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REVIEW ARTICLE

Mechanism and application of feedback loops formed by mechanotransduction and histone modifications

Han Sun [a], Yafang Gao [b], Xinyu Ma [b], Yizhou Deng [b], Lintao Bi [a,**], Lisha Li [b,*]

[a] *Department of Hematology and Oncology, China-Japan Union Hospital, Jilin University, Changchun, Jilin 130021, China*
[b] *The Key Laboratory of Pathobiology, Ministry of Education, College of Basic Medical Sciences, Jilin University, Changchun, Jilin 130021, China*

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Abstract Mechanical stimulation is the key physical factor in cell environment. Mechanotransduction acts as a fundamental regulator of cell behavior, regulating cell proliferation, differentiation, apoptosis, and exhibiting specific signature alterations during the pathological process. As research continues, the role of epigenetic science in mechanotransduction is attracting attention. However, the molecular mechanism of the synergistic effect between mechanotransduction and epigenetics in physiological and pathological processes has not been clarified. We focus on how histone modifications, as important components of epigenetics, are coordinated with multiple signaling pathways to control cell fate and disease progression. Specifically, we propose that histone modifications can form regulatory feedback loops with signaling pathways, that is, histone modifications can not only serve as downstream regulators of signaling pathways for target gene transcription but also provide feedback to regulate signaling pathways. Mechanotransduction and epigenetic changes could be potential markers and therapeutic targets in clinical practice.
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* Corresponding author.
** Corresponding author.
E-mail addresses: bilt@jlu.edu.cn (L. Bi), lilisha@jlu.edu.cn (L. Li).
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Introduction

There is mounting evidence that mechanical signals are the fundamental regulators of cell behavior.[1] Mechanotransduction is a physiological process in which cells perceive, interpret, and convert mechanical signals into biochemical signals.[2] Mechanical signals involve extracellular mechanical stimuli and intracellular forces (Fig. 1).[1]

Since the discovery of integrins, it has been recognized as the core of mechanotransduction.[4] Focal adhesion kinase (FAK) is a cytosolic tyrosine kinase, and it is activated by disrupting the autoinhibitory intra-molecular interaction between four-point-one, ezrin, radixin, moesin (FERM) domain and the kinase domain of integrins.[4] The activated FAK forms a complex with the Src family kinases that continue to regulate multiple downstream signaling pathways, such as the mitogen-associated protein kinase (MAPK), Rho kinase (RhoA), Hippo-Yes-associated protein 1/transcriptional co-activator with PDZ-binding motif (YAP/TAZ), and WNT/β-catenin.[14,5,15] FAK can also enter the nucleus and bind to transcription factors to regulate gene expression.[16] MAPK signaling pathway is a cascade, and there are four confirmed MAPK cascade reactions, namely extracellular signal-regulated kinase 1/2 (ERK1/2), c-Jun N-terminal kinase (JNK), p38 MAPK (p38), and extracellular signal-regulated kinase 5(ERK5) cascade.[10] Each MAPK cascade consists of three kinase cascades, where the first stage is MAPK kinase kinase (MAPKKK), the second is MAPK kinase (MAPKK), and the last is MAPK (ERK, JNK or p38).[10,17,18] MAPK cascade generally starts with the activation of small G proteins such as Ras, followed by a cascade of layer 3—5 cytoplasmic protein kinases to initiate the corresponding physiological processes.[18,19] Among them, JNK and p38 have similar functions and are related to

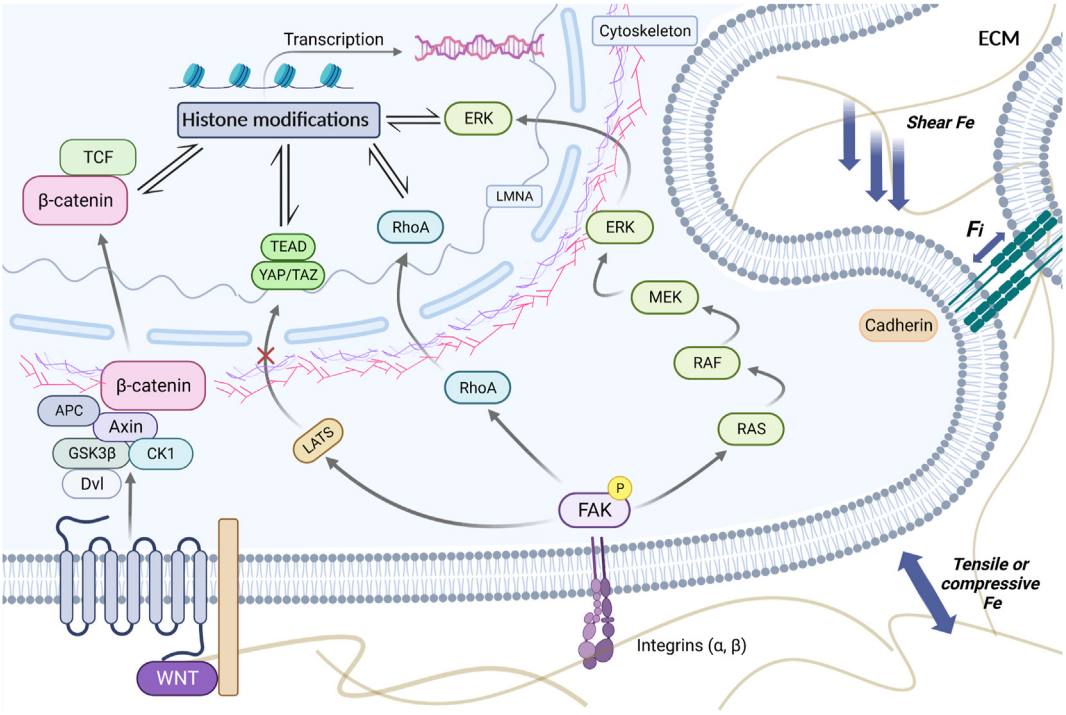

Figure 1 Mechanism and structure of mechanotransduction. ECM and intracellular pathways are biologically coupled through mechanical transduction. An external force (Fe) is a force exerted on a cell by shearing or compression, which can transmit signals to the nucleus through a variety of pathways, such as mechanically gated ion channels, changes in receptor-ligand binding, and deformation of the cytoskeleton.[3] Intracellular forces (Fi) are transferred to other cells via intercellular connections, such as cadherin receptors.[3] Integrins are a class of ubiquitous cell membrane adhesion receptors that control the activation of a variety of signal transduction pathways.[4] FAK mediates integrin signaling. FAK phosphorylate and activate mechanical response signaling elements such as RhoA and MAPK and YAP/TAZ.[5,6,7] YAP and TAZ are also effectors of the Hippo pathway, which can travel between the cytoplasm and the nucleus.[8] When YAP/TAZ is phosphorylated LAST, it enters the cytoplasm from the nucleus and inactivates transcription. Otherwise, if LAST is not activated, YAP/TAZ enters the nucleus and regulates transcription.[8] MAPK, a serine—threonine protein kinase is expressed by all eukaryotic cells and is highly conserved from yeast to humans.[9] MAPK is the general name of a family of proteins. ERKI was the first discovered MAPK. MAPK can be divided into four subfamilies: ERK, p38, JNK, and ERK5.[10] ERK1 belongs to the ERK subgroup. WNT signaling pathway is a complex regulatory network, the most classical of which is the WNT/β-catenin signaling pathway. When cells are not stimulated by WNT signal, axin, APC and GSK3β in the cytoplasm form the destruction complex, which degrades catenin. When cells are stimulated, DVL proteins receive upstream signals in the cytoplasm and stabilize β-catenin proteins in the cytoplasm by inhibiting the function of complexes formed by APC, axin, and GSK3β proteins.[11,12] The β-catenin protein accumulated in the cytoplasm enters the nucleus and binds to transcription factors of the T-cell family (TCF) to regulate the transcription of target genes.[13]

