



Review

SWI/SNF Complex in Vascular Smooth Muscle Cells and Its Implications in Cardiovascular Pathologies

Hongyu Liu ^{1,2,3}, Yang Zhao ¹ , Guizhen Zhao ¹, Yongjie Deng ¹, Y. Eugene Chen ^{1,4,*} and Jifeng Zhang ^{1,*} 

¹ Department of Internal Medicine, Cardiovascular Center, University of Michigan Medical Center, 2800 Plymouth Road, Ann Arbor, MI 48109, USA; hongyl@umich.edu (H.L.); ypharan@umich.edu (Y.Z.)

² Department of Molecular & Integrative Physiology, University of Michigan Medical Center, Ann Arbor, MI 48109, USA

³ Department of Vascular Surgery, The Second Xiangya Hospital, Central South University, Changsha 410011, China

⁴ Department of Cardiac Surgery, University of Michigan Medical Center, Ann Arbor, MI 48109, USA

* Correspondence: echenum@umich.edu (Y.E.C.); jifengz@umich.edu (J.Z.); Tel.: +1-734-936-9548 (Y.E.C.); +1-734-647-8975 (J.Z.)

Abstract: Mature vascular smooth muscle cells (VSMC) exhibit a remarkable degree of plasticity, a characteristic that has intrigued cardiovascular researchers for decades. Recently, it has become increasingly evident that the chromatin remodeler SWItch/Sucrose Non-Fermentable (SWI/SNF) complex plays a pivotal role in orchestrating chromatin conformation, which is critical for gene regulation. In this review, we provide a summary of research related to the involvement of the SWI/SNF complexes in VSMC and cardiovascular diseases (CVD), integrating these discoveries into the current landscape of epigenetic and transcriptional regulation in VSMC. These novel discoveries shed light on our understanding of VSMC biology and pave the way for developing innovative therapeutic strategies in CVD treatment.

Keywords: vascular smooth muscle cell; SWI/SNF complex; epigenetics; cardiovascular disease



Citation: Liu, H.; Zhao, Y.; Zhao, G.; Deng, Y.; Chen, Y.E.; Zhang, J. SWI/SNF Complex in Vascular Smooth Muscle Cells and Its Implications in Cardiovascular Pathologies. *Cells* **2024**, *13*, 168. <https://doi.org/10.3390/cells13020168>

Academic Editors: Jonathon Willets, Alejandra San Martin and Claire Holden

Received: 7 November 2023

Revised: 9 January 2024

Accepted: 12 January 2024

Published: 16 January 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Vascular smooth muscle cells (VSMCs) reside in the tunica media of vessels [1] and play critical roles in both vascular homeostasis and the pathogenesis of cardiovascular diseases (CVD). As early as the 1960s, it has been established that VSMC are enriched in atherosclerotic lesions in human specimens [2] and animal models [3,4]. The plasticity of VSMC has been identified as one of the major pathological factors in atherogenesis [5,6]. Key transcription factors and cofactors, like serum response factor (SRF) [7], myocardin [8], and Krüppel-like factor 4 (KLF4) [9], were identified during the investigation of SMC plasticity. Despite their essential role in DNA–protein interactions, the importance of chromatin remodelers in VSMC plasticity has often been overlooked. Summarizing the known and unknown of chromatin remodeling in VSMC research offers valuable insights into this understudied aspect. This review delves into the role of a primary ATP-dependent chromatin remodeler, the SWItch/Sucrose Non-Fermentable (SWI/SNF) complexes, in VSMC biology and its implications for cardiovascular diseases.

2. Roles of VSMCs from Physiology to Pathology

Like skeletal muscle cells and cardiomyocytes, the primary function of VSMCs is contraction. Under precise hormonal and neural control, VSMCs regulate blood distribution and blood pressure. To maintain the contractile phenotype, VSMC undergoes differentiation via the expression of a repertoire of contractile apparatus and regulators [10]. *Myosin heavy chain 11 (MYH11)*, also known as *smooth muscle myosin heavy chain (SMMHC)*, is responsible for encoding SMC-specific myosin. Different from myosins in other muscle

tissues, MYH11 lacks intrinsic ATPase activity. Instead, its activity is triggered when Ser 19 on the regulatory myosin light chain becomes phosphorylated. This phosphorylation is precisely controlled by myosin light chain kinase (MYLK) and myosin light chain phosphatase (MLCP). Thin myofilaments are composed of α -actin, also known as α -smooth muscle actin (α -SMA), which is encoded by *actin alpha 2 (ACTA2)* [11,12]. Of note, variants of those genes have already been well-documented in patients with inherited aortic diseases [13,14]. This underscores the importance of fully functional contractile machinery in VSMCs for maintaining aortic health.

Another important role of VSMCs is to regulate vascular extracellular matrix (ECM) homeostasis through the production of components including elastin, collagen [15], and proteoglycans and regulation of ECM remodelers including matrix metalloproteinase (MMP) and tissue inhibitor of matrix metalloproteinases (TIMPs). These determine the vessel wall's mechanical strength, compliance, and elastic recoil. As a result, ECM construction and maintenance of VSMC have emerged as central priorities in the field of bioengineering for blood vessel grafts [16].

Interestingly, the two major roles of VSMCs seem to be conflicting. During the initial embryonic development stage, VSMCs exhibit rapid proliferation [17], migrate, and actively secrete ECM components crucial for vasculogenesis. However, mature VSMCs lose those properties and become quiescent with a low proliferation rate and synthetic activity. In the mature aorta, VSMCs possess contractile apparatus and maintain mechanical strength. Nevertheless, during vascular injury, alterations in the environmental cues cause the loss of contractile markers, including MYH11 and α -SMA, coupled with increased proliferation, migration, and protein synthesis in VSMC. This type of dedifferentiated VSMC is essential for vascular repair. The transition between the contractile and synthetic states of VSMCs is termed "phenotypic switch". It is thus logical to infer that the intrinsic plasticity of VSMCs is beneficial for adaptation to complex environments and response to damage. However, substantial changes in diet and lifestyle may hijack this ability and disrupt vascular homeostasis.

