun Y, Zeng J, Waigel S, Yin Y, Fraig MM, Egilmez NK, Suttles J, Kong M, Liu S, Cleary MP, Sauter E, Li B. Circulating Adipose Fatty Acid Binding Protein Is a New Link Underlying Obesity-Associated Breast/Mammary Tumor Development. Cell Metab. 2018 Nov 6;28(5):689-705.e5. doi: 10.1016/j.cmet.2018.07.006.
12. WHO. Obesity and overweight. 9 June 2021. Available at: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
13. Cheng J, Song J, He X, Zhang M, Hu S, Zhang S, et al. Loss of Mbd2 Protects Mice Against High-Fat Diet-Induced Obesity and Insulin Resistance by Regulating the Homeostasis of Energy Storage and Expenditure. Diabetes. 2016 Nov;65(11):3384-3395. doi: 10.2337/db16-0151. Epub 2016 Aug 23. Erratum in: Diabetes. 2017 Sep;66(9):2531.
14. Heymsfield SB, Wadden TA. Mechanisms, Pathophysiology, and Management of Obesity. N Engl J Med. 2017 Jan 19;376(3):254-266. doi: 10.1056/NEJMra1514009. PMID: 28099824.
15. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, et al. Identification and importance of brown adipose tissue in adult humans. N Engl J Med. 2009 Apr 9;360(15):1509-17. doi: 10.1056/NEJMoa0810780.
16. Ying W, Riopel M, Bandyopadhyay G, Dong Y, Birmingham A, Seo JB, et al. Adipose Tissue Macrophage-Derived Exosomal miRNAs Can Modulate In Vivo and In Vitro Insulin Sensitivity. Cell. 2017 Oct 5;171(2):372-384.e12. doi: 10.1016/j.cell.2017.08.035.
17. Gaudet AD, Fonken LK, Gushchina LV, Aubrecht TG, Maurya SK, Periasamy M, et al. miR-155 Deletion in Female Mice Prevents Diet-Induced Obesity. Sci Rep. 2016 Mar 8;6:22862. doi: 10.1038/srep22862.
18. Jiang H, Ding X, Cao Y, Wang H, Zeng W. Dense Intra-adipose Sympathetic Arborizations Are Essential for Cold-Induced Beiging of Mouse White Adipose Tissue. Cell Metab. 2017 Oct 3;26(4):686-692.e3. doi: 10.1016/j.cmet.2017.08.016.
19. Li G, Xie C, Lu S, Nichols RG, Tian Y, Li L, et al. Intermittent Fasting Promotes White Adipose Browning and Decreases Obesity by Shaping the Gut Microbiota. Cell Metab. 2017 Oct 3;26(4):672-685.e4. doi: 10.1016/j.cmet.2017.08.019.
20. Chen Y, Ikeda K, Yoneshiro T, Scaramozza A, Tajima K, Wang Q, et al. Thermal stress induces glycolytic beige fat formation via a myogenic state. Nature. 2019 Jan;565(7738):180-185. doi: 10.1038/s41586-018-0801-z.
21. Wielosz E, Majdan M, Dryglewska M, Suszek D. Comparison of clinical and serological parameters in female and male patients with systemic sclerosis. Reumatologia. 2015;53(6):315-20. doi: 10.5114/reum.2015.57637.
22. Assassi S, Del Junco D, Sutter K, McNearney TA, Reveille JD, Karnavas A, et al. Clinical and genetic factors predictive of mortality in early systemic sclerosis. Arthritis Rheum. 2009 Oct 15;61(10):1403-11. doi: 10.1002/art.24734.
23. Varga J, Abraham D. Systemic sclerosis: a prototypic multisystem fibrotic disorder. J Clin Invest. 2007 Mar;117(3):557-67. doi: 10.1172/JCI31139.
24. Elkon R, Zlotorynski E, Zeller KI, Agami R. Major role for mRNA stability in shaping the kinetics of gene induction. BMC Genomics. 2010 Apr 21;11:259. doi: 10.1186/1471-2164-11-259.