inflammation, apoptosis, and growth, while ERK is responsible for cell growth and differentiation, and its upstream signal is the well-known Ras/Raf protein.[20] RhoA is one of the Rho-family small GTPases, which is a key regulator of cytoskeletal and cell adhesion dynamics.[21] In the GTP-bound state, RhoA interacts with and activates downstream effectors to initiate intracellular signaling cascades that influence cell behavior and morphology.[21,22] One of the main downstream effectors of RhoA is the serine—threonine kinase ROCK1/2.[23] RhoA-ROCK signaling drives actin cytoskeletal remodeling and cell death by phosphorylation.[22] The Hippo signaling pathway consists of a series of kinases that inhibit cell growth.[24] The membrane protein receptors upstream of the Hippo signaling pathway act as receptors for extracellular growth inhibition signaling to activate a series of kinase cascades of phosphorylation once the extracellular growth inhibition signal is felt. The mammalian STE20-like protein kinase 1/2 (MST1/2) kinase forms a complex with Salvador 1 protein (SAV1), and then phosphorylates large tumor suppressor 1/2 (LATS1/2); the activated LATS1/2 kinase immediately phosphorylates the key effectors, YAP and TAZ, downstream of the Hippo signaling pathway.[8] Cytoskeletal proteins will bind to phosphorylated YAP/TAZ, leaving them within the cytoplasm, while unphosphorylated YAP/TAZ will enter the nucleus to bind to TEA domain 1—4 (TEAD1—4) or other transcription factors, thereby inducing up-regulation of pro-proliferation and anti-apoptotic genes.[8] WNT/β -catenin signaling pathway is an extremely conserved mechanotransduction system in biological evolution.[25] In normal somatic cells, β-catenin is only used as a cytoskeletal protein to maintain the adhesion of the isotype of cells and to prevent cell migration.[26] Only when the extracellular WNT signaling molecules bind to the specific receptor Frizzled protein on the cell membrane to activate the intracellular Dishevelled (DVL) protein and inactivate glycogen synthase kinase 3β (GSK3β), preventing β-catenin from being degraded, can it accumulate in the cytoplasm.[11,12] Accumulated β-catenin proteins in the cytoplasm then enter into the nucleus to regulate the transcription of the target genes.[11,12] Various mechanical signaling pathways extensively regulate each other at different levels to complete signal transduction together.

How mechanical signals are perceived and transmitted at the molecular level to direct gene expression and determine cell fate has long remained enigmatic. In this review, we discuss the crucial role of histone modifications in regulation. Histone modifications affect chromosome dynamics and gene expression by recruitment of nonhistone proteins and altering chromatin structure.[27] Histone modifications include many types, such as histone acetylation, histone methylation, histone crotonylation, histone phosphorylation, and histone β-hydroxybutyrylation. The two main modifications covered in this paper are histone methylation and histone acetylation. Histone methylation can occur at different sites of histones, usually at lysine and arginine residues of histone H3 and H4, and it can be controlled by histone methyltransferases and histone demethylases to activate or inhibit transcription (Table 1).[53] This methylation is catalyzed by histone methyltransferases. It is generally believed that methylation at histone H3 lysine 4 (H3K4) and histone H3 lysine 36 (H3K36) are active markers promoting transcription. Methylation at histone H3 lysine 9 (H3K9), histone H3 lysine 27 (H3K27), and histone H4 lysine 20 (H4K20) are thought to be inhibitory markers.[54] Histone acetylation is generally considered to be an active histone mark.[55] Histone acetylation and deacetylation are regulated by a balance between histone acetyltransferase and histone deacetylase (HDAC), respectively (Table 1).[56] Each histone modification can produce different biochemical signals and play a key role in cell proliferation and differentiation, as well as specific changes in immune-related, tumor, and inflammatory diseases.[57—60] Many molecules in mechanical signaling pathways are themselves regulated by histone modifications and altered histone modifications are involved in transmitting signaling control target genes. Therefore, we linked mechanical signaling to the biological effects of histone modifications, that is, histone modifications can directly regulate the expression of transcription factors and genes downstream of mechanical signaling pathways, and can also act as sensors of mechanical stimuli to feedback the activation or suppression of signaling pathways.

Mechanotransduction influences histone modifications

FAK signaling pathway and RhoA signaling pathway affect histone modifications

FAK, as one of the crucial signaling pathways for mechanotransduction, has all been demonstrated to play an indispensable role in apoptosis, migration, proliferation, and disease progression.[61] As a downstream mechanical reaction signaling element for the signaling of FAK, RhoA functions as a molecular switch during signal transduction.[62] But the specific molecular mechanisms still need to be further elucidated. Based on previous studies, we suggest that it is closely related that FAK signaling and RhoA signaling can mediate the corresponding histone modifications (Fig. 2).

We hypothesized that histone modifications could act downstream of them, under the influence of FAK or RhoA, to modulate target genes and produce unique biological effects in mechanotransduction. It has been confirmed that venous endothelial cells and arterial endothelial cells respond differently to stimulation of arterial laminar shear stress.[63] Venous endothelial cells show impaired and inflammatory responses, while arterial endothelial cells stop DNA synthesis and become static.[63] The different manifestations of endothelial cells are related to mechanical signaling pathways and histone modifications.[63] In venous endothelial cells, FAK signaling is activated upon arterial laminar shear stress stimulation, subsequently increasing H3K9 trimethylation (H3K9me3) levels, whereas in arterial endothelial cells, FAK signaling is inhibited, as is H3K9me3.[63] The regulation of H3K9me3 by FAK is also influenced by the cellular matrix hardness, for example, H3K9me3 levels are down-regulated in cells cultured on soft matrix.[64] FAK signaling activation also raises both H3K4 trimethylation (H3K4me3) and H3K27 trimethylation (H3K27me3) levels and regulates cellular apoptosis and cancer progression, respectively.[65,66] FAK signaling can also

indirectly regulate histone modifications through the histone methylase Ezh2, histone demethylase SUV39H1, and HDAC.[66–68] For example, osteocytes regulate the translation and modification of HDAC4/5 through FAK signaling pathway to control the expression of specific genes after sensing fluid flow shear stress.[68] RhoA is a downstream part of FAK signaling pathway, and increasing evidence indicates that histone modifications can also participate in mechanotransduction process downstream of RhoA signaling pathway. For example, the activation of the RhoA signaling pathway up-regulates HDAC1/6/7.[69–71] Interestingly, HDAC6 can also activate other signaling pathways such as pannexin 1(PANX1).[70] However, unlike FAK signaling, decreased RhoA levels as well as elevated H3K9me3 levels were monitored on the soft substrate.[64] That is, RhoA does not activate H3K9me3 as FAK signaling but suppresses it. Therefore, we hypothesize that after FAK signaling increases H3K9me3 levels, its downstream RhoA regulates H3K9me3 by feedback, similar to the hypothalamic-pituitary feedback regulatory axis. This may be a self-protective mechanism of the cells, and possibly an inhibition of cell overgrowth and proliferation.

Taken together, both FAK signaling and RhoA signaling will control cell fate and disease progression through histone modifications. Activation of the FAK and RhoA signaling pathways promotes cell motility and maintains the normal cell cycle and cell survival. However, this effect also makes tumor cells more prone to metastatic spread and promotes tumor progression. But the results of FAK and RhoA signals on the same histone modifications are not completely consistent, and there may be feedback regulation between signaling pathways. But the effect of both on histone modifications is beyond doubt.

