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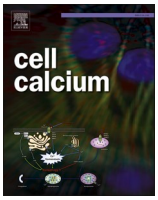

Review

The role of Ca^{2+}-signaling in the regulation of epigenetic mechanisms

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ABSTRACT

Epigenetic mechanisms regulate multiple cell functions like gene expression and chromatin conformation and stability, and its misregulation could lead to several diseases including cancer. Epigenetic drugs are currently under investigation in a broad range of diseases, but the cellular processes involved in regulating epigenetic mechanisms are not fully understood. Calcium (Ca^{2+}) signaling regulates several cellular mechanisms such as proliferation, gene expression, and metabolism, among others. Moreover, Ca^{2+} signaling is also involved in diseases such as neurological disorders, cardiac, and cancer. Evidence indicates that Ca^{2+} signaling and epigenetics are involved in the same cellular functions, which suggests a possible interplay between both mechanisms. Ca^{2+}-activated transcription factors regulate the recruitment of chromatin remodeling complexes into their target genes, and Ca^{2+}-sensing proteins modulate their activity and intracellular localization. Thus, Ca^{2+} signaling is an important regulator of epigenetic mechanisms. Moreover, Ca^{2+} signaling activates epigenetic mechanisms that in turn regulate genes involved in Ca^{2+} signaling, suggesting possible feedback between both mechanisms. The understanding of how epigenetics are regulated could lead to developing better therapeutical approaches.

1. Introduction

1.1. Overview of epigenetic mechanisms

Epigenetics mechanisms are major molecular processes that regulate gene expression without modifying the underlying DNA sequence and are involved in cellular functions such as development, differentiation, DNA repair, and replication, among many others [1]. Three major epigenetic mechanisms have been studied over the last decades. 1: Histone posttranslational modifications (HPMs) are dynamic covalent modifications that occur at the tails of histones that regulate chromatin structure and gene expression in a context-specific manner [1]. There are several described HPMs such as acetylation, methylation, phosphorylation, and ubiquitination, among many others. Each one of them could act directly on the chromatin conformation by altering the DNA – nucleosome interaction or being a recruiting signal for transcriptional activator/repressor complexes [2]. The dynamics of HPMs are mediated by enzymatic activity. For instance, histone acetylation is regulated by histone acetyltransferases (HATs), histone deacetylation by histone deacetylases (HDACs), and acetylation is associated with open chromatin and gene expression [2]. Another example is histone methylation which is orchestrated by histone methyltransferases (HMTs) and histone demethylases (HDMs), and either induces or represses gene expression depending upon the methylated site and number of added methyl groups [3]. 2: DNA methylation is another epigenetic checkpoint of gene expression and genomic stability, that consists in the addition of a methyl group to the 5′ carbon of the cytosine in CpG dinucleotides [4]. The dynamics of DNA methylation are orchestrated by DNA methyltransferases (DNMTs) and Ten-Eleven Translocation (TET) enzymes. DNMTs mediate DNA methylation by using S-adenosylmethionine as a methyl group donor. In counterpart, TET enzymes iterative oxidate methylated CpG to restore unmodified cytosines [5]. Also, CpG could be passively demethylated through successive cycles of DNA replication [5]. DNA methylation is usually associated with transcriptional repression due to the prevention of transcription factor binding and the recruitment of transcriptional repression complexes through methyl-binding transcription factors like MeCP2 [6]. 3: The third major epigenetic regulators are chromatin remodeling ATP-dependent complexes that modify chromatin structure by disruption of nucleosome from DNA, and removal or exchange of nucleosomes [7,8]. Four subfamilies of chromatin remodelers have been described so far: switch/-sucrose non-fermentable (SWI/SNF), imitation switch (ISWI), chromodomain helicase DNA-binding (CHD), and INO80 [9]. On one hand, all chromatin remodeling subfamilies shared an ATP-dependent

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DNA translocation mechanism. On the other hand, most subfamilies showed specialized functions. For instance, the SWI/SNF complex is involved in rendering more accessible chromatin by sliding nucleosomes across DNA, whereas ISWI and CHD complexes regulate the nucleosome assembly and organization. Both mechanisms are tightly associated with transcriptional regulation, since SWI/SNF activity often promotes gene expression, and ISWI and CHD activity promotes gene silencing [9].

Altered epigenetic mechanisms have been linked to several pathologies such as cancer, neurogenerative disorders, and cardiovascular diseases. A major feature during carcinogenesis is altered expression of tumor suppressor genes and oncogenes due to aberrant epigenetic mechanisms. The altered epigenetic function is in part explained by somatic mutations of the enzymes involved in mediating epigenetic modifications, as well as in the components of the transcriptional activator/repressor complexes. There are several described mutations in a broad range of cancers described elsewhere [10,1,11]. Also, altered expression of epigenetic regulators is a common feature in cancer. For instance, overexpression of DNMT1, DNMT3a, and DNMT3b has been reported in acute myeloid leukemia, glioma, breast cancer, gastric cancer, colorectal, hepatocellular carcinoma, prostate, and lung cancers [12]. The expression of SMARCA2 and ARID1A, both components of the SWI/SNF complex, is altered in hepatocellular carcinoma, breast, cervical, and bladder cancers, and correlates with patients' outcomes [13]. In addition to mutations and altered expression, proper regulation of epigenetic mechanisms plays a crucial role in health and disease. In neurodegenerative disorders such as Alzheimeŕs, dysregulation of histone modifying enzymes and HPMs are associated with loss of synapse, activation of neurodegeneration genes, Tau protein phosphorylation, and β-Amyloid aggregation [14]. Genome-wide alterations of DNA methylation patterns have been found in the temporal cortex and hippocampus of patients with Alzheimeŕs [15]. Also, gene-specific altered DNA methylation was found at the promoter of apolipoprotein E [16]. In rat nucleus accumbens, chronic stress dysregulates histone H3 acetylation and decreases nuclear HDAC2 levels [17]. Altered Global DNA or locus-specific methylation correlates with cardiovascular diseases such as coronary heart disease, acute myocardial infarction, heart failure, and hypertension. Similarly, altered regulation of HPMs like acetylation and methylation is associated with several cardiovascular diseases [18].

Given that epigenetic alterations are reversible and involved in a broad range of diseases, it is not surprising that are considered as an attractive therapeutic target. The use of epigenetic drugs for cancer therapy has been widely explored over the last decade, resulting in the approval of inhibitors of epigenetic mechanisms by the Food and Drug Administration (FDA). For example, 5-Azacitidine (Vidaza), and 5-Aza-2′-deoxycytidine (Dacogen), both DNMT inhibitors (DNMTi), are approved for myelodysplastic syndrome. Also, HDAC inhibitors (HDACi) suberoylanilide hydroxamic acid (Zolinza), and romidepsin (Istodax), are approved for the treatment of cutaneous T-cell lymphoma [12]. The application of epigenetic drugs in other diseases is still an emerging area of research. In a murine model of cardiac hypertrophy, treatment with Dacogen reverts hypermethylation, protein expression patterns, and phenotype induced by the chronic norepinephrine infusion [19]. Pretreatment with Entinostat, a class I HDACi, protects against ischemia-reperfusion, improves ventricular and contractile function, and increases the expression of SOD2 and catalase [20]. Mice under chronic social stress showed altered histone H3 acetylation levels in the nucleus accumbens, hippocampus, and amygdala, and loss of social interaction. Infuse of HDACi MS-275 into the amygdala reverses social avoidance, suggesting that HDACi could have a potential antidepressant effect [17,21]. Taken together, evidence indicates that epigenetic mechanisms are involved in a broad range of diseases, and the therapeutic use of epigenetic drugs shows promising results. However, to understand the potential use of epigenetics as a therapeutic approach, the mechanisms involved in the regulation of epigenetics need to be fully understood.

1.2. Regulation of epigenetic mechanisms

Fine regulation of epigenetic mechanisms depends on signaling pathways, the proper function of cellular organelles, and the abundance of intermediate metabolites necessary to generate epigenetic marks. The role of cellular pathways in the regulation of epigenetic mechanisms has been widely studied in stem cell development and cancer [22,23]. In response to extracellular signals, phosphorylation pathways regulate epigenetic mechanisms at different levels. Histone phosphorylation is involved in transcriptional regulation, chromatin condensation, and DNA damage response. Upstream signaling such as Mitogen-Activated Protein Kinases (MAPK), JAK/STAT, and PI3K-AKT pathways, activates a broad range of kinases that directly phosphorylates histones at different sites eliciting a variety of outcomes. During stem cell differentiation, MAPK signaling activates JUN N-terminal kinase (JKN) that phosphorylates histone H3 at S10, activating gene expression [24]. During androgen receptor signaling activated gene expression, protein kinase C β (PKCβ) phosphorylates histone H3 at T6, preventing the demethylation of histone H3 at K4 by histone demethylase LSD1 [25]. DNA methylation is also influenced by phosphorylation pathways. DNMT1 is phosphorylated at multiple sites with paradoxical functions. For example, phosphorylation at Ser154 and Ser143 by cyclin-dependent kinases (CDKs) and AKT1, respectively, is important for its activity and stability [26,27]. In contrast, phosphorylation of DNMT1 at Ser146 by casein-kinase 1 δ/ε (CK1δ/ε) decreases its affinity to DNA [28]. Similarly, phosphorylation of DNMT3a by CK2 decreases its ability to methylate repetitive elements and regulates its localization to heterochromatin [29]. Recently, the field of mechanobiology has demonstrated that mechanical signals have a major role in cell biology and disease. Fluctuation in the mechanical microenvironment is sensed by membrane proteins like integrins and transduced into the nucleus through the cytoskeleton [30,31]. In an atherosclerosis mouse model, cells under disturbed blood flow showed altered chromatin accessibility and gene expression compared to those under normal blood flow [32]. During epidermal lineage commitment, mechanical strain is sensed by a mechanosensory complex formed by emerin, non-muscle myosin IIA, and actin, and induces a switch from H3K9me2 and H3K9me3 to H3K27me3, regulating the expression of lineage genes [33]. Thus, not only chemical signals from extracellular space influence chromatin modifications but also physical fluctuations in the cell microenvironment will have a major role in cell fate. Cell organelles are major components in every cellular mechanism and play a critical role during pathway regulation. For example, mitochondria are the "powerhouse" of the cell, and in addition to its canonical role as an ATP factory, mitochondrial metabolism is crucial to producing intermediate metabolites that mediate a broad range of cellular mechanisms [34]. Particularly in epigenetics, mitochondria provide two key epigenetic cofactors through the activity of the tricarboxylic acid (TCA) cycle. On one hand, citrate exported from the TCA cycle is used to produce acetyl-CoA, which then is used as an acetyl group donor for HAT activity. On the other hand, produces α-ketoglutarate, used as a histone demethylase cofactor, and fumarate and succinate, which inhibit histone and DNA demethylation [35]. Another major organelle involved in epigenetic mechanisms is the endoplasmic reticulum (ER). The ER has three major functions: it serves as the major calcium ion (Ca^{2+}) reservoir and participates in protein synthesis and lipid metabolism. ER malfunction could lead to the accumulation of misfolded proteins, which in turn activate the unfolded protein response (UPR). UPR is an ER stress mechanism that is activated to restore the balance within the cell [36]. Activation of UPR induces alternative splicing of HAC1, which is necessary for the recruitment of SWI/SNF chromatin remodeling complexes at UPR-response gene promoters [37]. In renal cells, demethylation of H3K9 and H3K27 is necessary for thapsigargin (Tg)-induced ER stress transcriptional activation of UPR response transcription factors ATF4 and XBP1 [38]. During ER stress, YY1 interacts with the arginine methyltransferase PRMT1, and with HAT p300, to induce the expression

of the ER chaperon GRP78, through histone H3 acetylation and histone H4 methylation at R3 [39]. Overall, evidence indicates that epigenetics are regulated via different mechanisms that involve extra and intracellular signaling, cofactors abundance, and cell organelles. However, there is also evidence that suggests that these mechanisms involved in the regulation of epigenetics are part of a "master cell regulation signaling" that is involved in almost all (if not all) cellular processes.