25. Ghosh AK, Bhattacharyya S, Lafyatis R, Farina G, Yu J, Thimmapaya B, et al. p300 is elevated in systemic sclerosis and its expression is positively regulated by TGF-β: epigenetic feed-forward amplification of fibrosis. J Invest Dermatol. 2013 May;133(5):1302-10. doi: 10.1038/jid.2012.479.
26. Altorok N, Tsou PS, Coit P, Khanna D, Sawalha AH. Genome-wide DNA methylation analysis in dermal fibroblasts from patients with diffuse and limited systemic sclerosis reveals common and subset-specific DNA methylation aberrancies. Ann Rheum Dis. 2015 Aug;74(8):1612-20. doi: 10.1136/annrheumdis-2014-205303.
27. Wang YY, Wang Q, Sun XH, Liu RZ, Shu Y, Kanekura T, et al. DNA hypermethylation of the forkhead box protein 3 (FOXP3) promoter in CD4+ T cells of patients with systemic sclerosis. Br J Dermatol. 2014 Jul;171(1):39-47. doi: 10.1111/bjd.12913.
28. Romano E, Chora I, Manetti M, Mazzotta C, Rosa I, Bellando-Randone S, et al. Decreased expression of neuropilin-1 as a novel key factor contributing to peripheral microvasculopathy and defective angiogenesis in systemic sclerosis. Ann Rheum Dis. 2016 Aug;75(8):1541-9. doi: 10.1136/annrheumdis-2015-207483.
29. Henderson J, Brown M, Horsburgh S, Duffy L, Wilkinson S, Worrell J, Stratton R, O'Reilly S. Methyl cap binding protein 2: a key epigenetic protein in systemic sclerosis. Rheumatology (Oxford). 2019 Mar 1;58(3):527-535. doi: 10.1093/rheumatology/key327.
30. Miyagawa T, Asano Y, Saigusa R, Hirabayashi M, Yamashita T, Taniguchi T, et al. A potential contribution of trappin-2 to the development of vasculopathy in systemic

sclerosis. J Eur Acad Dermatol Venereol. 2019 Apr;33(4):753-760. doi: 10.1111/jdv.15387.
31. Mariotti B, Servaas NH, Rossato M, Tamassia N, Cassatella MA, Cossu M, et al. The Long Non-coding RNA NRIR Drives IFN-Response in Monocytes: Implication for Systemic Sclerosis. Front Immunol. 2019 Jan 31;10:100. doi: 10.3389/fimmu.2019.00100.
32. Angiolilli C, Marut W, van der Kroef M, Chouri E, Reedquist KA, Radstake TRDJ. New insights into the genetics and epigenetics of systemic sclerosis. Nat Rev Rheumatol. 2018 Nov;14(11):657-673. doi: 10.1038/s41584-018-0099-0.
33. Lu Q, Wu A, Tesmer L, Ray D, Yousif N, Richardson B. Demethylation of CD40LG on the inactive X in T cells from women with lupus. J Immunol. 2007 Nov 1;179(9):6352-8. doi: 10.4049/jimmunol.179.9.6352.
34. Lian X, Xiao R, Hu X, Kanekura T, Jiang H, Li Y, et al. DNA demethylation of CD40l in CD4+ T cells from women with systemic sclerosis: a possible explanation for female susceptibility. Arthritis Rheum. 2012 Jul;64(7):2338-45. doi: 10.1002/art.34376.
35. Liao J, Liang G, Xie S, Zhao H, Zuo X, Li F, et al. CD40L demethylation in CD4(+) T cells from women with rheumatoid arthritis. Clin Immunol. 2012 Oct;145(1):13-8. doi: 10.1016/j.clim.2012.07.006.
36. Oelke K, Lu Q, Richardson D, Wu A, Deng C, Hanash S, Richardson B. Overexpression of CD70 and overstimulation of IgG synthesis by lupus T cells and T cells treated with DNA methylation inhibitors. Arthritis Rheum. 2004 Jun;50(6):1850-60. doi: 10.1002/art.20255.
