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REVIEW

Advanced Progress of Histone Deacetylases in Rheumatic Diseases

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Abstract: Rheumatic disease is a disease which is not yet fully clarified to etiology and also involved in a local pathological injury or systemic disease. With the continuous improvement of clinical medical research in recent years, the development process of rheumatic diseases has been gradually elucidated; with the intensely study of epigenetics, it is realized that environmental changes can affect genetics, among which histone acetylation is one of the essential mechanisms in epigenetics. Histone deacetylases (HDACs) play an important role in regulating gene expression in various biological processes, including differentiation, development, stress response, and injury. HDACs are involved in a variety of physiological processes and are promising drug targets in various pathological conditions, such as cancer, cardiac and neurodegenerative diseases, inflammation, metabolic and immune disorders, and viral and parasitic infections. In this paper, we reviewed the roles of HDACs in rheumatic diseases in terms of their classification and function.

Keywords: histone deacetylase, histone deacetylase inhibitor, rheumatic diseases

Introduction

Epigenetic regulation plays a vital role in gene regulation through chemical modifications of DNA and post-translational modifications of histones. Many studies in recent years have found epigenetic involvement in the pathogenesis of rheumatic immune diseases, and histone acetylation is one of the crucial mechanisms in epigenetics.[1] So far, the family of mammalian zinc-dependent histone deacetylases (HDACs) can be divided into three classes:[2] Class I (HDACs 1–3, 8), Class II (IIa: HDACs 4, 5, 7, 9; IIb: HDACs 6, 10) and Class IV (HDAC 11); and Class III, a family of sirtuin proteins, including SIRT 1–7, where the deacetylation of histones and non-histones by HDACs alters the chromatin conformation and changes the activity of transcription factors, leading to changes in gene expression.[1,3,4] HDACs have different expression sites, distribution and regulation of target genes, Immune diseases are closely related to acetylation levels, and histone deacetylase inhibitors could prevent the onset and progression of disease and be a new approach to treating rheumatic disorders. This review focused on the progress of HDACs research about immune regulation involved in rheumatic diseases to provide a basis for clinical treatment (Table 1).

Histone Deacetylase and Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic synovitis with severe pain and swelling, joint damage and disability, ultimately leading to destruction and loss of function.[39] The current worldwide prevalence of RA is 0.5%.[40] Recently, it was suggested that epigenetic factors linking genetics and gene expression to disease risk could be a promising area.[41]

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Table 1 Effects of HDACs in Rheumatic Diseases

Class of HDACs	Diseases	HDACs	Targets or Pathway	References
Class I HDACs	RA	HDAC1	RASF, IL-17, IL-6, miR-124, JAK/STAT	[5–7]
		HDAC1, HDAC2	TRAF-6, NFATc1	[8]
		HDAC3	miR-19a-3p, IL-17RA	[9]
		HDAC2, HDAC8	Inflammatory cytokines	[10]
	SLE	HDAC1	miR-124, IRF1	[11]
	AS	HDAC1	Wnt-Smad	[12]
		HDAC3	miR-130a, TNF-1α	[13,14]
	OA	HDAC2	miR-503-5p/SGK1, Caspase-3, Bax, Bcl-2	[15–18]
Class IIa/IIb HDACs	RA	HDAC4	miR-138, PGRN, miR-216a-3p	[19,20]
		HDAC6	MyD88, NF-κB	[21]
	SLE	HDAC6	B cell	[22]
		HDAC9	IL-17A, IL-6, IFN-γ	[23]
	Gout	HDAC6	NLRP3 inflammasome	[24]
	OA	HDAC4	Runx2, IL-1β, COX-2, iNOS	[25]
		HDAC6, HDAC7	MMP-13, ECM	[26]
Class III HDACs (or Sirtuins)	RA	SIRT1	NF-κB, AP-1, IL-2, COX-2	[27–29]
		SIRT1, SIRT2	miR-140-3p	[30]
		SIRT6	NF-κB, TNF-α	[31]
	SLE	SIRT1	B cells, NF-κB, TNF-α, IL-17A, IL-22	[32,33]
	SSc	SIRT1	mTOR	[34]
		SIRT7	a-SMA, collagen I	[35]
	Gout	SIRT1	PI3K/AKT/STAT6	[36]
	OA	SIRT1, SIRT6	NF-κB	[37,38]

Zn^{2+}-Dependent HDACs

Histone deacetylase 1 (HDAC1) is closely associated with the development of RA. HDAC1 interferes with the differentiation, maturation, and apoptosis of osteoclasts and promotes the development of bone destruction in RA.[42] Hawtree et al found that HDAC1 expression was significantly higher in RA synovial fibroblasts (RASFs) than in osteoarthritic (OA) synovial fibroblasts (OASFs). It was demonstrated in vitro experiments that HDAC1 knockdown inhibited the proliferation, migration, and invasion of RASFs, and inhibition of HDAC1 significantly reduced joint swelling and attenuated cartilage and joint damage in RA animal models.[5] Moreover, many T cells could be detected in the synovium of RA patients. T cells were viewed to play a central role in the pathogenesis of RA due to their ability to drive the activation of B cells, monocytes, macrophages, and fibroblast-like synoviocytes.[6] Göschl et al found a significant reduction in inflammatory cytokines interleukin (IL)-17 and IL-6 in the serum from mice with T cell-specific deletion of HDAC1, demonstrating that mice with T cell-specific deletion of HDAC1 were resistant to the development of collagen-induced arthritis (CIA).[43] In addition, cytokines regulated gene expression and participated in cell activation, differentiation, and survival by activating intracellular Janus kinase/signal transduction and activator of transcription (JAK/STAT) signaling pathways. In a CIA mouse model, HDAC1 expression was significantly elevated in synovial tissue, whereas miR-124 and myristoylated alanine-rich C kinase substrate (MARCKS) were expressed inversely. HDAC1 deletion promoted H3 and H4 acetylation in the promoter regions of miR-124 and MARCKS. miR-124 alleviated synovial proliferation and synovitis by inhibiting the CIA's JAK/STAT signaling pathway, cell proliferation and synovial inflammation.[7]