2. Calcium signaling: a universal second messenger in health and disease

Ca^{2+} signaling plays an important role in regulating a wide range of cell mechanisms such as gene expression, muscle contraction, cell cycle, proliferation, apoptosis, excitation-contraction, synapsis, and embryonic development, among many others. Involves the interplay of cell organelles like mitochondria and ER, as well as the activity of receptors, channels, pumps, transcription factors, Ca^{2+} sensing proteins, and many other proteins involved in the generation and decodification of Ca^{2+} signals [40]. Ca^{2+} signaling initiates with extra and/or intracellular stimulus, and the subsequent Ca^{2+} entry from extracellular space or its release from intracellular stores such as ER. Ca^{2+} entry from extracellular space is mainly regulated by permeant Ca^{2+} channels such as voltage and ligand-gated Ca^{2+} channels. Also, depletion of ER Ca^{2+} is sensed by Stromal Interaction Molecules (STIM) which in turn interact and activate the store-operated Ca^{2+} channels Orai, in a mechanism known as Store Operated Calcium Entry (SOCE) [41]. On the other hand, Ca^{2+} release from intracellular stores is orchestrated by Ca^{2+} channels located at the membrane of intracellular organelles. For example, IP_3R and ryanodine receptor (RyR), both activated by different mechanisms, mediate Ca^{2+} release from ER into the cytoplasm [42]. The increase in intracellular Ca^{2+} levels activates a broad range of cellular functions, depending on the amplitude and magnitude of the Ca^{2+} signal. For instance, muscle contraction requires a millisecond Ca^{2+} signal, whereas gene transcription and cell proliferation require that the Ca^{2+} signal operates over minutes to hours [43]. An increase in Ca^{2+} concentrations is transduced by Ca^{2+} effector proteins such as calmodulin (CaM) or the S100 proteins, which in turn activate a broad range of proteins. For instance, CaM activation regulates the activity of the Ca^{2+}/Calmodulin-dependent kinases (CaMKs) proteins and the phosphatase Calcineurin [44]. To achieve a tight regulation of the Ca^{2+}-activated mechanisms, the amplitude and kinetics of Ca^{2+} signals are precisely regulated. This process, known as Ca^{2+} homeostasis, involves a continuous and fine-orchestrated Ca^{2+} transport out of the cells or into intracellular reservoirs [45]. Several proteins are involved in this process. For example, the Ca^{2+} pumps, located at the plasma membrane, ER, and Golgi system, transport Ca^{2+} out of the cell or into organelles, at the expense of ATP [46]. Altered Ca^{2+} signaling or malfunction of the proteins involved in its homeostasis is associated with several pathologic conditions that range from cardiac and neurodegenerative diseases to cancer. In the context of cancer, is involved in tumoral mechanisms that encompass sustained activation of mitogenic pathways to malfunction of the immune system by different branches of Ca^{2+} signaling [47]. In breast cancer cells, ANXA4, a Ca^{2+} binding protein, activates JAK-STAT signaling by upregulation of JAK1 and phosphorylation of STAT3 [48]. Also in breast cancer, the Ca^{2+} permeable channel TRPM7 regulates the EGF-induced phosphorylation of STAT3 and the induction of Epithelial-to-Mesenchymal Transition (EMT) [49]. Inhibition of protein convertases represses PD-1 expression by blocking Ca^{2+}-dependent NFAT signaling and enhances cytotoxic T lymphocyte infiltration in colorectal cancer [50]. Over the last decades, evidence indicates that altered Ca^{2+} signaling is a precursor and driver of neurodegenerative diseases. The ER Ca^{2+} channel RyR) has a dual effect in Alzheimer's Disease (AD) since the early stages of AD reduce neuronal excitability and Aβ production, whereas in advanced stages of AD deletion or blocking of RyR3 is beneficial for AD pathology [51]. In spiny neurons, expanded huntingtin protein binds and activates ER Ca^{2+} channel InsP3R1, resulting in enhanced Ca^{2+} response to glutamate and increased apoptosis [52]. Altered Ca^{2+} signaling is a key feature of cardiovascular diseases such as heart failure, cardiac infarction, and cardiac hypertrophy. During rat ischemia-reperfusion, Ca^{2+}-calmodulin-dependent protein kinase II (CaMKII) mediates an apoptotic-necrotic pathway that involves the phosphorylation of ER proteins and mitochondrial Ca^{2+} overload [53]. The sarco(endo)plasmic reticulum Ca^{2+} ATPase 2 isoform a (SERCA2a) protein expression and activity are decreased in failing human myocardium [54]. Given its versatility and involvement in a broad range of diseases, Ca^{2+} signaling has been an attractive target for therapy research. Inhibitors of the voltage-gated Ca^{2+} channels (VGCC), Mibefradil and KYS05047, are under clinical investigation for glioblastoma, and ovarian and lung cancers. Also, Mipsagargin and Curcumin, both inhibitors of SERCA enzymes, are in clinical trials for prostate and pancreatic cancers [47]. In cardiac diseases, SERCA2a has been widely studied as a potential therapeutic target, ranging from recovery of its expression through gene therapy to epigenetic drugs like Hydralazine and Resveratrol (RSV). Also, inhibitors of the mitochondrial Ca^{2+} uniporter (MCU) are studied to reduce mitochondrial Ca^{2+} overload [55]. Thus, Ca^{2+} signaling has direct or indirect involvement in most cellular mechanisms and during several diseases, and proteins involved in its signaling are currently under clinical investigation.

The versatility of Ca^{2+} signaling raises the question of whether it regulates major cellular mechanisms such as epigenetics. Evidence suggests that Ca^{2+} signaling is involved in the regulation of epigenetic mechanisms, however, this point of view has not been fully discussed and reviewed. This could have an impact on future therapeutic approaches since both Ca^{2+} signaling and epigenetics are currently under investigation as clinical targets for a broad range of diseases.

3. Calcium signaling emerges as a key regulator of epigenetic mechanisms

The first indirect evidence of the involvement of Ca^{2+} signaling in regulating epigenetics derives from experiments focused on understanding the role of Ca^{2+} in cell cycle and gene expression. The cell cycle, particularly the mitosis and division phases, are tightly regulated by epigenetic modifications [56]. Early experiments from the 1980s in HeLa cells indicate that phosphorylation of histone H3 is Ca^{2+}-dependent. Moreover, pretreatment with HDACi sodium butyrate potentiates Ca^{2+}-induced phosphorylation, suggesting a crosstalk between both HPMs [57]. Also in Hela cells, Ca^{2+} regulates the transition from chromosome compaction to relaxation during mitotic progression [58]. The major Ca^{2+}-dependent mechanism involved in cell cycle progression is the CaM pathway [59]. CaM also regulates chromatin remodeling by promoting nuclear actin assembly through the ER-associated forming INF2 [60]. As mentioned before, epigenetic mechanisms are involved in transcriptional regulation and gene expression is regulated by Ca^{2+} signaling (see Table 1). For instance, in hippocampal neurons, nuclear Ca^{2+} regulates the expression of 185 genes, among them, a set of genes that provides neuroprotection [61]. Fluctuations in Ca^{2+} concentrations regulate the expression of prolactin and correlate with an increase in histone acetylation at its promoter [62]. Ca^{2+} release from intracellular stores regulates the mRNA and protein expression of HAT p300, suggesting that Ca^{2+} also regulates the expression of chromatin modifiers enzymes [63]. Moreover, Ca^{2+} signaling drives the loss of heterochromatin marks H3K9me3 to prevent DNA damage induced by mechanical stretch [64].

Given that Ca^{2+} signaling and epigenetics regulate the same mechanisms, we could hypothesize that Ca^{2+} also regulates epigenetic mechanisms and *vice versa*. In the further section, we summarize the evidence regarding the role of Ca^{2+} signaling in the regulation of epigenetic mechanisms. Given the versatility and dynamics of Ca^{2+} signaling, its regulatory role could be at different steps of epigenetic control of gene expression. We focus on two major steps of epigenetic

Table 1
List of epigenetic terms and their corresponding definition.

Term	Definition
CHD	Chromodomain helicase DNA-binding
CpG	Cytosine – Guanine dinucleotide
DNMT	DNA methyltransferase
DNMTi	DNA methyltransferase inhibitor
H3K4me1	Monomethylation of histone H3 at lysin 4
H3K4me2	Dimethylation of histone H3 at lysin 4
H3K9me2	Dimethylation of histone H3 at lysin 9
H3K9me3	Trimethylation of histone H3 at lysin 9
H3K27ac	Acetylation of histone H3 at lysin 27
H3K27me3	Trimethylation of histone H3 at lysin 27
H3R17	Arginine 17 of histone H3
H3R26	Arginine 26 of histone H3
H4R3	Arginine 3 of histone H4
HAT	Histone acetyltransferase
HDAC	Histone deacetylase
HDACi	Histone deacetylase inhibitor
HDM	Histone demethylase
HPM	Histone posttranslational modification
ISWI	Imitation switch
PAD	Protein arginine deaminase
SWI/SNF	Switch/sucrose non-fermentable
TET	Ten-eleven translocation
ubH2A	Ubiquitination of histone H2A

regulation: [1] how Ca^{2+}-activated transcription factors regulate the recruitment of chromatin modifying complex into DNA, and [2] how the Ca^{2+}-sensitive proteins regulate the activity of the proteins involved in epigenetic processes.

3.1. *Ca^{2+}-induced transcription factors recruit epigenetic protein complexes to induce chromatin remodeling*

Ca^{2+} signaling regulates gene expression through multiple Ca^{2+}-induced transcription factors. The increase of intracellular Ca^{2+} concentrations activates Ca^{2+}-sensitive proteins such as CaM or the S100 superfamily, which in turn regulates hundreds of proteins [44,65]. On the one hand, CaMKs regulate the activation of multiple transcription factors like CREB, ATF1, NFκB, MeCP2, MEF2, and SRF. On the other hand, Calcineurin regulates the activity of transcription factors such as NFAT and MEF2 [44,66–69] (Fig. 1). In Jurkat T cells, activation of Ca^{2+}-signaling with ionomycin activates the expression of hundreds of genes and induces chromatin remodeling at regulatory regions containing NFAT binding sites [70]. In activated neutrophils, Ca^{2+} signaling instructs the recruitment of NIPBL, which regulates the loading of the Cohesin complex into active enhancers and promoters. NIPBL binding is coordinated by Ca^{2+}-sensitive transcription factors such as NFAT that recruit HATs such as p300 to maintain H3K27ac [71]. In neurons, membrane depolarization, which induces Ca^{2+} influx through L-type VGCCs, activates enhancer RNA synthesis by increasing H3K4me1 levels and CBP recruitment [72] Also, mediates the phosphorylation of MeCP2 by CaMKII, resulting in its release from BDNF promoter, a decrease in the methylation of lysine 9 at histone H3, an increase of acetylation at the same residue, and a decrease in CpG methylation frequency [73,74]. Acute exercise induces the phosphorylation of the Ca^{2+} channel RYR2, dephosphorylation and nuclear translocation of NFAT1c, and increased histone acetylation at H3K9, H3K14, and H3K27 [75]. In colon cancer cell lines, CaMK mediates the expression of tumor suppressor genes by inducing nuclear extrusion of MeCP2 [76]. During synapsis of hippocampal neurons, CaMKII regulates the function of MeCP2 through its phosphorylation on serine 421 [77]. During terminal muscle differentiation, MEF2D cooperates with myogenin to recruit SWI/SNF to the promoter of desmin and MCK [78]. In T cells, Calcineurin and NFAT2 induce TOX activation and initiation of the exhaustion program. TOX modulates genome-wide chromatin accessibility through the interaction with several chromatin remodeling proteins such as KAT7 and DNMT1 [79].