37. Jiang H, Xiao R, Lian X, Kanekura T, Luo Y, Yin Y, Zhang G, Yang Y, Wang Y, Zhao M, Lu Q. Demethylation of TNFSF7 contributes to CD70 overexpression in CD4+ T cells from patients with systemic sclerosis. Clin Immunol. 2012 Apr;143(1):39-44. doi: 10.1016/j.clim.2012.01.005.
38. Yin H, Zhao M, Wu X, Gao F, Luo Y, Ma L, et al. Hypomethylation and overexpression of CD70 (TNFSF7) in CD4+ T cells of patients with primary Sjögren's syndrome. J Dermatol Sci. 2010 Sep;59(3):198-203. doi: 10.1016/j.jdermsci.2010.06.011.
39. Li Y, Zhao M, Hou C, Liang G, Yang L, Tan Y, et al. Abnormal DNA methylation in CD4+ T cells from people with latent autoimmune diabetes in adults. Diabetes Res Clin Pract. 2011 Nov;94(2):242-8. doi: 10.1016/j.diabres.2011.07.027.
40. Janson PC, Linton LB, Bergman EA, Marits P, Eberhardson M, Piehl F, et al. Profiling of CD4+ T cells with epigenetic immune lineage analysis. J Immunol. 2011 Jan 1;186(1):92-102. doi: 10.4049/jimmunol.1000960.
41. Graves MC, Benton M, Lea RA, Boyle M, Tajouri L, Macartney-Coxson D, et al. Methylation differences at the HLA-DRB1 locus in CD4+ T-Cells are associated with multiple sclerosis. Mult Scler. 2014 Jul;20(8):1033-41. doi: 10.1177/1352458513516529.
42. Hedrich CM, Rauen T, Apostolidis SA, Grammatikos AP, Rodriguez Rodriguez N, Ioannidis C, et al. Stat3 promotes IL-10 expression in lupus T cells through trans-activation and chromatin remodeling. Proc Natl Acad Sci U S A. 2014 Sep 16;111(37):13457-62. doi: 10.1073/pnas.1408023111.
43. Zhao M, Tang J, Gao F, Wu X, Liang Y, Yin H, Lu Q. Hypomethylation of IL10 and IL13 promoters in CD4+ T cells of patients with systemic lupus erythematosus. J Biomed Biotechnol. 2010;2010:931018. doi: 10.1155/2010/931018.
44. Absher DM, Li X, Waite LL, Gibson A, Roberts K, Edberg J, et al. Genome-wide DNA methylation analysis of systemic lupus erythematosus reveals persistent hypomethylation of interferon genes and compositional changes to CD4+ T-cell populations. PLoS Genet. 2013;9(8):e1003678. doi: 10.1371/journal.pgen.1003678.
45. Lu Q, Kaplan M, Ray D, Ray D, Zacharek S, Gutsch D, Richardson B. Demethylation of ITGAL (CD11a) regulatory sequences in systemic lupus erythematosus. Arthritis Rheum. 2002 May;46(5):1282-91. doi: 10.1002/art.10234.
46. Kaplan MJ, Lu Q, Wu A, Attwood J, Richardson B. Demethylation of promoter regulatory elements contributes to perforin overexpression in CD4+ lupus T cells. J Immunol. 2004 Mar 15;172(6):3652-61. doi: 10.4049/jimmunol.172.6.3652.
47. Altorok N, Coit P, Hughes T, Koelsch KA, Stone DU, Rasmussen A, et al. Genome-wide DNA methylation patterns in naive CD4+ T cells from patients with primary Sjögren's syndrome. Arthritis Rheumatol. 2014 Mar;66(3):731-9. doi: 10.1002/art.38264.
48. Coit P, Jeffries M, Altorok N, Dozmorov MG, Koelsch KA, Wren JD, et al. Genome-wide DNA methylation study suggests epigenetic accessibility and transcriptional poising of interferon-regulated genes in naïve CD4+ T cells from lupus patients. J Autoimmun. 2013 Jun;43:78-84. doi: 10.1016/j.jaut.2013.04.003.