Many studies have revealed the anti-inflammatory and anti-osteoclastic activities of HDACs and HDACs inhibitors (HDACi). Algate et al found that HDAC 1 and 2 inhibitors suppressed osteoclast formation by inhibiting key intercellular signaling factors tumor necrosis receptor-related factors 6 (TRAF-6) and nuclear factor of activated T-cells 1 (NFATc1), and inhibited osteoclast formation by tumor necrosis factor (TNF)-stimulated osteoclasts to inhibit pathological bone resorption. A similar trend was also observed when HDAC1 and HDAC2 were respectively inhibited. However, it was found that their combination have the most extraordinary anti-inflammatory and anti-osteoclastic effects.[8]

Nearly 50% of RA patients had extra-articular lesions with frequent pulmonary involvement, and almost 10% of RA patients presented with clinically significant interstitial lung disease (ILD), which was one of the mainly causes of death in RA patients.[44,45] It has been shown that HDAC3 negatively regulated the expression of miR-17-92 through promoter region deacetylation.[46] Importantly, IL-17 receptor A (IL-17RA) was reported to play a direct role in pulmonary fibrosis and may be particularly relevant to RA-ILD.[47] Downregulation of HDAC3 could result in increased miR-19a-3p expression to suppress IL-17RA expression and reduced the presence of the fibrosis marker genes collagen type I alpha 1 (COL1A1), collagen type III alpha 1 (COL3A1) and fibronectin (FN), thereby reducing the occurrence of RA-ILD fibrosis.[9] In contrast, Li et al found that reduced activity and expression of Class I HDACs (HDAC1-3,8) in RA peripheral blood mononuclear cells (PBMCs) accompanied by enhanced histone acetyltransferase (HAT) activity could have the potential to act as biomarkers of disease activity. It suggested that, in addition to HDAC inhibitors, HAT inhibitors may be potential targets for RA treatment.[48]

Kim et al found that sodium butyrate, one of the metabolites of intestinal flora, administered to CIA mice significantly reduced the expression of inflammatory cytokines in various cell types and almost fully reversed bone and cartilage damage by inhibiting HDAC2 in osteoblasts and HDAC8 in T cells. Sodium butyrate was promising for the treatment of RA.[10]

Progranulin (PGRN) as an autocrine growth factor, which may play a key role and drug target in autoimmune diseases.[49] Shao et al found that miR-138 was significantly upregulated in serum and synovial tissues of RA patients compared with normal subjects to promote inflammatory cytokine expression in FLS cells, and that HDAC4, a direct target of miR-138, could be negatively regulated by miR-138 to block PGRN expression and thus attenuate RA development.[19] In addition, Chang et al demonstrated that reduced circFBXW7 and HDAC4, which derived from mesenchymal stem cells (MSC) in clinical RA samples, upregulated miR-216a-3p to inhibit the proliferation, migration and inflammatory response of RA-FLS.[20] Subsequently, Hao et al also found circ_0008360 expressed in RA synovial tissue and RA fibroblast-like synovial cells (RA-FLS), and circ_0008360 inhibited proliferation, migration and inflammation of RA-FLS and promoted apoptosis by sponging miR-135b-5p and upregulating HDAC4, providing potential targets for the prevention and treatment of RA[50].

The epigenetic enzyme HDAC6 not only deacetylated histones but also non-histones, including α-microtubulin and myeloid differentiation factor 88 (MyD88).[51,52] In addition, Li et al found that HDAC6 protein levels were elevated in the synovial tissue of adjuvant arthritic rats. Furthermore, It was revealed in vitro studies that mercapto specific protein 1 (Sp1) could regulate HDAC6 expression, and overexpression of HDAC6 improved RA by deacetylating MyD88 to activate the nuclear factor kappa-B (NF-κB) signaling pathway.[21]

NAD^+-Dependent HDACs

SIRT1 inhibited the inflammatory response in RA with reduced SIRT1 activity and reduced SIRT1 expression in RA patients compared to healthy population.[53,54] In a rat CIA model, SIRT1 inhibited the transcriptional activity of NF-κB by deacetylating p65 and p300, thereby downregulating NF-κB-dependent pro-inflammatory genes.[27,28] SIRT1 can also reduce the inflammatory response by interacting with c-Fos and c-Jun to suppress the transcriptional activity of activator protein-1 (AP-1) in macrophages and inhibit the expression of IL-2 and cyclooxygenase-2 (COX-2).[29] In addition, Sirt1 not only inhibited FLS proliferation, invasion, and migration but also reduced the secretion of proinflammatory mediators in RA synovial tissue by regulating NF-κB transcription.[55]

SIRT3 was a crucial regulator of mitochondrial protein acetylation.[56] Kara et al showed that increased SIRT3 mRNA expression caused by mitochondrial stress/disruption could result in metabolic complications of RA, such as insulin resistance and dyslipidemia,[57] However, SIRT2 mRNA expression was not increased in RA due to the different cellular localization of SIRT3 and SIRT2; In addition, it was shown that SIRT1 and SIRT3 acted as target genes for miR-140-3p, which binded more strongly to SIRT3, inhibited cell viability and promoted synovial fibroblasts (SFs) apoptosis.[30]

The anti-inflammatory effect of SIRT6 was associated with the transcriptional activity of NF-κB, which inhibited NF-κB-mediated inflammatory response by interacting with the RelA subunit of NF-κB[58] and SIRT6 overexpression downregulated proinflammatory cytokines levels to reduce bone destruction in CIA mice.[59] In addition, overexpression of SIRT6 in FLS could reduce the production of inflammatory mediators by inhibiting TNF-α through deacetylation of histone 3 lysine 9 (H3K9) at the promoter of NF-κB target genes.[31]

Histone Deacetylase and Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic diffuse connective tissue disease with unknown etiology that could be involved in joints, kidneys, blood cells and blood vessel walls. It mainly affects women of childbearing age (9:1 ratio of women to men).[60] The activation of the immune system in SLE is characterized by the over-reaction of B and T cells and loss of immune tolerance to autoantigens.[61] Although the direct etiology of SLE is unknown, many factors are thought to contribute to the autoimmunity of SLE, including genetic predisposition and epigenetic, hormonal, and environmental factors.[62]

It was well known that $CD4^{+}$T cells had a critical immunosuppressive role in SLE. It was documented that $CD4^{+}$ T cells were activated in peripheral blood in SLE patients and that the levels of surface activating molecules, such as CD69, CD137, CD40L and ICOS, were elevated in $CD4^{+}$ T cells. More importantly, miR-124 negatively regulated Interferon regulatory factor (IRF1) expression.[11] A previous study documented the upregulated levels of HDAC1 in SLE. Thus, it suggested that HDAC1 promoted SLE by inhibiting miR-124 to upregulate IRF1 expression and triggering the immune activity of $CD4^{+}$ T cells.