Similarly to CaM, the members of the S100 superfamily are Ca^{2+}-sensitive proteins that translate Ca^{2+} oscillations into cellular mechanisms such as proliferation, migration, differentiation, and gene expression, among others [80]. S100A10 and ANXA2 heterotetrameric form a complex with the chromatin remodeling factor SMARCA3 (member of the SWI/SNF complex), increasing its DNA binding affinity [81] (Fig. 1). In breast cancer stem cells, S100A4 and ANXA2 form a complex with the histone chaperone SPT6 and the histone demethylase KDM6A, which in turn removes the H3K27me3 histone mark [82].

The Protein Kinase C (PKC) family is composed of serine-threonine kinases divided into classical, novel, and atypical isoforms, that regulate a broad range of cellular mechanisms such as gene expression, proliferation, differentiation, and immune response, among others. The classical PKC isoforms (PKCα, PKCβI, PKCβII, and PKCγ) are regulated by Ca^{2+} [83]. PKCβII regulates NF-κB-mediated CCL11 transcription through activation of the HAT p/CAF by phosphorylation and the induction of histone H4 acetylation [84]. In T cells, a Ca^{2+}-dependent activation of PKC is necessary for chromatin decondensation via NF-κB

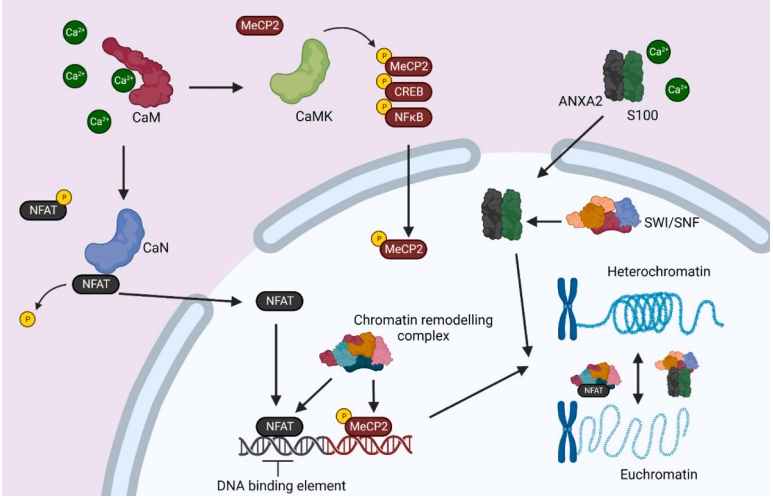

Fig. 1. Ca^{2+}-activated transcription factors recruit the chromatin-remodeling complex to induce epigenetic modifications. Ca^{2+} signaling through Ca^{2+}-sensitive proteins such as Calmodulin (CaM) activates downstream signaling mechanisms that induce the nuclear translocation through phosphorylation of transcription factors such as MeCP2, CREB, and NFκB, or dephosphorylation of NFAT. Subsequently, these activated transcription factors recruit chromatin remodeling complex into their target DNA binding elements, modulating the transition between heterochromatin and euchromatin.

and p38 [85].

3.2. Ca^{2+} signaling regulates the activity of epigenetic mechanisms

3.2.1. Chromatin remodeling complexes

During skeletal muscle differentiation, Ca^{2+} signaling shows opposing mechanisms that control SWI/SNF chromatin remodeling activity, since calcineurin activates it through the dephosphorylation of the ATPase BRG1, whereas PKCβ inhibits its activity [86]. The calcium-responsive transactivator (CREST), first described as a nuclear protein, plays an important role in the Ca^{2+}-dependent regulation of gene expression through its interaction with BRG1 and with the histone acetyltransferase and transcriptional coactivator CBP [87]. In resting conditions, CREST interacts with BRG1, which in turn forms a complex with the retinoblastoma protein (Rb) and HDAC1 to suppress the expression of c-fos. After Ca^{2+} stimulation, the HDAC1 complex is released from the promoter through the dephosphorylation of Rb by Calcineurin, and c-fos expression is upregulated through the recruitment of CBP by CREST [87,88]. Also, this Ca^{2+}-dependent mechanism regulates the reorganization of large chromatin domains, involving the redistribution of histone posttranslational modifications [89]. Moreover, during TLR4 activation it was observed that CaM directly regulates the chromatin remodeling mediated by the SWI/SNF complex by interacting with the BAF57 subunit [90] (Fig. 2).

3.2.2. DNA methylation and demethylation

The Ca^{2+}-dependent proteases, Calpain 1 and Calpain 2, regulate the protein levels of TET enzymes, which regulate the DNA demethylation process [91] (Fig. 2). Low intracellular Ca^{2+} concentrations reduce Calpain activity, increasing Tet1 and Tet2 protein expression as well as the abundance of 5hmC [92].

3.2.3. Histone posttranslational modifications

In pancreatic cancer cells, STIM1-dependent store-operated calcium entry (SOCE) regulates the expression of stress-response genes by modulating H3K27ac at their promoter [93]. In lung cancer cells, CaMKIIa regulates SOX2 expression by modulating the levels of H3K27me3 and the presence of the histone methyltransferase EZH2 at its promoter [94]. In mouse cardiomyocytes, membrane depolarization increases intracellular Ca^{2+} concentrations through L-type VGCCs and regulates the alternative splicing of the Nf1 gene through CaMKIIδ and PKD1 signaling pathways by decreasing the presence of class II HDACs at the nucleus, which in turn increase the binding of the HATs CBP/p300 and histone H3 acetylation at gene body [95]. Similarly, treatment with caffeine, an RYR2 ligand, leads to increased histone acetylation and activation of alternative splicing [96]. However, modulation of HAT/HDAC balance by Ca^{2+} signaling could have a dual effect. For example, CaMKII activates the acetyltransferase HAT1, which acetylates PLZF, which in turn interacts with HDAC3 resulting in the repress of NF-κB activity [97]. Also, Ca^{2+} release from ER regulates the transport of HDAC5 into the nucleus and the nuclear localization of HDAC4 [98]. Sustained Ca^{2+} entry through the PKD2/TRPP2 channel activates CaMKII, which in turn promotes the retention of HDAC4 in the cytosol [99]. In cardiomyocytes, activation of CaMKIV prevents the interaction of HDAC4 with the transcription factor SRF, exports HDAC4 from the nucleus, and activates the SRF-dependent gene expression [100]. During neuronal necrosis, Ca^{2+} influx activates the ERK1/2 pathway which induces the displacement of PRC1 and the loss of the histone mark ubH2A, the recruitment of Trithorax (Trx), and the gain of H3K4me3 [101].

Another major histone modification is citrullination, which is the conversion of an arginine residue into citrulline, altering the histone charge and chromatin accessibility. This mechanism is mediated by the Ca^{2+}-dependent protein arginine deiminases (PADs), particularly PAD1, PAD2, and PAD4 [102] (Fig. 2). In breast cancer cells, stimulation with 17β-estradiol induces the interaction of PAD2 with ERα, the citrullination of H3R26 at estrogen-response elements, and transcriptional activation [103]. Also, high expression levels of PAD2 correlate with increased survival of ER^{+} breast cancer patients [104]. PAD4 regulates pluripotency by citrullination of the linker histone H1, generating decondensation of the chromatin at the promoters and enhancers of genes involved in the pluripotency transcriptional network [105]. Citrullination of H4R3 by PAD4 is important in the p53-mediated apoptotic pathway in response to DNA damage. Also, citrullinated H4R3 is associated with smaller tumor size in non-squamous cell lung cancer patients [106]. In breast and liver cancer cells, PAD4 expression is induced by HIF and then recruited to HIF-response elements to induce histone citrullination and, in a HIF-PAD4-dependent manner, the expression of HIF target genes [107]. PAD4 is essential during neutrophils' response against pathogens since histone hypercitrullination is required for

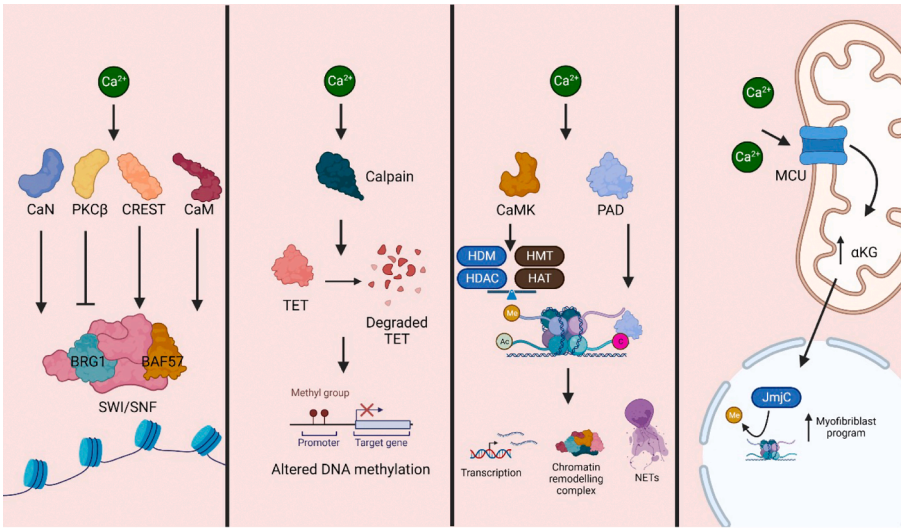

Fig. 2. Ca^{2+} signaling regulates the activity of chromatin remodeling complex and chromatin-modifying proteins. Ca^{2+}-activated proteins regulate the activity of epigenetic modifying proteins and various steps. BRG1 and BAF57 subunits of the SWI/SNF complex are a target of multiple Ca^{2+} signaling proteins that could either induce or decrease SWI/SNF activity. DNA methylation is regulated by Ca^{2+} signaling through the degradation of TET enzymes by Calpains. Histone posttranslational modifications such as acetylation, methylation, and citrullination, are regulated by Ca^{2+} through Calmodulin-dependent kinases and PAD enzymes. Mitochondrial Ca^{2+} uniporter (MCU) modulates the activity of histone demethylases through the regulation of mitochondrial metabolism.

chromatin decondensation and neutrophil extracellular traps (NETs) formation [108]. Histone citrullination is also associated with the repression of gene expression. PAD4 deiminates the unmodified and monomethylated arginine of histone H3 at the promoter of pS2, antagonizing the transcriptional activation of arginine methylation [109]. PAD4 interacts with p53 to repress the expression of p21 by decreasing histone H3R17 methylation and increasing citrullination at its promoter [110]. There is a crosstalk between PAD4, HDAC2, and p53 to regulate p21 expression, and the use of PAD4 and HDACi (Cl-amidine and SAHA, respectively) induces the expression of p21 in a p53-dependent manner [111].