49. Garaud S, Le Dantec C, Jousse-Joulin S, Hanrotel-Saliou C, Saraux A, Mageed RA, et al. IL-6 modulates CD5 expression in B cells from patients with lupus by regulating DNA methylation. J Immunol. 2009 May 1;182(9):5623-32. doi: 10.4049/jimmunol.0802412.
50. Fali T, Le Dantec C, Thabet Y, Jousse S, Hanrotel C, Youinou P, et al. DNA methylation modulates HRES1/p28 expression in B cells from patients with Lupus. Autoimmunity. 2014 Jun;47(4):265-71. doi: 10.3109/08916934.2013.826207.
51. Nile CJ, Read RC, Akil M, Duff GW, Wilson AG. Methylation status of a single CpG site in the IL6 promoter is related to IL6 messenger RNA levels and rheumatoid arthritis. Arthritis Rheum. 2008 Sep;58(9):2686-93. doi: 10.1002/art.23758.
52. Allanore Y, Borderie D, Meune C, Lemaréchal H, Weber S, Ekindjian OG, Kahan A. Increased plasma soluble CD40 ligand concentrations in systemic sclerosis and association with pulmonary arterial hypertension and digital ulcers. Ann Rheum Dis. 2005 Mar;64(3):481-3. doi: 10.1136/ard.2003.020040.
53. Kumagai C, Kalman B, Middleton FA, Vyshkina T, Massa PT. Increased promoter methylation of the immune regulatory gene SHP-1 in leukocytes of multiple sclerosis subjects. J Neuroimmunol. 2012 May 15;246(1-2):51-7. doi: 10.1016/j.jneuroim.2012.03.003.
54. Rakyan VK, Beyan H, Down TA, Hawa MI, Maslau S, Aden D, et al. Identification of type 1 diabetes-associated DNA methylation variable positions that precede disease diagnosis. PLoS Genet. 2011 Sep;7(9):e1002300. doi: 10.1371/journal.pgen.1002300.
55. Wang Y, Fan PS, Kahaleh B. Association between enhanced type I collagen expression and epigenetic repression of the FLI1 gene in scleroderma fibroblasts. Arthritis Rheum. 2006 Jul;54(7):2271-9. doi: 10.1002/art.21948.
56. Dees C, Schlottmann I, Funke R, Distler A, Palumbo-Zerr K, Zerr P, et al. The Wnt antagonists DKK1 and SFRP1 are downregulated by promoter hypermethylation in systemic sclerosis. Ann Rheum Dis. 2014 Jun;73(6):1232-9. doi: 10.1136/annrheumdis-2012-203194.
57. Trenkmann M, Brock M, Gay RE, Kolling C, Speich

R, Michel BA, Gay S, Huber LC. Expression and function of EZH2 in synovial fibroblasts: epigenetic repression of the Wnt inhibitor SFRP1 in rheumatoid arthritis. Ann Rheum Dis. 2011 Aug;70(8):1482-8. doi: 10.1136/ard.2010.143040.
58. Miao CG, Yang YY, He X, Huang C, Huang Y, Qin D, Du CL, Li J. MicroRNA-152 modulates the canonical Wnt pathway activation by targeting DNA methyltransferase 1 in arthritic rat model. Biochimie. 2014 Nov;106:149-56. doi: 10.1016/j.biochi.2014.08.016.
59. Takami N, Osawa K, Miura Y, Komai K, Taniguchi M, Shiraishi M, et al. Hypermethylated promoter region of DR3, the death receptor 3 gene, in rheumatoid arthritis synovial cells. Arthritis Rheum. 2006 Mar;54(3):779-87. doi: 10.1002/art.21637.
60. Mastronardi FG, Noor A, Wood DD, Paton T, Moscarello MA. Peptidyl argininedeiminase 2 CpG island in multiple sclerosis white matter is hypomethylated. J Neurosci Res. 2007 Jul;85(9):2006-16. doi: 10.1002/jnr.21329.