It found that HDAC2 transcript levels were opposite to the results of HDAC1.Decreased HDAC2 mRNA expression was found in peripheral blood of lupus patients.[63] Besides, it was described by Ito et al that HDAC2 expression deficiency leads to glucocorticoid insensitivity Thus, These increases the likelihood of inflammatory gene activation in lupus patients.[64]

Aberrant B-cell activation played an essential role in the NZB/W mouse model of lupus. It was found by Ren et al that HDAC6 inhibition in a lupus mouse model reduced B-cell activation signaling pathway, decreased plasma cell differentiation, and significantly reduced germinal center (GC) formation in SLE, suggesting that selective inhibition of HDAC6 may be a potential therapy for lupus nephropathy.[22] In addition, it was noted that, in a mouse model of SLE, the novel HDAC6-specific inhibitor CKD-506 could obviously improve the survival rate and reduce the incidence of severe proteinuria, blood urea nitrogen, renal inflammation, glomerular IgG, and C3 infiltration. It also reduced the levels of various pro-inflammatory cytokines and chemokines in the serum and kidney, thereby inhibiting cell migration and lupus nephritis without adverse effects.[65] Therefore, CKD-506 may also be a novel and effective therapeutic agent for SLE.

Further studies have identified HDAC9 as one of potential target genes for miR-101-3p, and it also showed that miR-101-3p expression was reduced in peripheral blood mononuclear cells of SLE patients compared with healthy individuals. Furthermore, miR-101-3p could inhibit Th17 cell differentiation by directly targeting HDAC9 and reduce the levels of IL-17A, IL-6, and interferon (IFN)-γ.[23]

Yang et al demonstrated that plasma SIRT1 levels were significantly higher in SLE patients and were positively correlated with disease activity.[66] Overexpression of SIRT1 promoted the proliferation of B lymphocytes, and inhibited apoptosis by activating the NF-κB.[32] In contrast, knockdown of SIRT1 in mouse macrophages activated c-Jun N-terminal kinase (an inhibitor of NF-κB kinase pathway) and increased TNF-α secretion, and resveratrol as the activator of SIRT1 reversed AhR-induced Th17/Treg imbalance, which upregulated IL-17A and IL-22 expressions in $CD4^{+}$ T cells.[33]

Histone Deacetylase and Systemic Sclerosis

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by severe progressive fibrosis of skin and other visceral organs, obvious alterations in the microvascular system, and numerous cellular and humoral immune abnormalities.[67] Although the exact etiology and pathogenesis are not elucidated, many studies have shown that activation of the immune system is a crucial factor in vascular abnormalities and fibrosis. Emerging evidence indicated that B cells played a pivotal role in animal models of SSc and SSc patients as well.[68]

Resveratrol is now widely shown to play an essential role in inhibiting the development of SSc.[69] Resveratrol plays a protective role against SSc. Yao et al identified the mTOR signaling pathway as a monumental KEGG pathway associated with resveratrol targeting genes, confirmed the elevated mTOR levels in the skin of SSc patients and also verified that resveratrol ameliorated bleomycin (BLM)-induced fibrosis and inflammation through activation of SIRT1-mediated mTOR degradation in vitro. In addition, the progressive fibrosis and inflammation were attenuated.[34] The study also showed that SIRT1 was not only used in the treatment of fibrosis, but also in SSc patients. And several studies indicated that not only SIRT1 but also SIRT3 and SIRT5 were directly targeted by resveratrol.[70–72] However, whether these SIRTs played key roles in the improvement of SSc by resveratrol needs to be further investigated.

Although SIRT7 was less studied compared to SIRT1, there were still several studies indicating that SIRT7 also significantly reduced mRNA and protein levels in lung fibroblasts from SSc patients.[35,73] Wyman et al also demonstrated that SIRT7 knockdown enhanced the expression of α-smooth muscle actin (a-SMA) and typed I collagen, while transfection with SIRT7 overexpression plasmids reduced the same markers by more than 30% in TGF-β -treated lung fibroblasts.[35] In addition, both sodium valproate and another HDACi butyrate attenuated bleomycin-induced pulmonary fibrosis when they were combined,[63] and the combined drugs had a synergistic effect of reducing NF-κB, TNF-α, IL-6, and TGF-β, which improved oxidative stress and reduced inflammatory cells.[74]

Histone Deacetylase and Gout

Gout is the most common form of inflammatory arthritis and usually presents as an acute, self-limiting inflammatory monoarthritis affecting the joints of the lower extremities. Elevated serum uric acid levels (hyperuricemia) constitute a significant risk factor for MSU crystal deposition and gout development.[75] It has a worldwide prevalence of approximately 2–4% and occurs predominantly in men over 40 years of age, especially those with underlying comorbidities such as obesity, hypertension, coronary artery disease, diabetes mellitus or metabolic disease.[76]

Aberrant activation of NLRP3 inflammasome may be associated with diverse inflammatory or metabolic diseases, such as sepsis, colitis, and gout.[75,77–79] Inhwa et al showed that HDAC6 negatively regulated NLRP3 inflammasome activation by interacting with ubiquitinated NLRP3.[24] The NLRP3 inflammasome pathway also played an essential role in acute gout.