Recent evidence showed that histone citrullination mediated by PAD proteins not only antagonizes arginine methylation but also disrupts histone methylglyoxal-induced glycation by the citrullination of unmodified arginines or through the modification of glycated arginines into citrulline [112]. However, more evidence is needed to understand the role of PAD proteins in the histone glycation-citrullination crosstalk. Also, PAD4 regulates chromatin status by the citrullination of non-histone proteins such as the heterochromatin protein 1 gamma, which plays a major role in the regulation of chromatin conformation and is an important reader of histone repressive marks H3K9me2/3 [113]. Thus, the role of the Ca^{2+}-dependent PAD proteins in the regulation of chromatin accessibility and gene expression is an emerging area of research.

3.2.4. *Metabolism*

During fibroblast to myofibroblast differentiation, the mitochondrial calcium uniporter (MCU) alters the mitochondrial Ca^{2+} signaling, which generates a metabolic reprogramming, activation of histone demethylases, and increased chromatin accessibility [114] (Fig. 2).

4. Feedback between Ca^{2+}-signaling and epigenetic mechanisms

In the last sections, we mentioned how Ca^{2+} signaling regulates the epigenetic mechanisms by modulating the function of the transcription factors that anchor the chromatin remodeling complexes into the DNA and how Ca^{2+}-sensitive proteins regulate the activity of the proteins involved in epigenetic mechanisms. Added to this, recent evidence showed that epigenetic mechanisms in turn, such as DNA methylation and HPMs regulate the expression of some genes involved in Ca^{2+} signaling [115]. Thus, we now present evidence of a possible interplay that showed that Ca^{2+}-activated epigenetic mechanisms regulate the expression of the genes involved in Ca^{2+} signaling (Fig. 3).

In the brain, Ca^{2+} entry through L-type VGCCs activates PKCγ, which in turn regulates the acetylation of histone H3 at the promoters of CaMKIIa and neurexin [116]. CaMKIIa is essential during CaM signaling and increasing its expression could in turn amplify the Ca^{2+} signaling response. Moreover, neurexin is a key modulator of Ca^{2+}-triggered neurotransmitter release by regulating the assembly of Ca^{2+} channels and the subsequent Ca^{2+} entry [117].

In cardiomyocytes, hypertrophic agonists increase the chromatin binding of CaMKII and the phosphorylation of the histone H3 at Ser10, at gene loci actively transcribed in cardiac hypertrophy [118]. Also, the CaMKII-H3 mechanism activates MEF2-dependent transcription, which is involved in hypertrophic signaling pathways [118]. MEF2 is also involved in the transcriptional regulation of genes that participate in the maintenance of Ca^{2+} concentrations such as SERCA2 and RyR2 [119]. In cardiomyocytes, activation of Ca^{2+} signaling by either membrane depolarization (activates membrane Ca^{2+}-channels) or caffeine (activate RYR), induces the alternative splicing of MEF2a, which in turn could have an impact at Ca^{2+} concentrations and signaling [95,96].

During hypoxia, STIM1 regulates the expression of HIF-1 through the

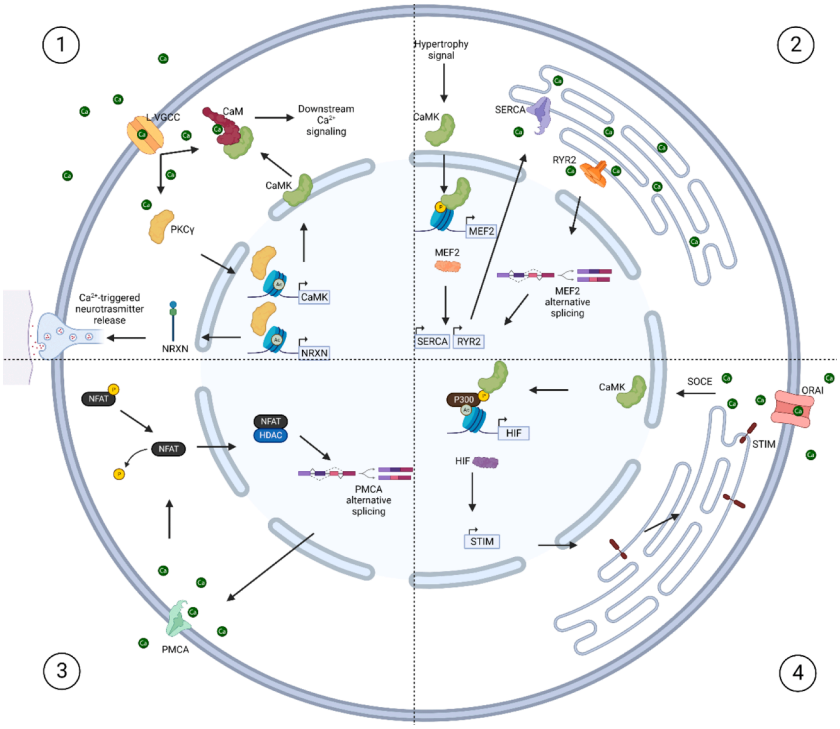

Fig. 3. Ca^{2+}-regulated epigenetic mechanisms regulate Ca^{2+} signaling. 1. Ca^{2+} entry through Ca^{2+} channels activates PKCγ, which in turn regulates histone acetylation at the promoters of CaMK and Neurexin. CaMK in turn is a key component of the Ca^{2+} signaling by being a downstream target of Calmodulin. 2. Hypertrophy signal activates CaMK which in turn mediates histone phosphorylation at the MEF2 gene promoter. MEF2 is a key transcription factor that regulates the activity of major Ca^{2+} signaling regulators such as RYR2 and the SERCA pump. 3. NFAT interacts with HDAC to regulate the alternative splicing of the Ca^{2+} pump PMCA. PMCA isoforms displayed different Ca^{2+} turnover and affinity, thus the switch between isoforms could have an impact on Ca^{2+} concentration and signaling. 4. Store-operated Ca^{2+} entry mediated by STIM1 regulates the expression of HIF-1 through the activation of CaMK, followed by phosphorylation of HAT p300. HIF-1 in turn regulates the expression of STIM1.

induction of SOCE-activation of CaMKII, and the subsequent phosphorylation of HAT p300. Moreover, HIF-1 in turn regulates the expression of STIM1, suggesting a positive feedback mechanism [120]. HIF complexes regulate the expression of their target genes by the recruitment of SET1B, which mediates the deposition of the histone mark H3K4me3 [121]. Ca^{2+} release from the ER through IP_3R stimulates the expression of SET2, which in turn regulates the expression of IP_3R by the placement of the histone mark H3K36me3 at the gene body [122].

In PC12 cells, NFAT1 and NFAT4 interact with HDAC4 to regulate alternative splicing of the plasma membrane Ca^{2+}-ATPase 2 (PMCA2), leading to specific regulation of PMCA2 isoforms [123]. PMCA2 isoforms displayed differences in Ca^{2+} affinity and turnover rate [124], and a switch between PMCA2 isoforms could lead to altered Ca^{2+} signaling and Ca^{2+}-activated transcription factor activity like NFAT2.

5. Perspectives and conclusions

Understanding the interplay between Ca^{2+} signaling and epigenetics could lead to therapeutic strategies for different diseases. In the context of cancer, the role of DNMTi and HDACi in the regulation of Ca^{2+}-signaling genes has been recently reviewed [115]. However, dietary compounds targeting epigenome and the Ca^{2+}-signaling toolkit are emerging as attractive therapeutic approaches for many diseases including cardiac diseases and cancer [125,126]. It has been reported that RSV has antioxidant, anti-inflammatory, cardioprotective, and anti-tumoral properties, and it is also an epigenetic modulator. RSV is currently used in type-2 diabetes and hypertensive patients, and in pre-clinical models and clinical trials of multiple types of cancer [125, 127]. Moreover, RSV modulates intracellular Ca^{2+} concentrations, regulates the expression of the Ca^{2+} pump SERCA3, and induces apoptosis in a SERCA3-dependent manner in breast cancer cells [128]. SERCA3 is a key regulator of Ca^{2+} homeostasis and its expression is decreased or lost in several types of cancer [129–131]. Similarly to RSV, curcumin possesses anti-cancer, cardioprotective, and neuroprotective properties, and is a regulator of epigenetic mechanisms [132,133]. In thyroid carcinoma cells, curcumin activates ER stress and UPR induces Ca^{2+} influx by inhibiting the SERCA2 pump and activates CaM-CaMKII signaling, and mitochondrial apoptosis [134]. Dietary styles also regulate epigenetics and Ca^{2+} signaling. High-fat diet (HFD) is associated with many diseases including cancer, and several studies indicate that the link between HFD and cancer is altered gene expression, being epigenetic mechanisms involved in many cases [126]. Moreover, HFD could also act directly on Ca^{2+}-signaling genes. For instance, HFD decreases the expression of the Ca^{2+} channel TRPV1 in the hypothalamus [135]. Thus, regulating the epigenome and Ca^{2+}-signaling with epigenetic inhibitors and/or dietary components is a promising area of research. However, targeting Ca^{2+}-signaling in disease will face many challenges such as the specificity of the therapy. For instance, in addition to its role in activating the CaM pathway, curcumin could also impair Ca^{2+} signaling by inhibiting NFAT activation [136]. Another example is CaMKII, since its basal activity is essential in cardiac excitation-contraction, while sustained activation is associated with heart failure [137,138]. In cancer, Ca^{2+} signaling is involved in pro-tumoral and anti-tumoral pathways such as cell cycling progression, cell growth, apoptosis, and resistance to therapies, and activation or inhibition of specific Ca^{2+}-signaling pathways or proteins could have undesirable effects.

In conclusion, epigenetic mechanisms are cellular processes that regulate cell fate in health and disease. The proper function of epigenetic mechanisms relies on multiple factors including metabolites abundance, fine activity of chromatin modifying enzymes, and crosstalk with other signaling pathways such as Ca^{2+} signaling. Ca^{2+}-activated transcription factors regulate the recruitment of chromatin-modifying complexes in multiple cell types, and Ca^{2+} signaling modulates the activity of the enzymes responsible for epigenetic mechanisms. Thus, Ca^{2+} signaling is a key regulator of epigenetics. Moreover, there is evidence supporting the existence of continuous feedback between Ca^{2+} signaling and epigenetics, since Ca^{2+}-activated proteins regulate the activity of chromatin-modifying complexes, which in turn regulate the expression of genes involved in Ca^{2+} signaling. Finally, targeting epigenetic mechanisms and Ca^{2+}-signaling in disease is an emerging area of research. However, more studies are needed to fully understand their role in disease and to develop a therapeutic approach without undesired effects.

CRediT authorship contribution statement

Andrés Hernández-Oliveras: Conceptualization, Writing – review & editing. **Angel Zarain-Herzberg:** Writing – review & editing.

Declaration of Competing Interest

Hereby we declare that both authors have reviewed and approved the submitted manuscript and have no conflict of interest to disclose. The material presented in this paper has not been published and is not under consideration to be published elsewhere.

Data availability

Data will be made available on request.