MAPK signaling pathway affects histone modifications

MAPK signaling pathway can help the adaption to mechanical stimulation by modulating histone modifications and regulating the expression of cell-related genes, and play an important role in regulating cell fate and function (Fig. 2).[72–75]

For example, down-regulation of MAPK signaling pathway inhibits histone acetylation, and the activation of ERK/MAPK promotes histone phosphorylation and acetylation.[76–78] The p44/42 MAPK inhibitor can alter the acetylation of histone H3 at lysine 9/14 and the methylation at lysine 9.[79] The researchers also found that MK-STYX (MAPK phosphoserine/threonine/tyrosine-binding protein) reduces the number of stress-induced HDAC6 polymeric under stress conditions.[80] There are many similar findings, for example, the activation of ERK1/2 under certain stimuli affects the acetylation of K14 in histone H3 by some mechanism; high osmotic pressure can affect the activity of Rpd3 histone deacetylase by activating MAPK Hog1 in yeast cells, which in turn helps the cells to adapt to this environment.[72,81] Activation of MAPK signaling through different mechanisms can play different regulatory roles in histone modifications, including regulating the intracellular localization of HDAC4, promoting the phosphorylation of histone H3 at serine 10, and then initiating the mitotic progression of cells.[82–84] In addition to direct regulation, the regulation of histones by MAPK signaling pathway may also be mediated by other substances. In studies of chondrocyte hypertrophy, MAPK signaling pathway can regulate HDAC4 degradation by affecting caspase activity, and then promote the development of chondrocytes[85]; stress stimulation, mitosis, and glutamate can activate mitogen and stress-activated kinase 1 (MSK1), and then regulate the phosphorylation of histone H3.[75,86]

In summary, MAPK signaling pathway plays an important role in regulating histone modifications, and its mechanism is related to histone-modifying enzymes, as well as other intermediate effector molecules.

YAP/TAZ signaling pathway affects histone modifications

YAP/TAZ is the major effector protein of the Hippo pathway, mediating a series of processes such as cell proliferation, morphogenesis, and death.[87] As a transcriptional cofactor, YAP/TAZ usually cooperates with transcription factors such as proteins containing the TEAD to regulate the expression of the target genes.[88] However, we believe that various effects of YAP/TAZ are closely related to histone modifications (Fig. 2).

YAP/TAZ inhibits the repair response of the myocardium after myocardial infarction by interacting with a repressor complex containing HDAC3 to reduce Arginase-I expression.[89] Moreover, TAZ can also activate TBX5, an important transcription factor derived from cardiac development, by interacting with the histone acetyltransferase p300.[90] YAP1 regulates the expression of HELLS, a chromatin remodeling enzyme with epigenetic functions such as histone modifications.[91] YAP1 also acts on the arginine methyltransferase CARM1 and regulates embryonic development by catalyzing the histone H3 arginine 17/26 methylation.[92] Some studies have also proved that YAP signaling regulates histone modifications. For example, a blocked YAP signaling decreases histone H3 phosphorylation.[93] YAP signaling can also regulate HDAC2 and H3K27 acetylation (H3K27ac).[94,95] Although there are few studies on the regulation of histone modifications by YAP signaling, there are still many experiments suggesting a correlation between the two. For example, during tumorigenesis, the cells were in a proliferative and regenerative state, where simultaneously elevated levels of YAP and the histone methyltransferase MLL1 were detected.[96] For another example, YAP signaling is usually activated in cancer patients, while numerous studies are showing that HMTs also show elevated levels in cancer patients.[1,97] All these suggest that the activation or inhibition of YAP signaling and the regulation of disease progression are closely related to histone modifications.

As mechanical transducers, YAP and TAZ also regulate histone modifications, providing insights into the molecular mechanisms by which normal cellular activity and abnormal cellular mechanics drive the pathogenesis of various diseases.

Table 1 Histone modification and modification enzymes.

Site	K-methyltransferases	Aliases	K-demethylases	Aliases	Reference
H3K4me1	KMT7	SET7/9			[28—36]
	KMT3C	SMYD2			
H3K4me3			KDM2A	JHDM1A	
			KDM2B	JHDM1B	
			KDM4A	JMJD2A	
			KDM4C	JMJD2C	
			KDM7B	JHDM1F	
				PHF8	
			KDM8	JMJD5	
H3K4me1/2	KMT2C	MLL3	KDM1	LSD1	
	KMT2D	MLL4			
H3K4me2/3	KMT3E	SMYD3	KDM5A	JARID1A	
			KDM5C	JARID1C	
			KDM5D	JARID1D	
H3K4me1/2/3	KMT2A	MLL1	KDM5B	JARID1B	
	KMT2B	MLL2			
	KMT2F	SETD1A			
	KMT2G	SETD1B			
	KMT8B	PRDM9			
H3K9me1	KMT8E	PRDM3			
	KMT8F	PRDM16			
H3K9me3			KDM5C	JARID1C	
			KDM6B	JMJD3	
			KDM8	JMJD5	
H3K9me1/2	KMT1C	G9a	KDM1	LSD1	
	KMT1D	GLP	KDM3A	JMJD1A	
				JHDM2A	
	KMT1E	SETDB1	KDM3B	JMJD1B	
				JHDM2B	
			KDM5A	JARID1A	
			KDM7B	JHDM1F	
				PHF8	
H3K9me2/3	KMT1A	SUV39H1	KDM4A	JMJD2A	
			KDM4B	JMJD2B	
	KMT1B	SUV39H2	KDM4C	JMJD2C	
			KDM4D	JMJD2D	
H3K27me1	KMT1C	G9a			
H3K27me2			KDM7B	JHDM1F	
				PHF8	
H3K27me3			KDM5C	JARID1C	
H3K27me2/3	KMT6B	Ezh1	KDM6A	UTX	
	KMT6A	Ezh2	KDM6B	JMJD3	
H3K36me1/2	KMT3B	NSD1	KDM2A	JHDM1A	
	KMT3G	NSD2	KDM2B	JHDM1B	
	KMT3F	NSD3			
H3K36me2	KMT3C	SMYD2	KDM4B	JMJD2B	
	KMT2H	ASH1L	KDM8	JMJD5	
H3K36me3	KMT3A	SETD2	KDM4D	JMJD2D	
	KMT8B	PRDM9	KDM5B	JARID1B	
H3K36me2/3			KDM4A	JMJD2A	
			KDM4C	JMJD2C	
H4K20me1	KMT5A	SET8	KDM7B	JHDM1F	
				PHF8	
H4K20me2/3	KMT5B	SUV4-20H1			
	KMT5C	SUV4-20H2			

(*continued on next page*)

Table 1 (*continued*)

Site	Acetyltransferases	Aliases	Deacetylases	Aliases	Reference
H3K9ac	KAT2A	GCN5	HDAC3	RPD3	[37–52]
				HD3	
H3K14ac	KAT2A	GCN5	HDAC1	RPD3L1	
				HD1	
H3K18ac	KAT2B	PCAF	HDAC1	RPD3L1	
	KAT3A	CBP		HD1	
H3K23ac	KAT3A	CBP	HDAC6	HD6	
	KAT6A	MOZ			
H3K27ac	KAT2A	GCN5	HDAC5	HD5	
	KAT3A	CBP			
H4K5ac	KAT7	HBO1	HDAC3	RPD3	
	KAT8	MYST1		HD3	
H4K8ac	KAT8	MYST1	HDAC3	RPD3	
				HD3	
H2AK5ac	KAT6A	MOZ	HDAC4	HD4	
			HDAC5	HD5	
			HDAC7	HD7	
				HD7A	
			HDAC9	HD9	
				HD7B	

WNT/β-catenin signaling pathway affects histone modifications

WNT signaling pathway is a complex network of protein interactions whose functions are mostly found in embryonic development and cancer, but are also involved in normal physiological processes in the human body.[98] By means of this signaling pathway, extracellular signals are transmitted to the cell through the activation process of the intracellular segment of the cell surface receptor. Studies have found that the WNT/β-catenin signaling pathway can affect histone modifications to control disease progression epigenetically (Fig. 2).