SIRT1 exerted an anti-acute gouty arthritis effect via reducing the polarization of macrophages to the M1 phenotype by activating the PI3K/Akt/STAT6 pathway. Elevated SIRT1 was observed in gouty model mice and peripheral blood mononuclear cells (PBMCs) from patients with acute gout as well. STAT1-dependent activation of signal transduction pathways that could inhibit inflammatory response.[36] In an in vitro experiment from our previous work, SIRT1 protein levels were downregulated in PBMCs from patients at interval after MSU crystals challenge, and resveratrol restored SIRT1 protein levels in a dose-dependent manner and had a regulatory effect on IL-1β release. In addition, the mRNA and protein levels of autophagic genes (Beclin-1, LC3) were also regulated by resveratrol. It indicated that resveratrol could improve gouty inflammation by upregulating SIRT1 to promote autophagy in gout patients.[80]

Histone Deacetylase and Ankylosing Spondylitis

Ankylosing spondylitis (AS) is an immune-mediated, insidious progressive seronegative spondylitis characterized by adhesive inflammation. AS gradually leads to inflammation, bone erosion, new bone formation, and ankylosis of the sacroiliac, vertebral and peripheral joints.[81] The patient's quality of life is seriously affected at the advanced stage.

It was found by Hu et al that serum levels of anti-SIRT1 antibodies were significantly higher in AS patients than RA or psoriatic arthritis (PsA) patients. Moreover, anti-SIRT1 antibody levels were significantly higher in those patients with first-year hip involvement, suggesting that SIRT1 may regulate the erosive bone destruction in AS.[82] A higher prevalence in women was in autoimmune diseases such as SLE, SSc, and RA. However, the majority of AS is higher in men than in women and the severity of disease as well.[83] It has been reported that testosterone may interact with SIRT1 to protect endothelial cells.[84] However, the exact regulatory process could be further investigated.

Zeng et al found that HDAC1 significantly affected the Wnt-Smad pathway in AS fibroblasts, and Dickkopf-1 (DKK-1) or specific inhibitor of Smad3 (SIS3) treatment significantly inhibited the effect of HDAC1 on AS fibroblasts. In addition. HDAC1 significantly activated transient receptor potential (TRP) ion channels and promoted AS fibroblast proliferation, inflammatory response, and osteogenic differentiation. Thus, HDAC1 promoted AS fibroblast proliferation, inflammatory response, and osteogenic differentiation via the Wnt-Smad pathway.[12]

More than 3-fold increase of HDAC3 mRNA and protein expression were showed in PBMCs from AS patients compared to Healthy controls. Conversely, miRNA-130a expression was significantly lower in PBMCs from AS patients compared with Healthy controls.[85] In addition, dysregulation of miRNAs were frequently observed in immunopathogenesis. The miRNA-130a is regulated by HDAC3 and is associated with AS.[13,14] From those results, it could indicate that HDAC3 has a significant role in the underlying molecular mechanisms of AS by forming a negative feedback loop with miR-130a and regulating miR-130a expression via its target TNF-1α.

Histone Deacetylase and Osteoarthritis

Osteoarthritis (OA) is a common degenerative disease characterized by joint pain and movement disorders.[86] OA is associated with major risk factors, including gender, age, obesity, and significant mechanical stress[87].

An accumulating literature suggested that differential expression patterns and altered activation of HDACs contributed to the onset and progression of OA. HDAC1 and HDAC2 were expressed at high levels in OA chondrocytes and inhibited the expression of collagen alpha-1(II) chain (COL2A1), collagen alpha-1(XI) chain (COL11A1), aggrecan core protein (ACAN), and cartilage oligomeric matrix protein (COMP). Moreover, HDAC2 repressed miR-503-5p expression, and serum- and glucocorticoid-inducible kinase-1 (SGK1) was viewed as a target gene of miR-503-5p. Upregulation of miR-503-5p or silencing of HDAC2 promoted OA rat chondrocyte proliferation, inflammatory response and inhibited apoptosis (decreased Caspase-3 and Bax expression and elevated Bcl2 expression). Therefore, HDAC2 could promote OA through miR-503-5p/SGK1 axis and may be a therapeutic target for OA treatment.[15–18]

It was demonstrated that HDAC4 was related to the inhibitory mechanism of Runx2. Overexpression of HDAC4 did not only decrease the expression of IL-1β, COX2 and iNOS, but also increase the expression of aggrecan which was characteristic of chondroprotection.[25]

It was found that HDAC6 expression was increased in articular surface cells in a destabilisation of the medial meniscus (DMM)-induced mouse OA model. In the in vivo experiments, it was demonstrated that inhibition of HDAC6 activity by intraperitoneal injection of saline-diluted Tubastatin A in a DMM-induced mouse OA model inhibited cartilage degradation, reduced development of synovitis, improved arthralgia and swelling, and delayed progression of OA.[86]

In addition, Higashiyama et al demonstrated that HDAC7 expression was enhanced in OA cartilage, which was associated with increased matrix metalloproteinase (MMP)-13 production and extracellular matrix (ECM) degradation,[26] while enhanced expression of certain HDACs increased articular cartilage destruction and OA progression. Other deacetylases, particularly SIRT1, were shown to inhibit cartilage destruction by increasing SIRT1 activity in mouse OA cartilage.[37] In addition to SIRT1, SIRT6 was also shown to play a protective role in OA. A recent study reported that SIRT6 protein levels were significantly reduced in OA chondrocytes compared to healthy controls and that SIRT6 overexpression in mouse joints protected cartilage from degeneration by reducing NF-κB dependent inflammatory gene expression.[38] Therefore, HDAC inhibitors could be promising as a therapeutic intervention for OA.

Conclusions

Collectively, many studies in rheumatic diseases have shown that through regulation of HDACs or their enzymatic activities, to some extent, cartilage destruction could be prevented, joint destruction could be reversed, synovial cell proliferation could be delayed, synovial inflammation could be improved, inflammatory cytokines could be inhibited, and anti-fibrosis could be achieved. Although HDACs played an important regulatory role in the pathophysiological process of rheumatic diseases, there were still many difficulties to overcome. For example, some other members of the HDACs family (HDACs 5, 7, 9, 10) were still unclear in terms of their target sites and the regulatory mechanisms in vivo. With the continuous progress of researches on HDACs, the mechanisms of HDAC-mediated epigenetic regulation could be improved. It is hoped that new targets and insights could be provided to explore HDAC-mediated epigenetic regulation for the prevention and treatment of rheumatic diseases.