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References

[1] M.A. Dawson, T. Kouzarides, Cancer epigenetics: from mechanism to therapy, Cell 150 (2012) 12–27, https://doi.org/10.1016/j.cell.2012.06.013.
[2] A.J. Bannister, T. Kouzarides, Regulation of chromatin by histone modifications, Cell Res. 21 (2011) 381–395, https://doi.org/10.1038/cr.2011.22.
[3] K. Hyun, J. Jeon, K. Park, J. Kim, Writing, erasing and reading histone lysine methylations, Exp. Mol. Med. 49 (2017) e324, https://doi.org/10.1038/emm.2017.11.
[4] M.V.C. Greenberg, D. Bourc'his, The diverse roles of DNA methylation in mammalian development and disease, Nat. Rev. Mol. Cell Biol. 20 (2019) 590–607, https://doi.org/10.1038/s41580-019-0159-6.
[5] H. Wu, Y. Zhang, Reversing DNA methylation: mechanisms, genomics, and biological functions, Cell 156 (2014) 45–68, https://doi.org/10.1016/j.cell.2013.12.019.
[6] A. Parry, S. Rulands, W. Reik, Active turnover of DNA methylation during cell fate decisions, Nat. Rev. Genet. 22 (2021) 59–66, https://doi.org/10.1038/s41576-020-00287-8.
[7] G.J. Narlikar, R. Sundaramoorthy, T. Owen-Hughes, Mechanisms and functions of ATP-dependent chromatin-remodeling enzymes, Cell 154 (2013) 490–503, https://doi.org/10.1016/j.cell.2013.07.011.
[8] D.C. Hargreaves, G.R. Crabtree, ATP-dependent chromatin remodeling: genetics, genomics and mechanisms, Cell Res. 21 (2011) 396–420, https://doi.org/10.1038/cr.2011.32.
[9] C.R. Clapier, J. Iwasa, B.R. Cairns, C.L. Peterson, Mechanisms of action and regulation of ATP-dependent chromatin-remodelling complexes, Nat. Rev. Mol. Cell Biol. 18 (2017) 407–422, https://doi.org/10.1038/nrm.2017.26.
[10] S.B. Baylin, P.A. Jones, Epigenetic Determinants of Cancer, Cold Spring Harb. Perspect. Biol. 8 (2016), a019505, https://doi.org/10.1101/cshperspect.a019505.
[11] M. Wanior, A. Krämer, S. Knapp, A.C. Joerger, Exploiting vulnerabilities of SWI/SNF chromatin remodelling complexes for cancer therapy, Oncogene 40 (2021) 3637–3654, https://doi.org/10.1038/s41388-021-01781-x.
[12] Y. Cheng, C. He, M. Wang, X. Ma, F. Mo, S. Yang, J. Han, X. Wei, Targeting epigenetic regulators for cancer therapy: mechanisms and advances in clinical trials, Signal Transduct. Target Ther. 4 (2019) 62, https://doi.org/10.1038/s41392-019-0095-0.
[13] P. Mittal, C.W.M. Roberts, The SWI/SNF complex in cancer—biology, biomarkers and therapy, Nat. Rev. Clin. Oncol. 17 (2020) 435–448, https://doi.org/10.1038/s41571-020-0357-3.
[14] J. Park, K. Lee, K. Kim, S.J. Yi, The role of histone modifications: from neurodevelopment to neurodiseases, Signal Transduct. Target Ther. 7 (2022) 217, https://doi.org/10.1038/s41392-022-01078-9.

[15] A.S. Yokoyama, J.C. Rutledge, V. Medici, DNA methylation alterations in Alzheimer's disease, Environ. Epigenet.. 3 (2017). https://doi.org/10.1093/eep/dvx008.

[16] S.C. Wang, B. Oelze, A. Schumacher, Age-specific epigenetic drift in late-onset Alzheimer's disease, PLoS One 3 (2008) e2698, https://doi.org/10.1371/journal.pone.0002698.

[17] H.E. Covington, I. Maze, Q.C. LaPlant, V.F. Vialou, Y.N. Ohnishi, O. Berton, D. M. Fass, W. Renthal, A.J. Rush, E.Y. Wu, S. Ghose, V. Krishnan, S.J. Russo, C. Tamminga, S.J. Haggarty, E.J. Nestler, Antidepressant actions of histone deacetylase inhibitors, J. Neurosci. 29 (2009) 11451–11460, https://doi.org/10.1523/JNEUROSCI.1758-09.2009.

[18] Y. Shi, H. Zhang, S. Huang, L. Yin, F. Wang, P. Luo, H. Huang, Epigenetic regulation in cardiovascular disease: mechanisms and advances in clinical trials, Signal Transduct. Target Ther. 7 (2022) 200, https://doi.org/10.1038/s41392-022-01055-2.

[19] D. Xiao, C. Dasgupta, M. Chen, K. Zhang, J. Buchholz, Z. Xu, L. Zhang, Inhibition of DNA methylation reverses norepinephrine-induced cardiac hypertrophy in rats, Cardiovasc. Res. 101 (2014) 373–382, https://doi.org/10.1093/cvr/cvt264.

[20] S.E. Aune, D.J. Herr, S.K. Mani, D.R. Menick, Selective inhibition of class I but not class IIb histone deacetylases exerts cardiac protection from ischemia reperfusion, J. Mol. Cell Cardiol. 72 (2014) 138–145, https://doi.org/10.1016/j.yjmcc.2014.03.005.

[21] H.E. Covington, V.F. Vialou, Q. LaPlant, Y.N. Ohnishi, E.J. Nestler, Hippocampal-dependent antidepressant-like activity of histone deacetylase inhibition, Neurosci. Lett. 493 (2011) 122–126, https://doi.org/10.1016/j.neulet.2011.02.022.

[22] L. Fagnocchi, S. Mazzoleni, A. Zippo, Integration of signaling pathways with the epigenetic machinery in the maintenance of stem cells, Stem Cells Int 2016 (2016) 1–13, https://doi.org/10.1155/2016/8652748.

[23] F. Liu, L. Wang, F. Perna, S.D. Nimer, Beyond transcription factors: how oncogenic signalling reshapes the epigenetic landscape, Nat. Rev. Cancer 16 (2016) 359–372, https://doi.org/10.1038/nrc.2016.41.

[24] V.K. Tiwari, M.B. Stadler, C. Wirbelauer, R. Paro, D. Schübeler, C. Beisel, A chromatin-modifying function of JNK during stem cell differentiation, Nat. Genet. 44 (2012) 94–100, https://doi.org/10.1038/ng.1036.

[25] E. Metzger, A. Imhof, D. Patel, P. Kahl, K. Hoffmeyer, N. Friedrichs, J.M. Müller, H. Greschik, J. Kirfel, S. Ji, N. Kunowska, C. Beisenherz-Huss, T. Günther, R. Buettner, R. Schüle, Phosphorylation of histone H3T6 by PKCβI controls demethylation at histone H3K4, Nature 464 (2010) 792–796, https://doi.org/10.1038/nature08839.

[26] G. Lavoie, Y. St-Pierre, Phosphorylation of human DNMT1: implication of cyclin-dependent kinases, Biochem. Biophys. Res. Commun. 409 (2011) 187–192, https://doi.org/10.1016/j.bbrc.2011.04.115.

[27] P.O. Estève, Y. Chang, M. Samaranayake, A.K. Upadhyay, J.R. Horton, G. R. Feehery, X. Cheng, S. Pradhan, A methylation and phosphorylation switch between an adjacent lysine and serine determines human DNMT1 stability, Nat. Struct. Mol. Biol. 18 (2011) 42–48, https://doi.org/10.1038/nsmb.1939.

[28] Y. Sugiyama, N. Hatano, N. Sueyoshi, I. Suetake, S. Tajima, E. Kinoshita, E. Kinoshita-Kikuta, T. Koike, I. Kameshita, The DNA-binding activity of mouse DNA methyltransferase 1 is regulated by phosphorylation with casein kinase 1δ/ε, Biochem. J. 427 (2010) 489–497, https://doi.org/10.1042/BJ20091856.

[29] R. Deplus, L. Blanchon, A. Rajavelu, A. Boukaba, M. Defrance, J. Luciani, F. Rothé, S. Dedeurwaerder, H. Denis, A.B. Brinkman, F. Simmer, F. Müller, B. Bertin, M. Berdasco, P. Putmans, E. Calonne, D.W. Litchfield, Y. de Launoit, T. P. Jurkowski, H.G. Stunnenberg, C. Bock, C. Sotiriou, M.F. Fraga, M. Esteller, A. Jeltsch, F. Fuks, Regulation of DNA methylation patterns by CK2-mediated phosphorylation of Dnmt3a, Cell Rep. 8 (2014) 743–753, https://doi.org/10.1016/j.celrep.2014.06.048.

[30] P. Swiatlowska, T. Iskratsch, Cardiovascular mechano-epigenetics: force-dependent regulation of histone modifications and gene regulation, Cardiovasc Drugs Ther. (2023), https://doi.org/10.1007/s10557-022-07422-z.

[31] T. Iskratsch, H. Wolfenson, M.P. Sheetz, Appreciating force and shape—the rise of mechanotransduction in cell biology, Nat. Rev. Mol. Cell Biol. 15 (2014) 825–833, https://doi.org/10.1038/nrm3903.

[32] A. Andueza, S. Kumar, J. Kim, D.W. Kang, H.L. Mumme, J.I. Perez, N. Villa-Roel, H. Jo, Endothelial reprogramming by disturbed flow revealed by single-cell rna and chromatin accessibility study, Cell Rep. 33 (2020), 108491, https://doi.org/10.1016/j.celrep.2020.108491.

[33] H.Q. Le, S. Ghatak, C.Y.C. Yeung, F. Tellkamp, C. Günschmann, C. Dieterich, A. Yeroslaviz, B. Habermann, A. Pombo, C.M. Niessen, S.A. Wickström, Mechanical regulation of transcription controls Polycomb-mediated gene silencing during lineage commitment, Nat. Cell Biol. 18 (2016) 864–875, https://doi.org/10.1038/ncb3387.

[34] R.P. Chakrabarty, N.S. Chandel, Mitochondria as signaling organelles control mammalian stem cell fate, Cell Stem Cell 28 (2021) 394–408, https://doi.org/10.1016/j.stem.2021.02.011.

[35] I. Martínez-Reyes, N.S. Chandel, Mitochondrial TCA cycle metabolites control physiology and disease, Nat. Commun. 11 (2020) 102, https://doi.org/10.1038/s41467-019-13668-3.

[36] D.S. Schwarz, M.D. Blower, The endoplasmic reticulum: structure, function and response to cellular signaling, Cell. Mol. Life Sci. 73 (2016) 79–94, https://doi.org/10.1007/s00018-015-2052-6.

[37] R.K. Sahu, S. Singh, R.S. Tomar, The ATP-dependent SWI/SNF and RSC chromatin remodelers cooperatively induce unfolded protein response genes during endoplasmic reticulum stress, Biochim.Biophys. Acta (BBA) - Gene Regul. Mech. 1864 (2021), 194748, https://doi.org/10.1016/j.bbagrm.2021.194748.

[38] P. Diaz-Bulnes, M.L. Saiz, V. Corte-Iglesias, R.R. Rodrigues-Diez, A.B. Florez, C. R. Bernet, C.M. Martin, M. Ruiz-Ortega, B. Suarez-Alvarez, C. López-Larrea, Demethylation of H3K9 and H3K27 contributes to the tubular renal damage triggered by endoplasmic reticulum stress, Antioxidants 11 (2022) 1355, https://doi.org/10.3390/antiox11071355.

[39] P. Baumeister, S. Luo, W.C. Skarnes, G. Sui, E. Seto, Y. Shi, A.S. Lee, Endoplasmic reticulum stress induction of the Grp78/BiP promoter: activating mechanisms mediated by YY1 and its interactive chromatin modifiers, Mol. Cell. Biol. 25 (2005) 4529–4540, https://doi.org/10.1128/MCB.25.11.4529-4540.2005.

[40] Md.S. Islam, Calcium signaling: from basic to bedside, in: 2020: pp. 1–6. https://doi.org/10.1007/978-3-030-12457-1_1.

[41] D.E. Clapham, Calcium signaling, Cell 131 (2007) 1047–1058, https://doi.org/10.1016/j.cell.2007.11.028.