The histone demethylase KDM4C is a new downstream target of the WNT/β-catenin signaling pathway.[99] WNT/β-catenin stabilizes the KDM4C protein by restraining both PKR and β-TrCP dependent ubiquitination, resulting in the accumulation of KDM4C in the nucleus.[99] Increased KDM4C interacts with β-catenin to demethylate H3K9me3 at the WNT target promoters. Alternatively, the stabilization of KMD4C is also essential for the development of glioblastoma.[99] Activation of the WNT pathway leads to the overexpression of KDM4C in glioblastoma cells, which affects histone demethylation.[99] This suggests to us that the process by which WNT causes KDM4C overexpression to demethylate target genes appears to be required for the subsequent cell proliferation and tumorigenicity of cancer cells. In addition to the above, it was found that Wnt3a stabilized KDM4C by inhibiting the ubiquitination of KDM4C induced by GSK3.[99] In short, the regulation of histone modifications by WNT is diverse and is the result of the concerted actions of multiple mechanisms. WNT/β-catenin signaling pathway also promotes H3K9 acetylation (H3K9ac).[100]

Although there are not many studies on the effect of WNT/β-catenin signaling pathway on histone modifications, we can still determine the existence of this role. Especially in the process of tumor occurrence and development, WNT/β-catenin signaling pathway is often activated, and the abnormal expression of oncogenes and the abnormal proliferation of tumor cells must also be related to epigenetics. The mutual regulation mechanism between the two still needs to be further elucidated.

Histone modifications influence the molecular expression of mechanical signaling pathways

Mechanotransduction does not stop after affecting histone modifications, and histone modifications can also affect the molecular expression of mechanical signaling pathways (Fig. 2).

Histone modifications affect FAK signaling pathway and RhoA signaling pathway

Histone modifications can in turn modulate both the FAK and RhoA signaling pathways. The histone demethylase KDM1 can be activated through FAK signaling pathway by regulating the integrin ligand through H3K4/9 demethylation.[101] The histone demethylase KDM2B is also considered to be a carcinogen, promoting cancer cell migration by activating FAK signaling pathway.[102] The methylase G9a activates the FAK signaling pathway as well.[103] Histone modifications also seem to respond directly to mechanical stimuli, and HDACs can be activated under the action of ALS, in which HDAC1 has an inhibitory effect on FAK signaling pathway.[63,104] Other studies have confirmed the activation effect of HDAC inhibitors on FAK and the inhibitory effect of acetyl transferase KAT1 on FAK.[105,106] As a downstream of FAK, RhoA is regulated not only by FAK but also by histone modifications in mechanotransduction. KDM2B blocks RhoA signaling pathway by inhibiting

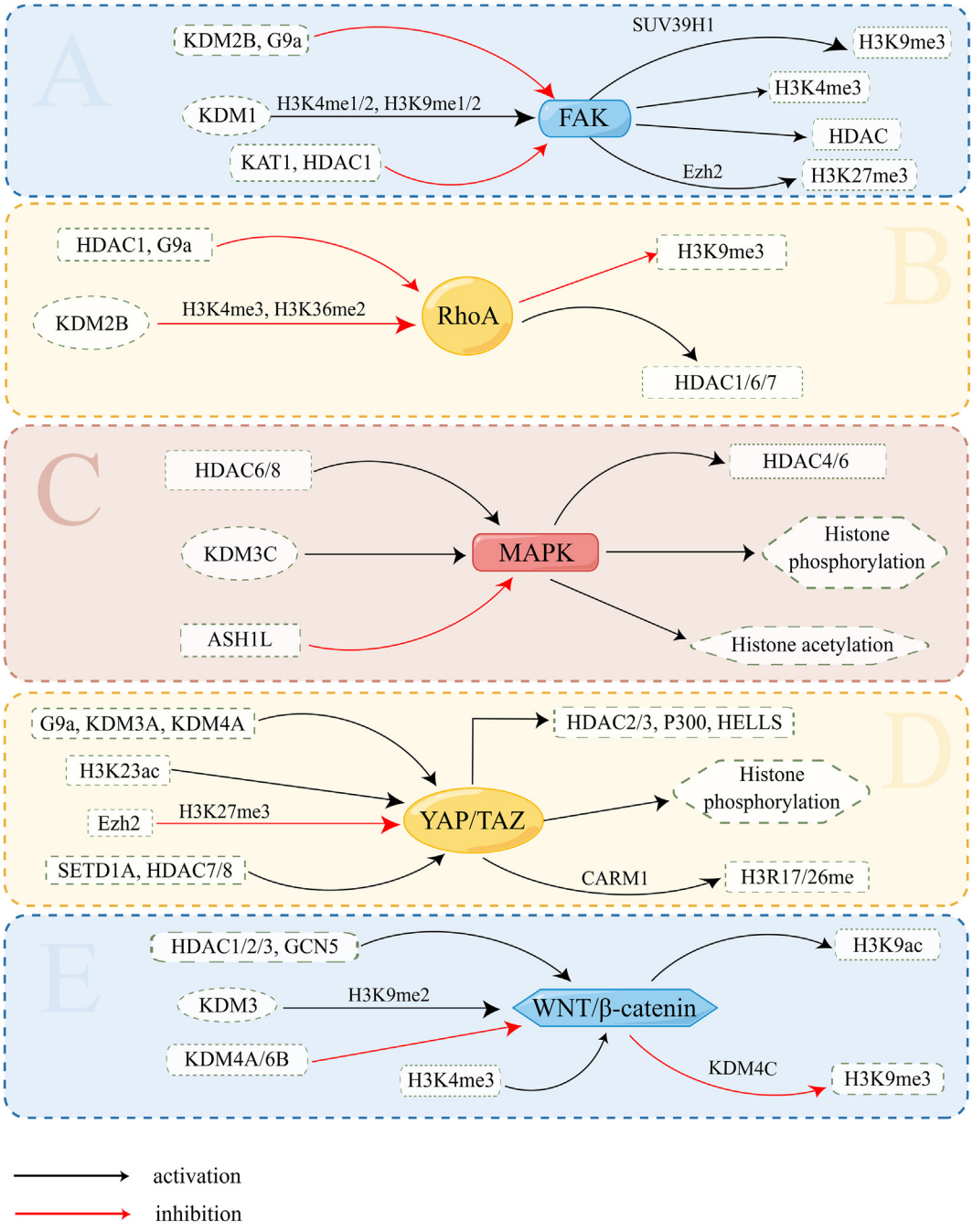

Figure 2 Mutual regulation of histone modifications and signaling pathways. Regulation of histone modifications by mechanical signaling pathways: **(A)** FAK signaling pathway can activate H3K4me3, H3K9me3 and histone methyltransferase SUV39H1 that regulates H3K9me3, H3K27me3 and histone methyltransferase Ezh2 that regulates H3K27me3, and HDAC. **(B)** RhoA signaling pathway inhibits H3K9me3 and modulates HDAC1, HDAC6, and HDAC7. HDAC6 continues to influence PANXI signaling pathway. **(C)** MAPK signaling pathway activates histone acetylation and phosphorylation and regulates HDAC4 and HDAC6. **(D)** YAP/TAZ signaling pathway activates histone phosphorylation and regulates HDAC2, HDAC3, P300, HELLS, and CARM1 (methylate histone H3 arginine 17/26). **(E)** WNT/β-catenin signaling pathway actives KDM4C (H3K9 demethylase) and H3K9ac. Regulation of mechanical signaling pathways by histone modifications: **(A)** KDM1 activates the FAK signaling pathway by demethylating H3K4 and H3K9. Histone demethylase KDM2B and histone methylase G9a activate FAK signaling pathway, while acetyltransferase KAT1 and HDAC inhibit FAK signaling pathway. **(B)** KDM2B inhibits RhoA signaling by demethylation of H3K4 and H3K36, as well as G9a and HDAC1. **(C)** KDM3C and HDAC6/8 can activate MAPK signaling pathway, while ASHL1 inhibits MAPK signal activation. **(D)** Ezh2 inhibits YAP/TAZ by H3K27me3. G9a, SETD1A, KDM3A, KDM4A, and HDAC7/8 all activate YAP/TAZ. H3K23ac also activates the YAP/TAZ signaling pathway. **(E)** KDM3, GCN5, and HDAC1-3 activate the WNT/β-catenin signaling pathway. KDM4A and KDM6B inhibit the WNT/β-catenin signaling pathway. H3K4me3 activates the WNT/β-catenin signaling pathway.