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Disclosure

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References

1. Seto E, Yoshida M. Erasers of histone acetylation: the histone deacetylase enzymes. *Cold Spring Harb Perspect Biol*. 2014;6(4):a018713. doi:10.1101/cshperspect.a018713
2. Asfaha Y, Schrenk C, Alves Avelar LA, et al. Recent advances in class IIa histone deacetylases research. *Bioorg Med Chem*. 2019;27(22):115087. doi:10.1016/j.bmc.2019.115087
3. Yang XJ, Seto E. The Rpd3/Hda1 family of lysine deacetylases: from bacteria and yeast to mice and men. *Nat Rev Mol Cell Biol*. 2008;9(3):206–218. doi:10.1038/nrm2346
4. Nakagawa T, Guarente L. Sirtuins at a glance. *J Cell Sci*. 2011;124(Pt 6):833–838. doi:10.1242/jcs.081067
5. Hawtree S, Muthana M, Wilkinson JM, Akil M, Wilson AG. Histone deacetylase 1 regulates tissue destruction in rheumatoid arthritis. *Hum Mol Genet*. 2015;24(19):5367–5377. doi:10.1093/hmg/ddv258
6. de Jager W, Hoppenreijs EP, Wulffraat NM, Wedderburn LR, Kuis W, Prakken BJ. Blood and synovial fluid cytokine signatures in patients with juvenile idiopathic arthritis: a cross-sectional study. *Ann Rheum Dis*. 2007;66(5):589–598. doi:10.1136/ard.2006.061853
7. Meng Q, Pan B, Sheng P. Histone deacetylase 1 is increased in rheumatoid arthritis synovium and promotes synovial cell hyperplasia and synovial inflammation in the collagen-induced arthritis mouse model via the microRNA-124-dependent MARCKS-JAK/STAT axis. *Clin Exp Rheumatol*. 2021;39(5):970–981. doi:10.55563/clinexprheumatol/1xsigp
8. Algate K, Haynes D, Fitzsimmons T, et al. Histone deacetylases 1 and 2 inhibition suppresses cytokine production and osteoclast bone resorption in vitro. *J Cell Biochem*. 2020;121(1):244–258. doi:10.1002/jcb.29137
9. Yuan H, Jiao L, Yu N, Duan H, Yu Y, Bai Y. Histone deacetylase 3-mediated inhibition of microRNA-19a-3p facilitates the development of rheumatoid arthritis-associated interstitial lung disease. *Front Physiol*. 2020;11:549656. doi:10.3389/fphys.2020.549656
10. Kim DS, Kwon JE, Lee SH, et al. Attenuation of rheumatoid inflammation by sodium butyrate through reciprocal targeting of HDAC2 in osteoclasts and HDAC8 in T cells. *Front Immunol*. 2018;9:1525. doi:10.3389/fimmu.2018.01525
11. Chen J, Peng L, Zhao Z, et al. HDAC1 potentiates CD4 + T cell activation by inhibiting miR-124 and promoting IRF1 in systemic lupus erythematosus. *Cell Immunol*. 2021;362:104284. doi:10.1016/j.cellimm.2021.104284
12. Zeng Y, He R, Liu Y, et al. HDAC1 regulates inflammation and osteogenic differentiation of ankylosing spondylitis fibroblasts through the Wnt-Smad signaling pathway. *J Orthop Surg Res*. 2022;17(1):343. doi:10.1186/s13018-022-03224-z
13. Lai NS, Yu HC, Chen HC, Yu CL, Huang HB, Lu MC. Aberrant expression of microRNAs in T cells from patients with ankylosing spondylitis contributes to the immunopathogenesis. *Clin Exp Immunol*. 2013;173(1):47–57. doi:10.1111/cei.12089
14. Zhang X, Chen X, Lin J, et al. Myc represses miR-15a/miR-16-1 expression through recruitment of HDAC3 in mantle cell and other non-Hodgkin B-cell lymphomas. *Oncogene*. 2012;31(24):3002–3008. doi:10.1038/onc.2011.470
15. Wang Z, Zhou N, Wang W, Yu Y, Xia L, Li N. HDAC2 interacts with microRNA-503-5p to regulate SGK1 in osteoarthritis. *Arthritis Res Ther*. 2021;23(1):78. doi:10.1186/s13075-020-02373-y
16. Liu CJ, Prazak L, Fajardo M, Yu S, Tyagi N, Di Cesare PE. Leukemia/lymphoma-related factor, a POZ domain-containing transcriptional repressor, interacts with histone deacetylase-1 and inhibits cartilage oligomeric matrix protein gene expression and chondrogenesis. *J Biol Chem*. 2004;279(45):47081–47091. doi:10.1074/jbc.M405288200
17. Hong S, Derfoul A, Pereira-Mouries L, Hall DJ. A novel domain in histone deacetylase 1 and 2 mediates repression of cartilage-specific genes in human chondrocytes. *FASEB j*. 2009;23(10):3539–3552. doi:10.1096/fj.09-133215
18. Huh YH, Ryu JH, Chun JS. Regulation of type II collagen expression by histone deacetylase in articular chondrocytes. *J Biol Chem*. 2007;282(23):17123–17131. doi:10.1074/jbc.M700599200
19. Shao L, Hou C. miR-138 activates NF-κB signaling and PGRN to promote rheumatoid arthritis via regulating HDAC4. *Biochem Biophys Res Commun*. 2019;519(1):166–171. doi:10.1016/j.bbrc.2019.08.092
20. Chang L, Kan L. Mesenchymal stem cell-originated exosomal circular RNA circFBXW7 attenuates cell proliferation, migration and inflammation of fibroblast-like synoviocytes by targeting miR-216a-3p/HDAC4 in rheumatoid arthritis. *J Inflamm Res*. 2021;14:6157–6171. doi:10.2147/JIR.S336099
21. Li M, Hu W, Wang R, et al. Sp1 S-sulfhydration induced by hydrogen sulfide inhibits inflammation via HDAC6/MyD88/NF-κB signaling pathway in adjuvant-induced arthritis. *Antioxidants*. 2022;11:4.
22. Ren J, Catalina MD, Eden K, et al. Selective histone deacetylase 6 inhibition normalizes B cell activation and germinal center formation in a model of systemic lupus erythematosus. *Front Immunol*. 2019;10:2512. doi:10.3389/fimmu.2019.02512
23. Sun H, Guo F, Xu L. Downregulation of microRNA-101-3p participates in systemic lupus erythematosus progression via negatively regulating HDAC9. *J Cell Biochem*. 2020;121(10):4310–4320. doi:10.1002/jcb.29624
24. Hwang I, Lee E, Jeon SA, Yu JW. Histone deacetylase 6 negatively regulates NLRP3 inflammasome activation. *Biochem Biophys Res Commun*. 2015;467(4):973–978. doi:10.1016/j.bbrc.2015.10.033
25. Cao K, Wei L, Zhang Z, et al. Decreased histone deacetylase 4 is associated with human osteoarthritis cartilage degeneration by releasing histone deacetylase 4 inhibition of runt-related transcription factor-2 and increasing osteoarthritis-related genes: a novel mechanism of human osteoarthritis cartilage degeneration. *Arthritis Res Ther*. 2014;16(6):491. doi:10.1186/s13075-014-0491-3
26. Higashiyama R, Miyaki S, Yamashita S, et al. Correlation between MMP-13 and HDAC7 expression in human knee osteoarthritis. *Mod Rheumatol*. 2010;20(1):11–17. doi:10.3109/s10165-009-0224-7
27. Kong S, McBurney MW, Fang D. Sirtuin 1 in immune regulation and autoimmunity. *Immunol Cell Biol*. 2012;90(1):6–13. doi:10.1038/icb.2011.102
28. Zhang J, Zhang Y, Xiao F, et al. The peroxisome proliferator-activated receptor γ agonist pioglitazone prevents NF-κB activation in cisplatin nephrotoxicity through the reduction of p65 acetylation via the AMPK-SIRT1/p300 pathway. *Biochem Pharmacol*. 2016;101:100–111. doi:10.1016/j.bcp.2015.11.027
29. Zhang R, Chen HZ, Liu JJ, et al. SIRT1 suppresses activator protein-1 transcriptional activity and cyclooxygenase-2 expression in macrophages. *J Biol Chem*. 2010;285(10):7097–7110. doi:10.1074/jbc.M109.038604
30. Zu B, Liu L, Wang J, Li M, Yang J. MiR-140-3p inhibits the cell viability and promotes apoptosis of synovial fibroblasts in rheumatoid arthritis through targeting sirtuin 3. *J Orthop Surg Res*. 2021;16(1):105. doi:10.1186/s13018-021-02236-5
31. Woo SJ, Noh HS, Lee NY, et al. Myeloid sirtuin 6 deficiency accelerates experimental rheumatoid arthritis by enhancing macrophage activation and infiltration into synovium. *EBioMedicine*. 2018;38:228–237. doi:10.1016/j.ebiom.2018.11.005