[42] G.R. Monteith, D. McAndrew, H.M. Faddy, S.J. Roberts-Thomson, Calcium and cancer: targeting Ca2+ transport, Nat. Rev. Cancer 7 (2007) 519–530, https://doi.org/10.1038/nrc2171.

[43] M.J. Berridge, M.D. Bootman, H.L. Roderick, Calcium signalling: dynamics, homeostasis and remodelling, Nat. Rev. Mol. Cell Biol. 4 (2003) 517–529, https://doi.org/10.1038/nrm1155.

[44] M. Dewenter, A. von der Lieth, H.A. Katus, J. Backs, Calcium signaling and transcriptional regulation in cardiomyocytes, Circ. Res. 121 (2017) 1000–1020, https://doi.org/10.1161/CIRCRESAHA.117.310355.

[45] J.A. Gilabert, Cytoplasmic calcium buffering: an integrative crosstalk, in: 2020: pp. 163–182. https://doi.org/10.1007/978-3-030-12457-1_7.

[46] M. Brini, E. Carafoli, Calcium pumps in health and disease, Physiol. Rev. 89 (2009) 1341–1378, https://doi.org/10.1152/physrev.00032.2008.

[47] L. Wu, W. Lian, L. Zhao, Calcium signaling in cancer progression and therapy, FEBS J. 288 (2021) 6187–6205, https://doi.org/10.1111/febs.16133.

[48] L. Li, R. Zhang, Y. Liu, G. Zhang, ANXA4 activates JAK-STAT3 signaling by interacting with ANXA1 in basal-like breast cancer, DNA Cell Biol. 39 (2020) 1649–1656, https://doi.org/10.1089/dna.2020.5570.

[49] F.M. Davis, I. Azimi, R.A. Faville, A.A. Peters, K. Jalink, J.W. Putney, G. J. Goodhill, E.W. Thompson, S.J. Roberts-Thomson, G.R. Monteith, Induction of epithelial–mesenchymal transition (EMT) in breast cancer cells is calcium signal dependent, Oncogene 33 (2014) 2307–2316, https://doi.org/10.1038/onc.2013.187.

[50] M. Tomé, A. Pappalardo, F. Soulet, J.J. López, J. Olaizola, Y. Leger, M. Dubreuil, A. Mouchard, D. Fessart, F. Delom, V. Pitard, D. Bechade, M. Fonck, J.A. Rosado, F. Ghiringhelli, J. Déchanet-Merville, I. Soubeyran, G. Siegfried, S. Evrard, A. M. Khatib, Inactivation of proprotein convertases in T cells inhibits PD-1 expression and creates a favorable immune microenvironment in colorectal cancer, Cancer Res. 79 (2019) 5008–5021, https://doi.org/10.1158/0008-5472.CAN-19-0086.

[51] E. Popugaeva, E. Pchitskaya, I. Bezprozvanny, Dysregulation of neuronal calcium homeostasis in Alzheimer's disease–a therapeutic opportunity? Biochem. Biophys. Res. Commun. 483 (2017) 998–1004, https://doi.org/10.1016/j.bbrc.2016.09.053.

[52] T.S. Tang, E. Slow, V. Lupu, I.G. Stavrovskaya, M. Sugimori, R. Llinás, B.S. Kristal, M.R. Hayden, I. Bezprozvanny, Disturbed Ca $^{2+}$ signaling and apoptosis of medium spiny neurons in Huntington's disease, in: 102, 2005, pp. 2602–2607, https://doi.org/10.1073/pnas.0409402102.

[53] M.A. Salas, C.A. Valverde, G. Sánchez, M. Said, J.S. Rodriguez, E.L. Portiansky, M. A. Kaetzel, J.R. Dedman, P. Donoso, E.G. Kranias, A. Mattiazzi, The signalling pathway of CaMKII-mediated apoptosis and necrosis in the ischemia/reperfusion injury, J. Mol. Cell Cardiol. 48 (2010) 1298–1306, https://doi.org/10.1016/j.yjmcc.2009.12.015.

[54] G. Hasenfuss, H. Reinecke, R. Studer, M. Meyer, B. Pieske, J. Holtz, C. Holubarsch, H. Posival, H. Just, H. Drexler, Relation between myocardial function and expression of sarcoplasmic reticulum Ca(2+)-ATPase in failing and nonfailing human myocardium, Circ. Res. 75 (1994) 434–442, https://doi.org/10.1161/01.RES.75.3.434.

[55] G. Morciano, A. Rimessi, S. Patergnani, V.A.M. Vitto, A. Danese, A. Kahsay, L. Palumbo, M. Bonora, M.R. Wieckowski, C. Giorgi, P. Pinton, Calcium dysregulation in heart diseases: targeting calcium channels to achieve a correct calcium homeostasis, Pharmacol. Res. 177 (2022), 106119, https://doi.org/10.1016/j.phrs.2022.106119.

[56] K.R. Stewart-Morgan, N. Petryk, A. Groth, Chromatin replication and epigenetic cell memory, Nat. Cell Biol. 22 (2020) 361–371, https://doi.org/10.1038/s41556-020-0487-y.

[57] J.P. Whitlock, R. Augustine, H. Schulman, Calcium-dependent phosphorylation of histone H3 in butyrate-treated HeLa cells, Nature 287 (1980) 74–76, https://doi.org/10.1038/287074a0.

[58] R. Phengchat, H. Takata, K. Morii, N. Inada, H. Murakoshi, S. Uchiyama, K. Fukui, Calcium ions function as a booster of chromosome condensation, Sci. Rep. 6 (2016) 1–10, https://doi.org/10.1038/srep38281.

[59] C.R. Kahl, A.R. Means, Regulation of cell cycle progression by calcium/calmodulin-dependent pathways, Endocr. Rev. 24 (2003) 719–736, https://doi.org/10.1210/er.2003-0008.

[60] Y. Wang, A. Sherrard, B. Zhao, M. Melak, J. Trautwein, E.M. Kleinschnitz, N. Tsopoulidis, O.T. Fackler, C. Schwan, R. Grosse, GPCR-induced calcium transients trigger nuclear actin assembly for chromatin dynamics, Nat. Commun. 10 (2019) 5271, https://doi.org/10.1038/s41467-019-13322-y.

[61] S.J. Zhang, M. Zou, L. Lu, D. Lau, D.A.W. Ditzel, C. Delucinge-Vivier, Y. Aso, P. Descombes, H. Bading, Nuclear calcium signaling controls expression of a large gene pool: identification of a gene program for acquired neuroprotection induced