H3K4me3 and H3K36 dimethylation (H3K36me2).[107] KDM2B can also restrain RhoA signaling pathway by regulating Ezh2.[107,108] Methyltransferase G9a also inhibits RhoA signaling pathway.[109] Other enzymes such as the demethylase PHF8, which regulates monomethylation of H4K20 (H4K20me1), have also been confirmed to associate with the expression of RhoA signaling.[110] Besides histone methylation, histone acetylation cannot be ignored either. HDAC1 can restrain RhoA by reducing H3/H4 acetylation, that is, RhoA is down-regulated when HDAC1 is up-regulated.[111] Histone acetyltransferase P300 associated with H3K27ac can up-regulate KTN1, thus affecting RhoA signaling pathway.[112] It is noteworthy that HDAC inhibitors may have both inhibitory and activating effects on RhoA. It has been shown that SAHA and HTPB can inhibit RhoA, while another HDAC inhibitor, TSA, has been confirmed to activate RhoA signaling pathway.[113–115] This also suggests that histone-modifying enzymes may not act directly on the signaling pathways, and there may be other targets between the two, resulting in different effects of enzymes with similar epigenetic effects on RhoA expression.

In conclusion, FAK and RhoA signaling pathways form feedback loops with histone modifications and mechanical signals to regulate cell fate and disease progression. However, other molecules are involved as intermediates in histone modifications regulating signaling pathways, which requires our special attention.

Histone modifications affect MAPK signaling pathway

Can histone modifications in turn affect MAPK signaling pathway? Here we infer that the interaction between them is reciprocal. HDAC inhibitors can reduce MAPK phosphorylation in mechanical stress-induced chondrocytes and inhibit the p38 MAPK expression in synaptic fibrosis E11 cells of human rheumatoid arthritis.[116,117] Compound 9a (an HDAC inhibitor) not only inhibits the phosphorylation of MAPK but also enhances the inhibitory effect of MAPK phosphate on MAPK signaling.[118] Meanwhile, in studies of convulsive rats in the development stage, the HDAC inhibitor MS275 reduces the protein expression of P38, thereby inhibiting p38 MAPK signaling pathway.[119] As mentioned above, MAPK signaling pathway can affect the number and location of HDAC. Interestingly, in studies on HDAC8 and myocardial hypertrophy and fibrosis, it was found that overexpression of HDAC8, in turn, promoted P38 MAPK phosphorylation.[120] In addition, as for the inflammatory response mentioned above, other studies have found that HDAC6 can increase the expression of pro-inflammatory cytokines in macrophages by activating complex and complete signaling pathways, and MAPK signaling pathway is a very important part of the above-mentioned pathways.[121] Inhibition of HDAC6 expression can also inhibit the activation of MAPK signaling pathway.[122] In addition, deletion of H3K4 methyltransferase ASHLl also leads to enhanced MAPK activation in macrophages under tumor necrosis factor stimulation.[123] Knockout of H3K9 demethylase JMJD1C in mouse embryonic stem cells activates ERK/MAPK signaling pathway and induces embryonic stem cell differentiation.[124] In terms of cancer, HDAC inhibitor Vorinostat induces phosphorylation of P38 MAPK and dephosphorylation of ERK1/2, and induces apoptosis of human breast cancer cells through this pathway, which is accompanied by changes in caspase-3 cleavage.[125]

In conclusion, the regulation of MAPK signaling pathway on histone modifications is not one-way, nor is it only directly regulated. In other words, after receiving stimulation, the two can directly regulate each other, or mediate this regulation through some substance, and finally achieve the purpose of regulating cell fate.

Histone modifications affect YAP/TAZ signaling pathway

Similarly, YAP and TAZ act as mechano-transductors reading various mechanical signals from shear stress to cell shape and ECM rigidity.[1] This process not only results in changes in histone modifications but is also regulated by various histone-modifying enzymes and histone modifications.

For example, short-term mechanical stimulation can activate YAP to induce cell proliferation, but long-term can lead to cell growth stagnation. This situation is closely related to histone modifications.[126] Long-term mechanical stimulation increases H3K27me3 levels, and this inhibitory histone modification affects the YAP pathway.[126] Other studies have confirmed this mechanism, for example, LncRNA H19 induces H3K27me3 through Ezh2 and then inhibits LATS1, thus affecting downstream effector YAP/TAZ of pathway.[127] Similarly, microRNA-1224 inhibits transcription and activation ofYAP signaling pathway by binding to CREB.[128] While CREB plays an inhibitory role through Ezh2-mediated H3K27me3.[128] In addition, studies have shown that KDM3A is a positive regulator of YAP signaling pathway.[129] KDM3A activates this signaling pathway by up-regulating the expression of YAP1, and regulates TEAD1 through H3K9 dimethylation (H3K9me2), affecting transcription.[129] Other studies have shown that HMTs are up-regulated in human cholangiocarcinoma and enhance the growth and invasiveness of cholangiocarcinoma cells by regulatingYAP signaling pathway.[130] For example, the deletion or inhibition of G9a reduces the level of H3K9me2 and restores the expression of LATS2, leading to the inhibition of YAP.[130] However, at the same time, histone demethylase also seems to promote tumor progression. For example, KDM4A can up-regulate YAP1 and drive the occurrence of prostate tumors.[131,132] A deficiency of enzymes that promotes other histone modifications, such as SETD1A, can impair phosphorylation and activation of YAP, and histone acetyltransferase is also a key regulator of Hippo pathway gene expression.[133,134] Although histone acetyltransferases are considered a negative regulator of the Hippo pathway, the reality seems to be even more complex. A large number of experimental data have proved that histone deacetylases can activate YAP signaling pathway, such as SIRT1, HDAC7, HDAC8, *etc.*[135–137] However, there are exceptions, for example, epigenetic regulatory factor KAT6A silencing will weaken H3K23 acetylation (H3K23ac) on the YAP promoter, resulting in inhibition of YAP

signaling pathway, indicating that H3K23ac is related to the activation of YAP.[138,139] In addition, histone modifications can also indirectly regulate mechanical signaling pathways. ARSD is a gene that affects YAP signaling, which is regulated by histone modifications.[140]

Therefore, we believe that when mechanical signals activate the signaling pathways, histone modifications can produce positive or negative regulation on genes, and the changed histone modifications in this process will continue to affect the normal conduction or block of the signaling pathways. In summary, various histone modifications play a corresponding role in the multiple stages of signal transmission to cells by mechanical stimulation, and each element of the pathway is individually regulated. Although histone modifications are not necessarily the first transducers to transmit mechanical signals, they must transmit corresponding mechanical signals and produce unique biological effects.

Histone modifications affect WNT/β-catenin signaling pathway

WNT signaling pathway is no exception, and there have been many studies on the control of the activation and inhibition of the WNT signaling pathway by histone modifications.