32. Wang Q, Yan C, Xin M, Han L, Zhang Y, Sun M. Sirtuin 1 (Sirt1) overexpression in BaF3 cells contributes to cell proliferation promotion, apoptosis resistance and pro-inflammatory cytokine production. *Med Sci Monit*. 2017;23:1477–1482. doi:10.12659/MSM.900754
33. Yoshizaki T, Schenk S, Imamura T, et al. SIRT1 inhibits inflammatory pathways in macrophages and modulates insulin sensitivity. *Am J Physiol Endocrinol Metab*. 2010;298(3):E419–E428. doi:10.1152/ajpendo.00417.2009
34. Yao Q, Wu Q, Xu X, et al. Resveratrol ameliorates systemic sclerosis via suppression of fibrosis and inflammation through activation of SIRT1/mTOR signaling. *Drug Des Devel Ther*. 2020;14:5337–5348. doi:10.2147/DDDT.S281209
35. Wyman AE, Noor Z, Fishelevich R, et al. Sirtuin 7 is decreased in pulmonary fibrosis and regulates the fibrotic phenotype of lung fibroblasts. *Am J Physiol Lung Cell Mol Physiol*. 2017;312(6):L945–L958. doi:10.1152/ajplung.00473.2016
36. Liu L, Zhu X, Zhao T, Yu Y, Xue Y, Zou H. Sirt1 ameliorates monosodium urate crystal-induced inflammation by altering macrophage polarization via the PI3K/Akt/STAT6 pathway. *Rheumatology*. 2019;58(9):1674–1683. doi:10.1093/rheumatology/kez165
37. Li W, Cai L, Zhang Y, Cui L, Shen G. Intra-articular resveratrol injection prevents osteoarthritis progression in a mouse model by activating SIRT1 and thereby silencing HIF-2α. *J Orthop Res*. 2015;33(7):1061–1070. doi:10.1002/jor.22859
38. Wu Y, Chen L, Wang Y, et al. Overexpression of Sirtuin 6 suppresses cellular senescence and NF-κB mediated inflammatory responses in osteoarthritis development. *Sci Rep*. 2015;5(1):17602. doi:10.1038/srep17602
39. Klein K, Gay S. Epigenetics in rheumatoid arthritis. *Curr Opin Rheumatol*. 2015;27(1):76–82. doi:10.1097/BOR.0000000000000128
40. Balandraud N, Roudier J. Epstein-Barr virus and rheumatoid arthritis. *Joint Bone Spine*. 2018;85(2):165–170. doi:10.1016/j.jbspin.2017.04.011
41. Viatte S, Plant D, Raychaudhuri S. Genetics and epigenetics of rheumatoid arthritis. *Nat Rev Rheumatol*. 2013;9(3):141–153. doi:10.1038/nrrheum.2012.237
42. Guo J, Cao X, Zhao W, et al. MicroRNA-449 targets histone deacetylase 1 to regulate the proliferation, invasion, and apoptosis of synovial fibroblasts in rheumatoid arthritis. *Ann Palliat Med*. 2021;10(7):7960–7969. doi:10.21037/apm-21-1383
43. Göschl L, Preglej T, Boucheron N, et al. Histone deacetylase 1 (HDAC1): a key player of T cell-mediated arthritis. *J Autoimmun*. 2020;108:102379. doi:10.1016/j.jaut.2019.102379
44. Juge PA, Borie R, Kannengiesser C, et al. Shared genetic predisposition in rheumatoid arthritis-interstitial lung disease and familial pulmonary fibrosis. *Eur Respir J*. 2017;49(5):1602314. doi:10.1183/13993003.02314-2016
45. Paulin F, Doyle TJ, Fletcher EA, Ascherman DP, Rosas IO. Rheumatoid arthritis-associated interstitial lung disease and idiopathic pulmonary fibrosis: shared mechanistic and phenotypic traits suggest overlapping disease mechanisms. *Rev Invest Clin*. 2015;67(5):280–286.
46. Wang Y, Frank DB, Morley MP, et al. HDAC3-dependent epigenetic pathway controls lung alveolar epithelial cell remodeling and spreading via miR-17-92 and TGF-β signaling regulation. *Dev Cell*. 2016;36(3):303–315. doi:10.1016/j.devcel.2015.12.031
47. Zhang J, Wang D, Wang L, et al. Profibrotic effect of IL-17A and elevated IL-17RA in idiopathic pulmonary fibrosis and rheumatoid arthritis-associated lung disease support a direct role for IL-17A/IL-17RA in human fibrotic interstitial lung disease. *Am J Physiol Lung Cell Mol Physiol*. 2019;316(3):L487–L497. doi:10.1152/ajplung.00301.2018