by synaptic activity, PLos Genet. 5 (2009), e1000604, https://doi.org/10.1371/journal.pgen.1000604.
[62] C.V. Harper, A.V. McNamara, D.G. Spiller, J.C. Charnock, M.R.H. White, J.R. E. Davis, Calcium dynamics and chromatin remodelling underlie heterogeneity in prolactin transcription, J. Mol. Endocrinol. 66 (2021) 59–69, https://doi.org/10.1530/JME-20-0223.
[63] A.M. Nair, B. Michael, A. Datta, S. Fernandez, M.D. Lairmore, Calcium-dependent enhancement of transcription of p300 by human T-lymphotropic type 1 p12I, Virology 353 (2006) 247–257, https://doi.org/10.1016/j.virol.2006.06.005.
[64] M.M. Nava, Y.A. Miroshnikova, L.C. Biggs, D.B. Whitefield, F. Metge, J. Boucas, H. Vihinen, E. Jokitalo, X. Li, J.M. García Arcos, B. Hoffmann, R. Merkel, C. M. Niessen, K.N. Dahl, S.A. Wickström, Heterochromatin-driven nuclear softening protects the genome against mechanical stress-induced damage, Cell 181 (2020) 800–817, https://doi.org/10.1016/j.cell.2020.03.052, e22.
[65] A. Villalobo, M. González-Muñoz, M.W. Berchtold, Proteins with calmodulin-like domains: structures and functional roles, Cell. Mol. Life Sci. 76 (2019) 2299–2328, https://doi.org/10.1007/s00018-019-03062-z.
[66] F. Macian, NFAT proteins: key regulators of T-cell development and function, Nat. Rev. Immunol. 5 (2005) 472–484, https://doi.org/10.1038/nri1632.
[67] J.M. Kornhauser, C.W. Cowan, A.J. Shaywitz, R.E. Dolmetsch, E.C. Griffith, L. S. Hu, C. Haddad, Z. Xia, M.E. Greenberg, CREB transcriptional activity in neurons is regulated by multiple, calcium-specific phosphorylation events, Neuron 34 (2002) 221–233, https://doi.org/10.1016/S0896-6273(02)00655-4.
[68] T.A. McKinsey, C.L. Zhang, E.N. Olson, MEF2: a calcium-dependent regulator of cell division, differentiation and death, Trends Biochem. Sci. 27 (2002) 40–47, https://doi.org/10.1016/S0968-0004(01)02031-X.
[69] L. Zhu, S. Song, Y. Pi, Y. Yu, W. She, H. Ye, Y. Su, Q. Hu, Cumulated Ca2+ spike duration underlies Ca2+ oscillation frequency-regulated NFκB transcriptional activity, J. Cell Sci. 124 (2011) 2591–2601, https://doi.org/10.1242/jcs.082727.
[70] R. Brignall, P. Cauchy, S.L. Bevington, B. Gorman, A.O. Pisco, J. Bagnall, C. Boddington, W. Rowe, H. England, K. Rich, L. Schmidt, N.P. Dyer, M.A. Travis, S. Ott, D.A. Jackson, P.N. Cockerill, P. Paszek, Integration of kinase and calcium signaling at the level of chromatin underlies inducible gene activation in T cells, J. Immunol. 199 (2017) 2652–2667, https://doi.org/10.4049/jimmunol.1602033.
[71] Y. Zhu, M. Denholtz, H. Lu, C. Murre, Calcium signaling instructs NIPBL recruitment at active enhancers and promoters via distinct mechanisms to reconstruct genome compartmentalization, Genes Dev. 35 (2021) 65–81, https://doi.org/10.1101/gad.343475.120.
[72] T.K. Kim, M. Hemberg, J.M. Gray, A.M. Costa, D.M. Bear, J. Wu, D.A. Harmin, M. Laptewicz, K. Barbara-Haley, S. Kuersten, E. Markenscoff-Papadimitriou, D. Kuhl, H. Bito, P.F. Worley, G. Kreiman, M.E. Greenberg, Widespread transcription at neuronal activity-regulated enhancers, Nature 465 (2010) 182–187, https://doi.org/10.1038/nature09033.
[73] W.G. Chen, Q. Chang, Y. Lin, A. Meissner, A.E. West, E.C. Griffith, R. Jaenisch, M. E. Greenberg, Derepression of BDNF transcription involves calcium-dependent phosphorylation of MeCP2, Science 302 (2003) 885–889, https://doi.org/10.1126/science.1086446.
[74] Z. Zhou, E.J. Hong, S. Cohen, W. ning Zhao, H. yi H. Ho, L. Schmidt, W.G. Chen, Y. Lin, E. Savner, E.C. Griffith, L. Hu, J.A.J. Steen, C.J. Weitz, M.E. Greenberg, Brain-specific phosphorylation of MeCP2 regulates activity-dependent bdnf transcription, dendritic growth, and spine maturation, Neuron 52 (2006) 255–269, https://doi.org/10.1016/j.neuron.2006.09.037.
[75] F. Suhr, Acute skeletal muscle contractions orchestrate signaling mechanisms to trigger nuclear NFATc1 shuttling and epigenetic histone modifications, Cell. Physiol. Biochem. 52 (2019) 633–652, https://doi.org/10.33594/000000045.
[76] N.J.M. Raynal, J.T. Lee, Y. Wang, A. Beaudry, P. Madireddi, J. Garriga, G. G. Malouf, S. Dumont, E.J. Dettman, V. Gharibyan, S. Ahmed, W. Chung, W. E. Childers, M. Abou-Gharbia, R.A. Henry, A.J. Andrews, J. Jelinek, Y. Cui, S. B. Baylin, D.L. Gill, J.P.J. Issa, Targeting calcium signaling induces epigenetic reactivation of tumor suppressor genes in cancer, Cancer Res. 76 (2016) 1494–1505, https://doi.org/10.1158/0008-5472.CAN-14-2391.
[77] B. Buchthal, D. Lau, U. Weiss, J.M. Weislogel, H. Bading, Nuclear calcium signaling controls methyl-CpG-binding Protein 2 (MeCP2) phosphorylation on serine 421 following synaptic activity, J. Biol. Chem. 287 (2012) 30967–30974, https://doi.org/10.1074/jbc.M112.382507.
[78] Y. Ohkawa, C.G.A. Marfella, A.N. Imbalzano, Skeletal muscle specification by myogenin and Mef2D via the SWI/SNF ATPase Brg1, EMBO J. 25 (2006) 490–501, https://doi.org/10.1038/sj.emboj.7600943.
[79] O. Khan, J.R. Giles, S. McDonald, S. Manne, S.F. Ngiow, K.P. Patel, M.T. Werner, A.C. Huang, K.A. Alexander, J.E. Wu, J. Attanasio, P. Yan, S.M. George, B. Bengsch, R.P. Staupe, G. Donahue, W. Xu, R.K. Amaravadi, X. Xu, G. C. Karakousis, T.C. Mitchell, L.M. Schuchter, J. Kaye, S.L. Berger, E.J. Wherry, TOX transcriptionally and epigenetically programs CD8+ T cell exhaustion, Nature 571 (2019) 211–218, https://doi.org/10.1038/s41586-019-1325-x.
[80] A.R. Bresnick, D.J. Weber, D.B. Zimmer, S100 proteins in cancer, Nat. Rev. Cancer 15 (2015) 96–109, https://doi.org/10.1038/nrc3893.
[81] Y.S. Oh, P. Gao, K.W. Lee, I. Ceglia, J.S. Seo, X. Zhang, J.H. Ahn, B.T. Chait, D. J. Patel, Y. Kim, P. Greengard, SMARCA3, a chromatin-remodeling factor, is required for P11-dependent antidepressant action, Cell 152 (2013) 831–843, https://doi.org/10.1016/j.cell.2013.01.014.
[82] H. Lu, Y. Xie, L. Tran, J. Lan, Y. Yang, N.L. Murugan, R. Wang, Y.J. Wang, G. L. Semenza, Chemotherapy-induced S100A10 recruits KDM6A to facilitate OCT4-mediated breast cancer stemness, J. Clin. Invest. 130 (2020) 4607–4623, https://doi.org/10.1172/JCI138577.
[83] M. Spitaler, D.A. Cantrell, Protein kinase C and beyond, Nat. Immunol. 5 (2004) 785–790, https://doi.org/10.1038/ni1097.
[84] D.L. Clarke, A. Sutcliffe, K. Deacon, D. Bradbury, L. Corbett, A.J. Knox, PKCβII augments NF-κB-dependent transcription at the CCL11 promoter via p300/CBP-associated factor recruitment and histone H4 acetylation, J. Immunol. 181 (2008) 3503–3514, https://doi.org/10.4049/jimmunol.181.5.3503.
[85] J.R. Funsten, K.O. Murillo Brizuela, H.E. Swatzel, A.S. Ward, T.A. Scott, S. M. Eikenbusch, M.C. Shields, J.L. Meredith, T.Y. Mitchell, M.L. Hanna, K. N. Bingham, J.S. Rawlings, PKC signaling contributes to chromatin decondensation and is required for competence to respond to IL-2 during T cell activation, Cell. Immunol. 347 (2020), 104027, https://doi.org/10.1016/j.cellimm.2019.104027.
[86] B.T. Nasipak, T. Padilla-Benavides, K.M. Green, J.D. Leszyk, W. Mao, S. Konda, S. Sif, S.A. Shaffer, Y. Ohkawa, A.N. Imbalzano, Opposing calcium-dependent signalling pathways control skeletal muscle differentiation by regulating a chromatin remodelling enzyme, Nat. Commun. 6 (2015), https://doi.org/10.1038/ncomms8441.
[87] H. Aizawa, S.C. Hu, K. Bobb, K. Balakrishnan, G. Ince, I. Gurevich, M. Cowan, A. Ghosh, Dendrite development regulated by CREST, a calcium-regulated transcriptional activator, Science 303 (2004) 197–202, https://doi.org/10.1126/science.1089845.
[88] Z. Qiu, A. Ghosh, A calcium-dependent switch in a crest-brg1 complex regulates activity-dependent gene expression, Neuron 60 (2008) 775–787, https://doi.org/10.1016/j.neuron.2008.09.040.
[89] A. Grabowska, H. Sas-Nowosielska, B. Wojtas, D. Holm-Kaczmarek, E. Januszewicz, Y. Yushkevich, I. Czaban, P. Trzaskoma, K. Krawczyk, B. Gielniewski, A. Martin-Gonzalez, R.K. Filipkowski, K.H. Olszynski, T. Bernas, A.A. Szczepankiewicz, M.A. Sliwinska, T. Kanhema, C.R. Bramham, G. Bokota, D. Plewczynski, G.M. Wilczynski, A. Magalska, Activation-induced chromatin reorganization in neurons depends on HDAC1 activity, Cell Rep. 38 (2022), 110352, https://doi.org/10.1016/j.celrep.2022.110352.
[90] D. Lai, M. Wan, J. Wu, P. Preston-Hurlburt, R. Kushwaha, T. Grundstrom, A. N. Imbalzano, T. Chi, Induction of TLR4-target genes entails calcium/calmodulin-dependent regulation of chromatin remodeling, Proc. Natl. Acad. Sci. 106 (2009) 1169–1174, https://doi.org/10.1073/pnas.0811274106.
[91] Y. Wang, Y. Zhang, Regulation of TET protein stability by calpains, Cell Rep. 6 (2014) 278–284, https://doi.org/10.1016/j.celrep.2013.12.031.
[92] L.L. Luchsinger, A. Strikoudis, N.M. Danzl, E.C. Bush, M.O. Finlayson, P. Satwani, M. Sykes, M. Yazawa, H.W. Snoeck, Harnessing hematopoietic stem cell low intracellular calcium improves their maintenance in vitro, Cell Stem Cell 25 (2019) 225–240, https://doi.org/10.1016/j.stem.2019.05.002, e7.
[93] A.P. Kutschat, F.H. Hamdan, X. Wang, A.Q. Wixom, Z. Najafova, C.S. Gibhardt, W. Kopp, J. Gaedcke, P. Ströbel, V. Ellenrieder, I. Bogeski, E. Hessmann, S. A. Johnsen, STIM1 mediates calcium-dependent epigenetic reprogramming in pancreatic cancer, Cancer Res. 81 (2021) 2943–2955, https://doi.org/10.1158/0008-5472.CAN-20-2874.
[94] S.Q. Wang, J. Liu, J. Qin, Y. Zhu, V.P.-C. Tin, J.W.P. Yam, M.P. Wong, Z.J. Xiao, CAMK2A supported tumor initiating cells of lung adenocarcinoma by upregulating SOX2 through EZH2 phosphorylation, Cell Death. Dis. 11 (2020) 410, https://doi.org/10.1038/s41419-020-2553-6.
[95] A. Sharma, H. Nguyen, C. Geng, M.N. Hinman, G. Luo, H. Lou, Calcium-mediated histone modifications regulate alternative splicing in cardiomyocytes, Proc. Natl. Acad. Sci. USA 111 (2014) E4920–E4928, https://doi.org/10.1073/pnas.1408964111.
[96] A. Sharma, H. Nguyen, L. Cai, H. Lou, Histone hyperacetylation and exon skipping: a calcium-mediated dynamic regulation in cardiomyocytes, Nucleus 6 (2015) 273–278, https://doi.org/10.1080/19491034.2015.1081324.
[97] A.J. Sadler, B.A. Suliman, L. Yu, X. Yuan, D. Wang, A.T. Irving, S.T. Sarvestani, A. Banerjee, A.S. Mansell, J.P. Liu, S. Gerondakis, B.R.G. Williams, D. Xu, The acetyltransferase HAT1 moderates the NF-κB response by regulating the transcription factor PLZF, Nat. Commun. 6 (2015) 6795, https://doi.org/10.1038/ncomms7795.
[98] S. Karppinen, S.L. Hänninen, R. Rapila, P. Tavi, Sarcoplasmic reticulum Ca2+-induced Ca2+ release regulates class IIa HDAC localization in mouse embryonic cardiomyocytes, Physiol. Rep. 6 (2018) 1–12, https://doi.org/10.14814/phy2.13522.
[99] S.C. Rothschild, H.J. Lee, S.R. Ingram, D.K. Mohammadi, G.S. Walsh, R. M. Tombes, Calcium signals act through histone deacetylase to mediate pronephric kidney morphogenesis, Dev. Dyn. 247 (2018) 807–817, https://doi.org/10.1002/dvdy.24632.
[100] F.J. Davis, M. Gupta, B. Camoretti-Mercado, R.J. Schwartz, M.P. Gupta, Calcium/calmodulin-dependent protein kinase activates serum response factor transcription activity by its dissociation from histone deacetylase, HDAC4, J. Biol. Chem. 278 (2003) 20047–20058, https://doi.org/10.1074/jbc.M209998200.
[101] K. Liu, L. Ding, Y. Li, H. Yang, C. Zhao, Y. Lei, S. Han, W. Tao, D. Miao, H. Steller, M.J. Welsh, L. Liu, Neuronal necrosis is regulated by a conserved chromatin-modifying cascade, Proc. Natl. Acad. Sci. 111 (2014) 13960–13965, https://doi.org/10.1073/pnas.1413644111.
[102] H. Zhang, Y.P. Shang, H.Y. Chen, J. Li, Histone deacetylases function as a novel potential therapeutic target for cancer, Hepatol. Res. (2016), https://doi.org/10.1111/hepr.12757.
[103] X. Zhang, M. Bolt, M.J. Guertin, W. Chen, S. Zhang, B.D. Cherrington, D.J. Slade, C.J. Dreyton, V. Subramanian, K.L. Bicker, P.R. Thompson, M.A. Mancini, J.T. Lis, S.A. Coonrod, Peptidylarginine deiminase 2-catalyzed histone H3 arginine 26 citrullination facilitates estrogen receptor α target gene activation, in: 109, 2012, pp. 13331–13336, https://doi.org/10.1073/pnas.1203280109.