For example, the histone demethylase KDM3 family controls the oncogenic potential of human colorectal cancer stem cell epigenetics through WNT/β-catenin, and consumption of KDM3 can inhibit the oncogenic growth and chemotherapy resistance of human colorectal cancer stem cells.[98] Mechanically, KDM3 not only directly removes inhibitory H3K9me2 markers, but also helps recruit MLL1 to promote H3K4 methylation, thereby promoting transcription of WNT/β-catenin target genes.[98] Histone modifications affect WNT/β-catenin not only in colorectal cancer stem cells but also in posttraumatic stress disorder.[141] Studies have found that the expression of WNT/β-catenin signaling pathway is up-regulated in posttraumatic stress disorder, and the overexpression of WNT is associated with the high expression of H3K4me3 histone modification around the WNT promoter.[141] In addition, the use of siRNA to knock out histone demethylase specific to H3K4me3 resulted in increased WNT expression, providing conclusive evidence that H3K4me3 does control WNT expression.[142] Other studies confirmed that the overexpression of histone demethylase KDM6B and KDM4A reduced the expression level of β-catenin and blocked WNT/β-catenin signaling pathway.[143,144] However, another study suggested that the KDM4 family activated WNT/β-catenin signaling pathway.[145] This also means that there are other influencing factors involved in the regulation of signal pathways by histone modification, not all of which are direct regulation. Other more intuitive data suggest that reduced expression levels of H3K9me1, H3K9me2, H3K27me2, and H4K20me1 activate WNT/β-catenin signaling pathway.[146] Alternatively, WNT/β-catenin signaling pathway is also closely related to cell differentiation. For example, Ezh2 regulates Wnt4 through H3K27me3 to promote osteoblast differentiation and mineralization.[147] Stimulated by cyclic mechanical stress, GCN5, as an important member of the histone acetyltransferase family, mediates the osteogenic differentiation of mesenchymal stem cells through WNT/β-catenin signaling pathway.[148] JHDM1D, KMT2D, SETD2, *etc.*, are also involved in osteogenic differentiation and regulate the process of osteogenic differentiation through WNT/β-catenin signaling pathway.[149–151] WNT/β-catenin signaling pathway is the main downstream of KDM6 in early neural induction and controls neuroectoderm differentiation.[152] In addition, inhibition of class I HDACs (HDAC1–3) activates WNT/β-catenin signaling pathway by increasing histone H3 acetylation levels.[153] Other HDACs, such as HDAC6, can activate WNT/β-catenin signaling pathway.[154]

In summary, the activation of WNT/β-catenin involves many types of histone modifications, which control gene expression by affecting WNT/β-catenin and even lead to the occurrence of diseases. In addition, histone modifications can feedback and regulate WNT/β-catenin signaling pathway or directly regulate WNT/β-catenin signaling pathway as a receiver of mechanical signals. They regulate each other in response to mechanical signals and jointly determine the fate of cells.

Mechanical signals and histone modifications form feedback loops

It is clear from the foregoing that the ultimate biological effects of mechanotransduction depend on histone modifications. However, the signaling pathways are formed by the coordination of many different links, which involve many molecules, so these components become the target of histone modifications, controlled by epigenetic changes. Interestingly, when abnormal conditions occur in the body, cells are not only the result of necrosis, but also can adapt to changes in the abnormal microenvironment around cells, and even resist and protect themselves.

Therefore, we believe that mechanotransduction signaling pathways and epigenetics can form feedback loops. In FAK signaling pathway, FAK increased the expression level of H3K9me3, and H3K9me3 could promote the activation of FAK signaling pathway.[63,155] FAK can also interact with G9a[64,103]; in the YAP/TAZ signaling pathway, YAP is subject to the feedback regulation of HDAC[89,94,133,134]; in the WNT/β-catenin signaling pathway, KDM4C is not only the downstream target of WN but also one of the factors that activate the WNT/β-catenin signaling pathway.[99,145,156] WNT/β-catenin signaling pathway and H3K9ac are also mutually activated.[100,157] But this feedback is not all positive feedback, there will be negative feedback. For example, RhoA can upregulate HDAC1, while HDAC1 inhibits RhoA signaling pathway[69,111]; in MAPK signaling pathway, HDAC6 activates this signaling pathway, but some modified products of MAPK will reduce the amount of HDAC6.[80,121,122] However, other studies have come to the opposite conclusion that MAPK activates HDAC6, and the down-regulation of HDAC6 is beneficial to the activation of MAPK.[158,159] This suggests that more research is warranted to reconcile these feedback pathways. The feedback regulation of histone modifications not only acts on the signaling pathways that cause the alteration but also acts on other signaling pathways. For example, overexpression of FAK in hepatocellular carcinoma can increase the expression level of Ezh2.[160] Ezh2

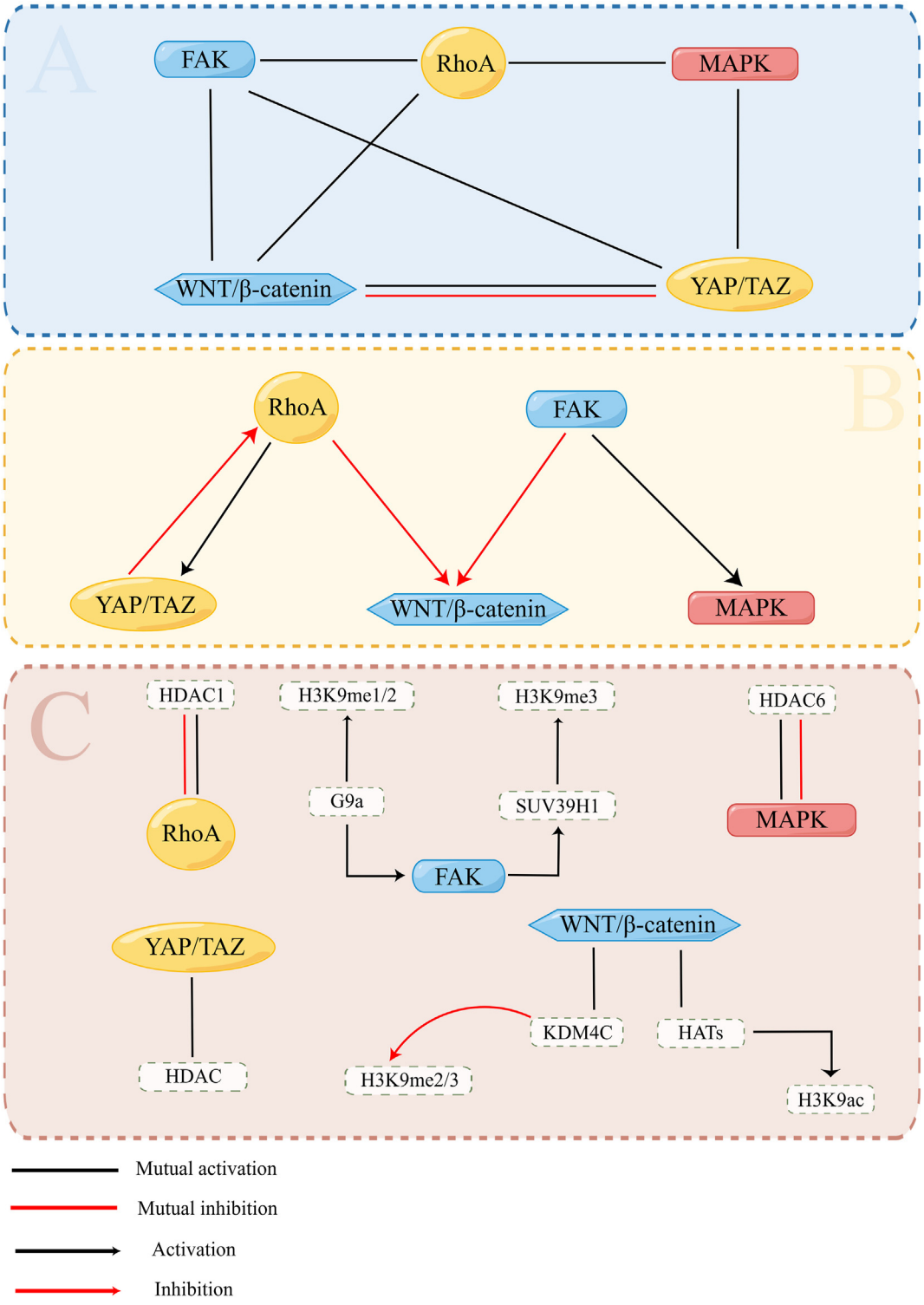

Figure 3 The relationship between mechanical signaling pathways and the feedback loops formed by pathways and histone modifications. Although most of the current research is based on these signaling pathways individually, there is growing evidence that there is functional crosstalk between these signaling pathways during disease development and progression. The main relationship is shown in the figure: FAK can activate RhoA signaling pathway, and RhoA signaling pathway plays a key role in FAK phosphorylation[14,163]; MAPK is generally the downstream of FAK signaling pathway, and FAK can activate MAPK signaling pathway[164]; FAK can activate YAP/TAZ and can also be induced by YAP-TEAD[165,166]; the mutual regulation between FAK and WNT/β-catenin signaling pathways seems to be more complex, showing different regulatory relationships in different diseases. FAK can activate or inhibit WNT/β-catenin signaling pathway, and FAK can also act as the downstream of WNT[15,167]; RhoA activates MAPK signaling pathway, and RhoA is also activated by MAPK signaling[14,168]; RhoA mainly activates YAP/TAZ in the regulation between