48. Angiolilli C, Kabala PA, Grabiec AM, et al. Histone deacetylase 3 regulates the inflammatory gene expression programme of rheumatoid arthritis fibroblast-like synoviocytes. *Ann Rheum Dis*. 2017;76(1):277–285. doi:10.1136/annrheumdis-2015-209064
49. Wei J, Hettinghouse A, Liu C. The role of progranulin in arthritis. *Ann N Y Acad Sci*. 2016;1383(1):5–20. doi:10.1111/nyas.13191
50. Hao J, Chen Y, Yu Y. Circular RNA circ_0008360 inhibits the proliferation, migration, and inflammation and promotes apoptosis of fibroblast-like synoviocytes by regulating miR-135b-5p/HDAC4 axis in rheumatoid arthritis. *Inflammation*. 2022;45(1):196–211. doi:10.1007/s10753-021-01538-4
51. Li G, Jiang H, Chang M, Xie H, Hu L. HDAC6 α-tubulin deacetylase: a potential therapeutic target in neurodegenerative diseases. *J Neurol Sci*. 2011;304(1–2):1–8. doi:10.1016/j.jns.2011.02.017
52. Menden H, Xia S, Mabry SM, et al. Histone deacetylase 6 regulates endothelial MyD88-dependent canonical TLR signaling, lung inflammation, and alveolar remodeling in the developing lung. *Am J Physiol Lung Cell Mol Physiol*. 2019;317(3):L332–L346. doi:10.1152/ajplung.00247.2018
53. Wendling D, Vidon C, Abbas W, Guillot X, Toussirot E, Herbein G. Sirt1 activity in peripheral blood mononuclear cells from patients with rheumatoid arthritis. *Joint Bone Spine*. 2014;81(5):462–463. doi:10.1016/j.jbspin.2014.02.006
54. Wendling D, Abbas W, Godfrin-Valnet M, et al. Dysregulated serum IL-23 and SIRT1 activity in peripheral blood mononuclear cells of patients with rheumatoid arthritis. *PLoS One*. 2015;10(3):e0119981. doi:10.1371/journal.pone.0119981
55. Li G, Xia Z, Liu Y, et al. SIRT1 inhibits rheumatoid arthritis fibroblast-like synoviocyte aggressiveness and inflammatory response via suppressing NF-κB pathway. *Biosci Rep*. 2018;38:3.
56. Pillai VB, Sundaresan NR, Jeevanandam V, Gupta MP. Mitochondrial SIRT3 and heart disease. *Cardiovasc Res*. 2010;88(2):250–256. doi:10.1093/cvr/cvq250
57. Kara M, Yolbaş S, Şahin C, Koca SS. Changes in sirtuin 2 and sirtuin 3 mRNA expressions in rheumatoid arthritis. *Eur J Rheumatol*. 2017;4(2):83–86. doi:10.5152/eurjrheum.2017.16056
58. Kawahara TL, Michishita E, Adler AS, et al. SIRT6 links histone H3 lysine 9 deacetylation to NF-kappaB-dependent gene expression and organismal life span. *Cell*. 2009;136(1):62–74. doi:10.1016/j.cell.2008.10.052
59. Hou KL, Lin SK, Chao LH, et al. Sirtuin 6 suppresses hypoxia-induced inflammatory response in human osteoblasts via inhibition of reactive oxygen species production and glycolysis-A therapeutic implication in inflammatory bone resorption. *Biofactors*. 2017;43(2):170–180. doi:10.1002/biof.1320
60. D'Cruz DP, Khamashta MA, Hughes GR. Systemic lupus erythematosus. *Lancet*. 2007;369(9561):587–596. doi:10.1016/S0140-6736(07)60279-7
61. Kiriakidou M, Ching CL. Systemic lupus erythematosus. *Ann Intern Med*. 2020;172(11):ITC81–ITC96. doi:10.7326/AITC202006020
62. Gatto M, Zen M, Ghirardello A, et al. Emerging and critical issues in the pathogenesis of lupus. *Autoimmun Rev*. 2013;12(4):523–536. doi:10.1016/j.autrev.2012.09.003
63. Nawrocki MJ, Strugała AJ, Piotrowski P, Wudarski M, Olesińska M, Jagodziński PP. JHDM1D and HDAC1-3 mRNA expression levels in peripheral blood mononuclear cells of patients with systemic lupus erythematosus. *Z Rheumatol*. 2015;74(10):902–910. doi:10.1007/s00393-015-1619-9
64. Ito K, Yamamura S, Essilfie-Quaye S, et al. Histone deacetylase 2-mediated deacetylation of the glucocorticoid receptor enables NF-kappaB suppression. *J Exp Med*. 2006;203(1):7–13. doi:10.1084/jem.20050466
65. Choi EW, Song JW, Ha N, Choi YI, Kim S. CKD-506, a novel HDAC6-selective inhibitor, improves renal outcomes and survival in a mouse model of systemic lupus erythematosus. *Sci Rep*. 2018;8(1):17297. doi:10.1038/s41598-018-35602-1