61. González S, Aguilera S, Alliende C, Urzúa U, Quest AF, Herrera L, et al. Alterations in type I hemidesmosome components suggestive of epigenetic control in the salivary glands of patients with Sjögren's syndrome. Arthritis Rheum. 2011 Apr;63(4):1106-15. doi: 10.1002/art.30212.
62. Hu N, Qiu X, Luo Y, Yuan J, Li Y, Lei W, et al. Abnormal histone modification patterns in lupus CD4+ T cells. J Rheumatol. 2008 May;35(5):804-10.
63. Zhou Y, Qiu X, Luo Y, Yuan J, Li Y, Zhong Q, Zhao M, Lu Q. Histone modifications and methyl-CpG-binding domain protein levels at the TNFSF7 (CD70) promoter in SLE CD4+ T cells. Lupus. 2011 Nov;20(13):1365-71. doi: 10.1177/0961203311413412.
64. Miao F, Smith DD, Zhang L, Min A, Feng W, Natarajan R. Lymphocytes from patients with type 1 diabetes display a distinct profile of chromatin histone H3 lysine 9 dimethylation: an epigenetic study in diabetes. Diabetes. 2008 Dec;57(12):3189-98. doi: 10.2337/db08-0645.
65. Miao F, Chen Z, Zhang L, Liu Z, Wu X, Yuan YC, Natarajan R. Profiles of epigenetic histone post-translational modifications at type 1 diabetes susceptible genes. J Biol Chem. 2012 May 11;287(20):16335-45. doi: 10.1074/jbc.M111.330373.
66. Zhang Z, Song L, Maurer K, Petri MA, Sullivan KE. Global H4 acetylation analysis by ChIP-chip in systemic lupus erythematosus monocytes. Genes Immun. 2010 Mar;11(2):124-33. doi: 10.1038/gene.2009.66.
67. Krämer M, Dees C, Huang J, Schlottmann I, Palumbo-Zerr K, Zerr P, et al. Inhibition of H3K27 histone trimethylation activates fibroblasts and induces fibrosis. Ann Rheum Dis. 2013 Apr;72(4):614-20. doi: 10.1136/annrheumdis-2012-201615.
68. Niederer F, Ospelt C, Brentano F, Hottiger MO, Gay RE, Gay S, et al. SIRT1 overexpression in the rheumatoid arthritis synovium contributes to proinflammatory cytokine production and apoptosis resistance. Ann Rheum Dis. 2011 Oct;70(10):1866-73. doi: 10.1136/ard.2010.148957.
69. Pedre X, Mastronardi F, Bruck W, López-Rodas G, Kuhlmann T, Casaccia P. Changed histone acetylation patterns in normal-appearing white matter and early multiple sclerosis lesions. J Neurosci. 2011 Mar 2;31(9):3435-45. doi: 10.1523/JNEUROSCI.4507-10.2011. Erratum in: J Neurosci. 2011 Jun 1;31(22):8325.
70. Ma Y, Yue J, Zhang Y, Shi C, Odenwald M, Liang WG, et al. ACF7 regulates inflammatory colitis and intestinal wound response by orchestrating tight junction dynamics. Nat Commun. 2017 May 25;8:15375. doi: 10.1038/ncomms15375. Erratum in: Nat Commun. 2017 Jul 11;8:16121.
71. Barkas F, Liberopoulos E, Kei A, Elisaf M. Electrolyte and acid-base disorders in inflammatory bowel disease. Ann Gastroenterol. 2013;26(1):23-28. PMID: 24714322; PMCID: PMC3959504.
72. Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. Pharmacotherapy: A Pathophysiologic Approach, ed: McGraw-Hill Medical, New York; 2014.
73. Harris RA, Shah R, Hollister EB, Tronstad RR, Hovdenak N, Szigeti R, et al. Colonic Mucosal Epigenome and Microbiome Development in Children and Adolescents. J Immunol Res. 2016;2016:9170162. doi: 10.1155/2016/9170162.