overexpression activates the WNT/β-catenin signaling pathway.[161] For another example, the YAP pathway combined with MLL1 locks cells in a state of proliferation and regeneration, making them prone to tumor.[96] H3K4me3 also activates the WNT/β-catenin signaling pathway, further promoting the progression of cancer.[98] It should also be noted that the same histone modifications have different effects on different mechanical signaling pathways. For example, the decrease of H3K9me2 expression level is conducive to the activation of WNT/β-catenin signaling pathway but is not conducive to the activation of YAP and MAPK signaling pathways.[130,146,162] Interestingly, some pathological processes are feedback loops. For example, fibroblast activation in pathological fibrosis is both the result and cause of ECM hardening and seems to be understood as a macro manifestation of feedback regulation by histone modifications and mechanical signaling pathways. In the process of cell differentiation, the same gene will show different expression levels at different stages, and the clinical manifestations of temporary improvement will also appear in the process of disease development, which suggests that the mechanical signaling pathways and histone modifications are not a stable process of unidirectional regulation, but a dynamic change of mutual regulation through the formation of feedback loops.

In other words, when a mechanical signaling pathway is activated or inhibited, the corresponding histone modifications downstream will change. Histone modifications not only produce biological effects but also contribute to the feedback regulation of the mechanical signaling pathways and even other signaling pathways. This feedback regulation can be either positive or negative, which makes the regulatory network formed by the mechanical signaling pathways more complicated (Fig. 3). The feedback loop formed by the mechanical signaling pathway-histone modification-mechanical signaling pathway plays an indispensable role in cell proliferation, differentiation, apoptosis, and disease progression, which also suggests that mechanical signaling pathways and histone modifications can become new therapeutic targets and prognostic markers.

The clinical application value of feedback loop formed by mechanical signaling pathways and histone modifications

The abnormal activities of mechanical signaling pathways and histone modifications in human cancer indicate that each component of the signaling pathways, each kinase, upstream and downstream effectors, and the interaction between the signaling pathways and histone modifications may become the targets for cancer treatment.

First, in clinical practice, there are many treatments targeting signaling pathways. FAK promotes tumor progression and metastasis by acting on cancer cells and stromal cells in the tumor microenvironment.[183] In addition to cancer, FAK inhibition also has clinical benefits such as limiting edema and inflammation.[184] The effect of FAK on vascular permeability also helps to overcome the resistance of patients to chemotherapy drugs. For example, FAK inhibitor PF-562,271 can be used for the treatment of ovarian serous carcinoma.[185] Furthermore, FAK inhibitors TAE-226, CEP-37440, VS-6063, and GSK2256098 have also been proven to have anti-cancer effects in clinical trials.[185–190] For RhoA signaling pathway, inhibiting RhoA-ROCK signal has become a promising method for the treatment of central nervous system disorders.[22] At present, many ROCK inhibitors are available, such as fasudil, Y-27632, H-1152, KD-025, hydroxyfasudil, ripasudil, netarsudil, and AMA-0076.[191–193] At present, only fasudil, its derivative ripasudil, and netarsudil have been licensed for clinical use.[192,193] Inhibitors targeting various components of MAPK signaling pathway such as RAF265 (Raf inhibitor), PD325901 and ADZ6244 (MEK1/2 specific inhibitors), and FTI and SCH-66336 (Ras inhibitors) also show great potential in the treatment of cancer.[194] In clinical practice, oral MK-8353 (ERK inhibitor) showed anti-tumor activity in patients with BRAF V600 mutant melanoma.[195] The molecularly targeted drug dabrafenib also plays an important role in the treatment of melanoma by targeting MAPK signaling pathway.[196] In addition, MS275 can inhibit the p38 MAPK signaling pathway induced by convulsion, providing a new approach and theoretical direction for the treatment of convulsion.[119] The best-characterized molecular targets for Hippo signaling pathway are YAP/TAZ and TEAD transcription factors, as well as their interaction, which are important in the pathological changes of fibrosis in the heart, liver, lung, and kidney and cancer.[197] For example, inhibitor MYF-01-37 destroys the combination with YAP/TAZ and TEADs, and it can effectively target EGFR-mutant non-small cell lung cancer cells when combined with EGFR and MEK inhibitors in clinics.[197,198] Similar YAP/TAZ-TEAD active inhibitors include verteporfin, CA3, C19, *etc.*[197,199–201] Similar to the above signaling pathways, abnormal activation of WNT/β-catenin signaling pathway can also lead to tumor deterioration and metastasis.[202] Targeted inhibition of WNT/β-catenin pathway can also reduce the self-renewal ability of cancer stem cells.[203] Studies have shown that the WNT/β-

RhoA and YAP/TAZ[169,170]; the regulation between RhoA and WNT/β-catenin signaling pathway is also not fixed. RhoA can activate and inhibit WNT/β-catenin signaling pathways.[171,172] However, RhoA is downstream of WNT in the atypical planar cell polarity pathway[173]; MAPK promotes YAP activation, and YAP activates MAPK pathway[174–176]; MAPK can activate the WNT signaling pathway, and both typical and atypical WNT signaling pathways can activate MAPK[177,178]; YAP/TAZ is a downstream effector of WNT signaling pathway, and WNT can activate or inhibit YAP/TAZ.[179,180] The role of YAP/TAZ in WNT signaling pathway is also complex, with both positive and negative effects.[181] Moreover, YAP/TAZ can bind to β-catenin to inhibit WNT signaling.[182] More importantly, these pathways regulate each other, are also regulated by histone modifications, and can form feedback regulation. The FAK signaling pathway is mutually activated with H3K9 methyltransferases SUV39H1 (trimethylated H3K9) and G9a (monomethylate and demethylate H3K9); MAPK signaling pathway is mutually activated and mutually inhibited with HDAC6; RhoA activates HDAC1 while HDAC1 inhibits RhoA; YAP/TAZ is mutually activated with HDAC; WNT/β-catenin signaling pathway is mutually activated with KDM4C and histone acetylases (HATs).

Table 2 Different cell signaling pathways and histone modification in a specific disease or cell response ('/' means not exactly given).

Signaling pathways	Type of histone modification	Specific modification	Modifying enzymes	Disease or environmental stimuli	Function	Refs
FAK	Histone methylation	H3K9me3	/	Arterial laminar shear stress by ALS stimulation	In venous endothelial cells, FAK signaling is activated and H3K9me3 levels is increased; In arterial endothelial cells, FAK signaling is activated and H3K9me3 levels is decreased.	63
		H3K4me3	/	Gastric cancer	FAK signaling promotes cancer progression by activating H3K4me3 or H3K27me3.	65
		H3K27me3	Ezh2	Pediatric hepatocellular carcinoma		66
	Histone acetylation	/	HDAC5	Fluid flow shear stress	FAK signaling pathway regulates the translation and modification of HDAC5 to control the expression of specific genes during bone formation.	68
RhoA	Histone methylation	H3K9me3	/	Soft substrate	RhoA is inhibited, and then H3K9me3 levels increased.	64
	Histone acetylation	/	HDAC1	Retinoblastoma	RhoA activates HDAC1, resulting in the downregulation of cell-cycle regulatory proteins.	69
		/	HDAC6	Pannexin 1 (PANX1) ion channels	Activation of HDAC by FAK signaling pathway is an ion channel activation mechanism.	70
		/	HDAC7	An inhibitor of ROCK, Y-27632	In induced pluripotent stem cells, inhibition of RhoA pathway leads to nuclear export of HDAC7, regulating actin remodeling.	71
MAPK	Histone methylation	H3K9me2	/	An inhibitor of p44 / 42 MAPK, PD98059	The treatment with PD98059 leads to di-methylation at H3K9 on the upstream 74 regions of the GLUT5 gene.	79
	Histone acetylation	H3K9/14ac	/	An inhibitor of p44 / 42 MAPK, PD98059	The treatment with PD98059 results in the acetylation of histone H3K9/14 on the GLUT5 gene, as well as its gene expression.	79