66. Yang C, Li R, Xu WD, Huang AF. Increased levels of sirtuin-1 in systemic lupus erythematosus. *Int J Rheum Dis*. 2022;25(8):869–876. doi:10.1111/1756-185X.14360
67. Broen JC, Coenen MJ, Radstake TR. Genetics of systemic sclerosis: an update. *Curr Rheumatol Rep*. 2012;14(1):11–21. doi:10.1007/s11926-011-0221-7
68. Hasegawa M. B lymphocytes: shedding new light on the pathogenesis of systemic sclerosis. *J Dermatol*. 2010;37(1):3–10. doi:10.1111/j.1346-8138.2009.00763.x
69. Gianchecchi E, Fierabracci A. Insights on the effects of resveratrol and some of its derivatives in cancer and autoimmunity: a molecule with a dual activity. *Antioxidants*. 2020;9(2):2. doi:10.3390/antiox9020091
70. Chang HC, Guarente L. SIRT1 and other sirtuins in metabolism. *Trends Endocrinol Metab*. 2014;25(3):138–145. doi:10.1016/j.tem.2013.12.001
71. Guarente L. Calorie restriction and sirtuins revisited. *Genes Dev*. 2013;27(19):2072–2085. doi:10.1101/gad.227439.113
72. Lee IH, Chathuranga K, Lee J-S. Mechanisms and disease implications of sirtuin-mediated autophagic regulation. *Exp Mol Med*. 2019;51(9):1–11. doi:10.1038/s12276-019-0299-y
73. Barber MF, Michishita-Kioi E, Xi Y, et al. SIRT7 links H3K18 deacetylation to maintenance of oncogenic transformation. *Nature*. 2012;487(7405):114–118. doi:10.1038/nature11043
74. Kabel AM, Omar MS, Elmaaboud MAA. Amelioration of bleomycin-induced lung fibrosis in rats by valproic acid and butyrate: role of nuclear factor kappa-B, proinflammatory cytokines and oxidative stress. *Int Immunopharmacol*. 2016;39:335–342. doi:10.1016/j.intimp.2016.08.008
75. Dalbeth N, Choi HK, Joosten LAB, et al. Gout. *Nat Rev Dis Primers*. 2019;5(1):69. doi:10.1038/s41572-019-0115-y
76. Galozzi P, Bindoli S, Doria A, Oliviero F, Sfriso P. Autoinflammatory features in gouty arthritis. *J Clin Med*. 2021;10(9):1880. doi:10.3390/jcm10091880
77. Wang L, Hauenstein AV. The NLRP3 inflammasome: mechanism of action, role in disease and therapies. *Mol Aspects Med*. 2020;76:100889. doi:10.1016/j.mam.2020.100889
78. Danielski LG, Giustina AD, Bonfante S, Barichello T, Petronilho F. The NLRP3 inflammasome and its role in sepsis development. *Inflammation*. 2020;43(1):24–31. doi:10.1007/s10753-019-01124-9
79. Irrera N, Russo M, Pallio G, et al. The role of NLRP3 inflammasome in the pathogenesis of traumatic brain injury. *Int J Mol Sci*. 2020;21(17):6204. doi:10.3390/ijms21176204
80. Yang QB, He YL, Zhong XW, Xie WG, Zhou JG. Resveratrol ameliorates gouty inflammation via upregulation of sirtuin 1 to promote autophagy in gout patients. *Inflammopharmacology*. 2019;27(1):47–56. doi:10.1007/s10787-018-00555-4
81. Brown MA, Kenna T, Wordsworth BP. Genetics of ankylosing spondylitis--insights into pathogenesis. *Nat Rev Rheumatol*. 2016;12(2):81–91. doi:10.1038/nrrheum.2015.133
82. Hu Q, Sun Y, Li Y, et al. Anti-SIRT1 autoantibody is elevated in ankylosing spondylitis: a potential disease biomarker. *BMC Immunol*. 2018;19(1):38. doi:10.1186/s12865-018-0280-x
83. Taurog JD, Chhabra A, Colbert RA, Longo DL. Ankylosing spondylitis and axial spondyloarthritis. *N Engl J Med*. 2016;374(26):2563–2574. doi:10.1056/NEJMra1406182
84. Ota H, Akishita M, Akiyoshi T, et al. Testosterone deficiency accelerates neuronal and vascular aging of SAMP8 mice: protective role of eNOS and SIRT1. *PLoS One*. 2012;7(1):e29598. doi:10.1371/journal.pone.0029598
85. Jiang Y, Wang L. Role of histone deacetylase 3 in ankylosing spondylitis via negative feedback loop with microRNA-130a and enhancement of tumor necrosis factor-1α expression in peripheral blood mononuclear cells. *Mol Med Rep*. 2016;13(1):35–40. doi:10.3892/mmr.2015.4494
86. Zheng Y, Chen Y, Lu X, et al. Inhibition of histone deacetylase 6 by tubastatin a attenuates the progress of osteoarthritis via improving mitochondrial function. *Am J Pathol*. 2020;190(12):2376–2386. doi:10.1016/j.ajpath.2020.08.013
87. Lambova SN, Müller-Ladner U. Osteoarthritis - current insights in pathogenesis, diagnosis and treatment. *Curr Rheumatol Rev*. 2018;14(2):91–97. doi:10.2174/1573397114021807061447577