74. Howell KJ, Kraiczy J, Nayak KM, Gasparetto M, Ross A, Lee C, et al. DNA Methylation and Transcription Patterns in Intestinal Epithelial Cells From Pediatric Patients With Inflammatory Bowel Diseases Differentiate Disease Subtypes and Associate With Outcome. Gastroenterology. 2018 Feb;154(3):585-598. doi: 10.1053/j.gastro.2017.10.007.
75. Liu Y, Peng J, Sun T, Li N, Zhang L, Ren J, et al. Epithelial EZH2 serves as an epigenetic determinant in experimental colitis by inhibiting TNFα-mediated inflammation and apoptosis. Proc Natl Acad Sci U S A. 2017 May 9;114(19):E3796-E3805. doi: 10.1073/pnas.1700909114.
76. Taman H, Fenton CG, Hensel IV, Anderssen E, Florholmen J, Paulssen RH. Genome-wide DNA Methylation in Treatment-naïve Ulcerative Colitis. J Crohns Colitis. 2018 Nov 15;12(11):1338-1347. doi: 10.1093/ecco-jcc/jjy117.
77. Barnicle A, Seoighe C, Greally JM, Golden A, Egan LJ. Inflammation-associated DNA methylation patterns in epithelium of ulcerative colitis. Epigenetics. 2017 Aug;12(8):591-606. doi: 10.1080/15592294.2017.1334023.
78. McDermott E, Ryan EJ, Tosetto M, Gibson D, Burrage J, Keegan D, et al. DNA Methylation Profiling in Inflammatory Bowel Disease Provides New Insights into Disease Pathogenesis. J Crohns Colitis. 2016 Jan;10(1):77-86. doi: 10.1093/ecco-jcc/jjv176.
79. Kumar A, Malhotra P, Coffing H, Priyamvada S, Anbazhagan AN, Krishnan HR, et al. Epigenetic modulation of intestinal Na^+/H^+ exchanger-3 expression. Am J Physiol Gastrointest Liver Physiol. 2018 Mar 1;314(3):G309-G318. doi: 10.1152/ajpgi.00293.2017.
80. Kelly D, Kotliar M, Woo V, Jagannathan S, Whitt J, Moncivaiz J, et al. Microbiota-sensitive epigenetic signature predicts inflammation in Crohn's disease. JCI Insight. 2018 Sep 20;3(18):e122104. doi: 10.1172/jci.insight.122104.
81. Klasić M, Markulin D, Vojta A, Samaržija I, Biruš I, Dobrinić P, et al.; IBD consortium, Lauc G, Zoldoš V. Promoter methylation of the *MGAT3* and *BACH2* genes correlates with the composition of the immunoglobulin G glycome in inflammatory bowel disease. Clin Epigenetics. 2018 Jun 4;10:75. doi: 10.1186/s13148-018-0507-y.
82. Khan FA, Pandupuspitasari NS, Chun-Jie H, Ao Z, Jamal M, Zohaib A, et al. CRISPR/Cas9 therapeutics: a cure for cancer and other genetic diseases. Oncotarget. 2016 Aug 9;7(32):52541-52552. doi: 10.18632/oncotarget.9646.
83. Mohan C, Putterman C. Genetics and pathogenesis of systemic lupus erythematosus and lupus nephritis. Nat Rev Nephrol. 2015 Jun;11(6):329-41. doi: 10.1038/nrneph.2015.33.
84. Gensterblum E, Renauer P, Coit P, Strickland FM, Kilian NC, Miller S, et al.. CD4+CD28+KIR+CD11a^{hi} T cells correlate with disease activity and are characterized by a pro-

inflammatory epigenetic and transcriptional profile in lupus patients. J Autoimmun. 2018 Jan;86:19-28. doi: 10.1016/j.jaut.2017.09.011.
85. Chen L, Morris DL, Vyse TJ. Genetic advances in systemic lupus erythematosus: an update. Curr Opin Rheumatol. 2017 Sep;29(5):423-433. doi: 10.1097/BOR.0000000000000411.