[104] M.J. Guertin, X. Zhang, L. Anguish, S. Kim, L. Varticovski, J.T. Lis, G.L. Hager, S. A. Coonrod, Targeted H3R26 deimination specifically facilitates estrogen receptor binding by modifying nucleosome structure, PLos Genet. 10 (2014), e1004613, https://doi.org/10.1371/journal.pgen.1004613.
[105] M.A. Christophorou, G. Castelo-Branco, R.P. Halley-Stott, C.S. Oliveira, R. Loos, A. Radzisheuskaya, K.A. Mowen, P. Bertone, J.C.R. Silva, M. Zernicka-Goetz, M. L. Nielsen, J.B. Gurdon, T. Kouzarides, Citrullination regulates pluripotency and histone H1 binding to chromatin, Nature 507 (2014) 104–108, https://doi.org/10.1038/nature12942.
[106] C. Tanikawa, M. Espinosa, A. Suzuki, K. Masuda, K. Yamamoto, E. Tsuchiya, K. Ueda, Y. Daigo, Y. Nakamura, K. Matsuda, Regulation of histone modification and chromatin structure by the p53–PADI4 pathway, Nat. Commun. 3 (2012) 676, https://doi.org/10.1038/ncomms1676.
[107] Y. Wang, Y. Lyu, K. Tu, Q. Xu, Y. Yang, S. Salman, N. Le, H. Lu, C. Chen, Y. Zhu, R. Wang, Q. Liu, G.L. Semenza, Histone citrullination by PADI4 is required for HIF-dependent transcriptional responses to hypoxia and tumor vascularization, Sci Adv. 7 (2021), https://doi.org/10.1126/sciadv.abe3771.
[108] P. Li, M. Li, M.R. Lindberg, M.J. Kennett, N. Xiong, Y. Wang, PAD4 is essential for antibacterial innate immunity mediated by neutrophil extracellular traps, J. Exp. Med. 207 (2010) 1853–1862, https://doi.org/10.1084/jem.20100239.
[109] G.L. Cuthbert, S. Daujat, A.W. Snowden, H. Erdjument-Bromage, T. Hagiwara, M. Yamada, R. Schneider, P.D. Gregory, P. Tempst, A.J. Bannister, T. Kouzarides, Histone deimination antagonizes arginine methylation, Cell 118 (2004) 545–553, https://doi.org/10.1016/j.cell.2004.08.020.
[110] P. Li, H. Yao, Z. Zhang, M. Li, Y. Luo, P.R. Thompson, D.S. Gilmour, Y. Wang, Regulation of p53 target gene expression by peptidylarginine deiminase 4, Mol. Cell. Biol. 28 (2008) 4745–4758, https://doi.org/10.1128/MCB.01747-07.
[111] P. Li, D. Wang, H. Yao, P. Doret, G. Hao, Q. Shen, H. Qiu, X. Zhang, Y. Wang, G. Chen, Y. Wang, Coordination of PAD4 and HDAC2 in the regulation of p53-target gene expression, Oncogene 29 (2010) 3153–3162, https://doi.org/10.1038/onc.2010.51.
[112] Q. Zheng, A. Osunsade, Y. David, Protein arginine deiminase 4 antagonizes methylglyoxal-induced histone glycation, Nat. Commun. 11 (2020) 3241, https://doi.org/10.1038/s41467-020-17066-y.
[113] M. Wiese, A.J. Bannister, S. Basu, W. Boucher, K. Wohlfahrt, M.A. Christophorou, M.L. Nielsen, D. Klenerman, E.D. Laue, T. Kouzarides, Citrullination of HP1γ chromodomain affects association with chromatin, Epigenetics Chrom. 12 (2019) 21, https://doi.org/10.1186/s13072-019-0265-x.
[114] A.A. Lombardi, A.A. Gibb, E. Arif, D.W. Kolmetzky, D. Tomar, T.S. Luongo, P. Jadiya, E.K. Murray, P.K. Lorkiewicz, G. Hajnóczky, E. Murphy, Z.P. Arany, D. P. Kelly, K.B. Margulies, B.G. Hill, J.W. Elrod, Mitochondrial calcium exchange links metabolism with the epigenome to control cellular differentiation, Nat. Commun. 10 (2019) 4509, https://doi.org/10.1038/s41467-019-12103-x.
[115] E. Izquierdo-Torres, A. Hernández-Oliveras, G. Fuentes-García, Á. Zarain-Herzberg, Calcium signaling and epigenetics: a key point to understand carcinogenesis, Cell Calcium 91 (2020), 102285, https://doi.org/10.1016/j.ceca.2020.102285.
[116] M. Shibasaki, K. Mizuno, K. Kurokawa, S. Ohkuma, L-type voltage-dependent calcium channels facilitate acetylation of histone H3 through PKCγ phosphorylation in mice with methamphetamine-induced place preference, J. Neurochem. 118 (2011) 1056–1066, https://doi.org/10.1111/j.1471-4159.2011.07387.x.
[117] M. Missler, W. Zhang, A. Rohlmann, G. Kattenstroth, R.E. Hammer, K. Gottmann, T.C. Südhof, α-Neurexins couple Ca2+ channels to synaptic vesicle exocytosis, Nature 423 (2003) 939–948, https://doi.org/10.1038/nature01755.
[118] S. Awad, M. Kunhi, G.H. Little, Y. Bai, W. An, D. Bers, L. Kedes, C. Poizat, Nuclear CaMKII enhances histone H3 phosphorylation and remodels chromatin during cardiac hypertrophy, Nucleic. Acids. Res. 41 (2013) 7656–7672, https://doi.org/10.1093/nar/gkt500.
[119] K.K. Baskin, C.A. Makarewich, S.M. DeLeon, W. Ye, B. Chen, N. Beetz, H. Schrewe, R. Bassel-Duby, E.N. Olson, MED12 regulates a transcriptional network of calcium-handling genes in the heart, JCI Insight 2 (2017), https://doi.org/10.1172/jci.insight.91920.
[120] Y. Li, B. Guo, Q. Xie, D. Ye, D. Zhang, Y. Zhu, H. Chen, B. Zhu, STIM1 mediates hypoxia-driven hepatocarcinogenesis via interaction with HIF-1, Cell Rep. 12 (2015) 388–395, https://doi.org/10.1016/j.celrep.2015.06.033.
[121] B.M. Ortmann, N. Burrows, I.T. Lobb, E. Arnaiz, N. Wit, P.S.J. Bailey, L.H. Jordon, O. Lombardi, A. Peñalver, J. McCaffrey, R. Seear, D.R. Mole, P.J. Ratcliffe, P. H. Maxwell, J.A. Nathan, The HIF complex recruits the histone methyltransferase SET1B to activate specific hypoxia-inducible genes, Nat. Genet. 53 (2021) 1022–1035, https://doi.org/10.1038/s41588-021-00887-y.
[122] R. Mitra, S. Richhariya, S. Jayakumar, D. Notani, G. Hasan, IP3-mediated Ca2+ signals regulate larval to pupal transition under nutrient stress through the H3K36 methyltransferase Set2, Development (2021) 148, https://doi.org/10.1242/dev.199018.
[123] M. Kosiorek, P. Podszywalow-Bartnicka, L. Zylinska, S. Pikula, NFAT1 and NFAT3 Cooperate with HDAC4 during Regulation of Alternative Splicing of PMCA Isoforms in PC12 Cells, PLoS One 9 (2014) e99118, https://doi.org/10.1371/journal.pone.0099118.
[124] E.E. STREHLER, A.J. CARIDE, A.G. FILOTEO, Y. XIONG, J.T. PENNISTON, A. ENYEDI, Plasma membrane Ca2+ ATPases as dynamic regulators of cellular calcium handling, Ann NY Acad. Sci. 1099 (2007) 226–236, https://doi.org/10.1196/annals.1387.023.
[125] V. Lionetti, B.S. Tuana, V. Casieri, M. Parikh, G.N. Pierce, Importance of functional food compounds in cardioprotection through action on the epigenome, Eur. Heart J. 40 (2019) 575–582, https://doi.org/10.1093/eurheartj/ehy597.
[126] E. Izquierdo-Torres, A. Hernández-Oliveras, D. Lozano-Arriaga, Á. Zarain-Herzberg, Obesity, the other pandemic: linking diet and carcinogenesis by epigenetic mechanisms, J. Nutr. Biochem. 108 (2022), 109092, https://doi.org/10.1016/j.jnutbio.2022.109092.
[127] J.H. Ko, G. Sethi, J.Y. Um, M.K. Shanmugam, F. Arfuso, A.P. Kumar, A. Bishayee, K.S. Ahn, The role of resveratrol in cancer therapy, Int. J. Mol. Sci. 18 (2017) 2589, https://doi.org/10.3390/ijms18122589.
[128] E. Izquierdo-Torres, G. Rodríguez, I. Meneses-Morales, A. Zarain-Herzberg, *ATP2A3* gene as an important player for resveratrol anticancer activity in breast cancer cells, Mol. Carcinog. 56 (2017) 1703–1711, https://doi.org/10.1002/mc.22625.
[129] A. Arbabian, J. Brouland, Á. Apáti, K. Pászty, L. Hegedűs, Á. Enyedi, C. Chomienne, B. Papp, Modulation of endoplasmic reticulum calcium pump expression during lung cancer cell differentiation, FEBS J. 280 (2013) 5408–5418, https://doi.org/10.1111/febs.12064.
[130] B. Papp, J.P. Brouland, A. Arbabian, P. Gélébart, T. Kovács, R. Bobe, J. Enouf, N. Varin-Blank, Á. Apáti, Endoplasmic reticulum calcium pumps and cancer cell differentiation, Biomolecules 2 (2012) 165–186, https://doi.org/10.3390/biom2010165.
[131] L. Ait-Ghezali, A. Arbabian, A. Jeibmann, M. Hasselblatt, G.G. Hallaert, C. Van den Broecke, F. Gray, J. Brouland, N. Varin-Blank, B. Papp, Loss of endoplasmic reticulum calcium pump expression in choroid plexus tumours, Neuropathol. Appl. Neurobiol. 40 (2014) 726–735, https://doi.org/10.1111/nan.12098.
[132] P. Liczbiński, J. Michałowicz, B. Bukowska, Molecular mechanism of curcumin action in signaling pathways: review of the latest research, Phytother. Res. 34 (2020) 1992–2005, https://doi.org/10.1002/ptr.6663.
[133] F. Hassan, M.S. Rehman, M.S. Khan, M.A. Ali, A. Javed, A. Nawaz, C. Yang, Curcumin as an alternative epigenetic modulator: mechanism of action and potential effects, Front. Genet. 10 (2019), https://doi.org/10.3389/fgene.2019.00514.
[134] L. Zhang, X. Cheng, S. Xu, J. Bao, H. Yu, Curcumin induces endoplasmic reticulum stress-associated apoptosis in human papillary thyroid carcinoma BCPAP cells via disruption of intracellular calcium homeostasis, Medicine 97 (2018) e11095, https://doi.org/10.1097/MD.0000000000011095.
[135] R. Kida, T. Noguchi, M. Murakami, O. Hashimoto, T. Kawada, T. Matsui, M. Funaba, Supra-pharmacological concentration of capsaicin stimulates brown adipogenesis through induction of endoplasmic reticulum stress, Sci. Rep. 8 (2018) 845, https://doi.org/10.1038/s41598-018-19223-2.
[136] C. Kliem, A. Merling, M. Giaisi, R. Köhler, P.H. Krammer, M. Li-Weber, Curcumin suppresses T cell activation by blocking Ca2+ mobilization and nuclear factor of activated T cells (NFAT) activation, J. Biol. Chem. 287 (2012) 10200–10209, https://doi.org/10.1074/jbc.M111.318733.
[137] J.R. Erickson, M.E. Anderson, CaMKII and its role in cardiac arrhythmia, J. Cardiovasc. Electrophysiol. 19 (2008) 1332–1336, https://doi.org/10.1111/j.1540-8167.2008.01295.x.
[138] D.M. Bers, E. Grandi, Calcium/calmodulin-dependent kinase ii regulation of cardiac ion channels, J. Cardiovasc. Pharmacol. 54 (2009) 180–187, https://doi.org/10.1097/FJC.0b013e3181a25078.