Table 2 (*continued*)

Signaling pathways	Type of histone modification	Specific modification	Modifying enzymes	Disease or environmental stimuli	Function	Refs
		H3K14ac	HDAC2	Fear memory	HDAC2 potentially underlies memory formation by regulating ERK.	210
		/	The Rpd 3 histone deacetylase	Osmostress	MAPK Hog1 is activated to promote Rpd 3 histone deacetylase expression, helping yeast cells to adapt to high osmotic pressure environment.	72
		/	HDAC4	Growth plate development	MAPK signaling pathway regulates HDAC4 degradation by affecting the caspase activity, which in turn promotes chondrocyte hypertrophy and bone formation.	85
YAP/TAZ	Histone methylation	H3K9me2	G9a	Cholangiocarcinoma	G9a enhances cancer cell growth and invasiveness by activating YAP/TAZ signaling pathway.	130
		/	KDM4A	Prostate cancer	KDM4A up-regulates YAP1 and drives the occurrence of prostate cancer.	132
	Arginine methylation	Methylation of histone H3 arginine 17/26 (H3R17/26me)	CARM1	Fetal embryos	YAP/TAZ acts downstream of CARM1 to regulate the embryonic development.	92
	Histone acetylation	/	HDAC3	Myocardial infarction	YAP/TAZ impedes reparative response through interaction with the HDAC3-nuclear receptor corepressor 1 repressor complex.	89
		/	P300, TBX5	Cardiac and limb development	YAP/TAZ stimulates transcription factor expression through histone acetyltransferase.	90
WNT/β-catenin	Histone methylation	H3K9me2	KDM3	Human colorectal cancer	KDM3 plays a significant role in the tumorigenic potential and survival of colorectal cancer stem cells by activating WNT target	98

(*continued on next page*)

Table 2 (*continued*)

Signaling pathways	Type of histone modification	Specific modification	Modifying enzymes	Disease or environmental stimuli	Function	Refs
					gene transcription.	
		H3K27me3	KDM6	Differential neuroectoderm induction	WNT is downstream of KDM6, controlling neuroectoderm differentiation in human pluripotent stem cells.	152
		H3K4me3	/	Posttraumatic stress disorder	WNT/β-catenin signaling pathway is upregulated in patients resulting from H3K4me3.	141
		H3K27me3	Ezh2	A small molecular inhibitor of Ezh2, 3-Deazaneplanocin (DZNep)	Ezh2-H3K27me3-WNT4 axis promotes osteoblast differentiation and mineralization.	147
		H3K9me3	KDM4C	Glioblastoma	KDM4C promotes tumorigenesis and survival of glioblastoma cells by activating the transcription of WNT.	99
		/	JHDM1D	SATB2-associated syndrome	The upregulation of JHDM1D inhibits WNT/β-catenin signaling pathway.	149
		H3K4me3	MLL1	Human Patient-Derived Colorectal Cancer	YAP and MLL1 regulate growth and viability of cancer organoids together.	96
	Histone acetylation	/	GCN5	Cyclic mechanical stress	GCN5 through WNT/β-catenin mediates the differentiation of MSCs in the osteogenic direction under the stimulation of cyclic mechanical stress.	148

catenin pathway inhibitor niclosamide showed anti-tumor properties targeting ovarian cancer stem cells.[202,204] XAV939 inhibits β-catenin signal transduction and inhibits the progression of head and neck squamous cell carcinoma.[205] Similarly, WNT inhibitors WNT-C59 and IC-2 control the progress of nasopharyngeal carcinoma and hepatocellular carcinoma, respectively.[206,207]

Currently, many articles have described the targeted therapy of the above signaling pathways from multiple aspects, but more importantly, the close relationship between histone modifications and signaling pathways can be utilized to improve the therapeutic effect in collaboration with anti-tumor treatment, so that patients can have more choices. Presently, some targeted therapies have indirectly altered signaling pathways by targeting histone modifications. For example, HTPB, an HDAC inhibitor, delayed the growth of lung cancer cells and induced cell cycle arrest by inhibiting the integrin-FAK-RhoA signaling pathway to achieve apoptosis of cancer cells.[114] The inhibitor has no side effects in mice.[114] It is worth noting that some studies have shown that targeted G9a can inhibit the transcription activity of NF-κB in NSCLC cells by stabilizing NF-κB inhibitor alpha (IκBα), thereby blocking the activation of FAK.[103] In other words, targeting histone modifications can not only directly affect the signaling pathways, but also stabilize the effect of other inhibitors to coordinate the regulation of signaling pathways. Another novel dual inhibitor of HDAC2 and FAK, 5-pyridyl-1,2,4-triazole, can resist the increase of Akt activity after long-term application of HDAC inhibitors.[208]

Just as the increase of H3K27me3 level can improve the sensitivity of the body to cisplatin,[209] histone modifications can also improve the sensitivity of the human body to many drugs targeting signaling pathways and reduce drug resistance.

Abnormal histone modifications and signaling pathways promote almost every stage of disease development. Communication between signaling pathways and between pathways and histone modifications complicates their role. However, it is also because they are interrelated that they provide more ideas for the treatment and research of diseases.

Conclusions and perspectives

In this review, we highlight how histone modifications, as a molecular regulator of mechanical signaling pathways, affect cell fate and disease progression through interweaving with mechanical signaling pathways (Table 2). In other words, histone modifications can be either the cause or the result of changes in mechanical signaling pathways, and there are feedback loops between them.

Although there are many studies to confirm our conjecture, there are still many unanswered questions. For example, is the regulation of signaling pathways by histone modifications a major controlling factor or only a synergistic effect when cells are mechanically stimulated? How is one signaling pathway balanced when it is regulated by multiple histone modifications? These questions need to be further explored, but mechanistic signaling pathways and histone modifications still have great value and potential in cancer diagnosis, treatment, and prognosis prediction. In cancer diagnosis, some patients in the early stages of cancer may miss the best time for treatment because of the absence of obvious signs and symptoms. In such cases, mechanical signaling pathways and epigenetic alterations in the patient's body can be complementary diagnostic components as well as tumor markers. Although the diagnosis cannot be confirmed on this basis, it can be used as a cue for review and monitoring. There are currently significant limitations in the treatment of cancer patients and safer treatment options are yet to be discovered.[211,212] Mechanistic signaling pathways and epigenetics as potential targets for cancer treatment offer a wider variety of therapeutic options, and many studies have already demonstrated their feasibility. For example, tumor phosphatases may impede tumor growth and motility by regulating MAPK signaling pathway, so both tumor phosphatases and their downstream MAPK signaling pathways can be used as targets for tumor therapy.[213,214] There are also studies demonstrating the feasibility of targeting Hippo pathway in the treatment of glioma.[8] In addition, many studies suggest that stem cells also have a key role in tumor treatment and that mechanistic signaling pathways and epigenetic pairs can precisely regulate stem cells. In addition, alterations in mechanistic signaling and epigenetics can also be used as potential markers to predict prognosis, monitor patient recurrence, and evaluate treatment efficacy.

In conclusion, the feedback loops formed by mechanical signaling pathways and histone modifications are helpful to further clarify the molecular mechanism of mechanotransduction. However, although mechanical signaling pathways and epigenetics hold great promise, finding the ideal combination for disease remains a challenge.

Author contributions

Han Sun, Yafang Gao, Xinyu Ma, and Yizhou Deng participated in the writing. Han Sun and Yizhou Deng designed the figures. Han Sun and YaFang Gao designed and prepared the tables. All authors were in charge of proofreading manuscripts. Lisha Li and Lintao Bi designed and polished the paper.

Conflict of interests

The authors declare that they have no conflict of interests.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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