86. Yung R, Kaplan M, Ray D, Schneider K, Mo RR, Johnson K, Richardson B. Autoreactive murine Th1 and Th2 cells kill syngeneic macrophages and induce autoantibodies. Lupus. 2001;10(8):539-46. doi: 10.1191/096120301701549660.
87. Long H, Yin H, Wang L, Gershwin ME, Lu Q. The critical role of epigenetics in systemic lupus erythematosus and autoimmunity. J Autoimmun. 2016 Nov;74:118-138. doi: 10.1016/j.jaut.2016.06.020.
88. Ulff-Møller CJ, Asmar F, Liu Y, Svendsen AJ, Busato F, Grønbaek K, Tost J, Jacobsen S. Twin DNA Methylation Profiling Reveals Flare-Dependent Interferon Signature and B Cell Promoter Hypermethylation in Systemic Lupus Erythematosus. Arthritis Rheumatol. 2018 Jun;70(6):878-890. doi: 10.1002/art.40422.
89. Zhao H, Wang L, Luo H, Li QZ, Zuo X. TNFAIP3 downregulation mediated by histone modification contributes to T-cell dysfunction in systemic lupus erythematosus. Rheumatology (Oxford). 2017 May 1;56(5):835-843. doi: 10.1093/rheumatology/kew508.
90. Bentham J, Morris DL, Graham DSC, Pinder CL, Tombleson P, Behrens TW, et al. Genetic association analyses implicate aberrant regulation of innate and adaptive immunity genes in the pathogenesis of systemic lupus erythematosus. Nat Genet. 2015 Dec;47(12):1457-1464. doi: 10.1038/ng.3434.
91. Farh KK, Marson A, Zhu J, Kleinewietfeld M, Housley WJ, Beik S, et al. Genetic and epigenetic fine mapping of causal autoimmune disease variants. Nature. 2015 Feb 19;518(7539):337-43. doi: 10.1038/nature13835.
92. Rubin AJ, Parker KR, Satpathy AT, Qi Y, Wu B, Ong AJ, et al. Coupled Single-Cell CRISPR Screening and Epigenomic Profiling Reveals Causal Gene Regulatory Networks. Cell. 2019 Jan 10;176(1-2):361-376.e17. doi: 10.1016/j.cell.2018.11.022.
93. Coit P, Dozmorov MG, Merrill JT, McCune WJ, Maksimowicz-McKinnon K, Wren JD, Sawalha AH. Epigenetic Reprogramming in Naive CD4+ T Cells Favoring T Cell Activation and Non-Th1 Effector T Cell Immune Response as an Early Event in Lupus Flares. Arthritis Rheumatol. 2016 Sep;68(9):2200-9. doi: 10.1002/art.39720.
94. Tsou PS, Coit P, Kilian NC, Sawalha AH. EZH2 Modulates the DNA Methylome and Controls T Cell Adhesion Through Junctional Adhesion Molecule A in Lupus Patients. Arthritis Rheumatol. 2018 Jan;70(1):98-108. doi: 10.1002/art.40338.
95. Zouali M. Chapter 28—epigenetics and autoimmune diseases A2—Rose, Noel R. In: Mackay IR (ed) The autoimmune diseases. Academic Press, Boston, 2014; pp 381–401.
96. Thiagalingam S, Cheng KH, Lee HJ, Mineva N, Thiagalingam A, Ponte JF. Histone deacetylases: unique players in shaping the epigenetic histone code. Ann N Y Acad Sci. 2003 Mar;983:84-100. doi: 10.1111/j.1749-6632.2003.tb05964.x.
97. Guan KL, Xiong Y. Regulation of intermediary metabolism by protein acetylation. Trends Biochem Sci. 2011 Feb;36(2):108-16. doi: 10.1016/j.tibs.2010.09.003.
98. Xiong Y, Guan KL. Mechanistic insights into the regulation of metabolic enzymes by acetylation. J Cell Biol.