3. Epigenetic and Transcriptional Regulation of VSMC Plasticity in Health and Diseases

Vascular smooth muscle cell plasticity in CVD, including atherosclerosis, has been well-documented [2]. Especially in the past decade, the emergence of new technologies, such as lineage tracing, single-cell RNA sequencing (scRNA-Seq), and spatial transcriptomics [18–21], has largely extended our knowledge of cell origin, characteristics, and transcriptomic profiles in the atherosclerotic lesions. Under pathological conditions, VSMCs transdifferentiate into various cell types such as foam cells [22,23], mesenchymal-stem-cell (MSC)-like cells [24], macrophage-like cells [25,26], adipocyte-like cells [27], osteochondrogenic cells [28,29], fibromyocytes [19]. Multiple reviews thoroughly discuss this phenomenon [5,30–34]. A dramatic shift in gene expression occurs during dedifferentiation or transdifferentiation. Such changes necessitate a sophisticated transcriptional regulation network in VSMCs to precisely control specific gene expression in response to environmental changes [34–36].

In differentiated VSMC, the expressions of contractile genes are governed by an array of transcription factors and coactivators [35–37] (Table 1; Figures 1 and 2). In 1985, CC(A/T)₆GG, also referred to as the CArG element, was identified in the promoter of the human cardiac actin gene [38]. Subsequent research has highlighted the crucial role of the CArG element in regulating muscle-specific genes [39]. Serum response factor (SRF) was then identified to bind with CArG elements and regulate downstream gene expression [7,40]. In addition, the discovery of myocardin [8] and its competition with Elk-1 for SRF interaction [41] revealed the delicate regulation of the VSMC phenotype.

Table 1. Regulators of contractile gene transcription.

Gene	Category	Function	Effect on Contractile Gene Transcription	Reference
SMARCA4 SMARCD3 SRF	Chromatin remodeler Chromatin remodeler Transcription factor	Mediate chromatin accessibility Mediate chromatin accessibility Bind at CARG elements	Dependent on interactors Promotion Dependent on interactors	[42,43] [44] [8]
Myocardin MRTFA/B	Cofactor Cofactor	Interact with SRF Interact with SRF	Promotion Promotion	[8,41,45] [41,46,47]
Smad2/3 GATA4/6 CSRP2 NKX3-2	Transcription factor Transcription factor Cofactor Transcription factor	Bind DNA Bind DNA Interact with SRF, GATA6 Bind DNA	Promotion Promotion Promotion Promotion	[48] [49–53] [54,55] [52]
Prx1 PITX2	Transcription factor Transcription factor	Bind DNA Bind DNA	Promotion Promotion	[56] [57]
PIAS1	Transcription factor	Bind DNA	Promotion	[58]
MEF2	Transcription factor	Bind DNA	Promotion	[59]
Notch/RBPJ	Transcription factor	Bind DNA	Promotion	[60,61]
KLF4	Transcription factor	Bind G/C repressor element	Repression	[9,62–65]
Elk1	Cofactor	Interact with SRF	Repression	[47,63,64]
p300	Histone acetyltransferase	Increase histone acetylation	Promotion	[51,66,67]
HDAC	Histone deacetylase	Decrease Histone modification	Repression	[47,63,64]
SMYD2	Histone lysine methyltransferase	Increase H3K4me1, H3K4me3	Promotion	[68]
JMJD1A	Histone demethylase	Decrease H3K9me2	Promotion	[69]
WDR5	Cofactor	Increase H3K4me1, H3K4me3	Promotion	[70]
PRDM6	Histone lysine methyltransferase	Increase H4K20me2	Repression	[71,72]
SUV39H1	Histone lysine methyltransferase	Increase H3K9me3	Repression	[73]
EZH2	Histone lysine methyltransferase	Increase H3K27me3	Repression	[74,75]
TET2	Methylcytosine dioxygenase	DNA demethylation	Promotion	[76,77]
PRMT5	Histone arginine methyltransferase	H3R8me2, H4R3me2	Repression	[78]

Aside from myocardin/SRF, other transcription factors also play essential roles in regulating contractile genes [35]. The roles of transforming growth factor- β (TGF β) in VSMC differentiation have been documented [79]. In 1997, the TGF β control element (TCE), proximal to two CARG elements, was discovered in the promoter of *ACTA2* [80]. TGF β increases contractile gene expression by facilitating the binding of SRF to the CARG elements, possibly through interactions between Smad3 and p300 [81]. Subsequent research on the synergetic function and direct interaction of Smad3 and myocardin has further elucidates the roles of TGF β signaling in VSMC differentiation [48]. Another transcription factor, GATA binding protein 6 (GATA6), was found to be highly expressed in the VSMCs during development [82], and it was shown to protect against injury-induced VSMC phenotypic switch [50]. Further study has revealed that GATA6, NK3 homeobox 2 (NKX3-2), and SRF form a triad complex to regulate contractile gene expressions [52].

Conversely, in dedifferentiated VSMC, KLF4 plays an essential role [83]. The significance of KLF4 in VSMC was first discovered through yeast one-hybrid cloning against TCE [84]. Subsequent studies have firmly demonstrated that KLF4 was a potent repressor for VSMC differentiation [62,85]. In response to PDGF-BB treatment, Sp1, pELK1, and KLF4 cooperatively bind to the G/C repressor element flanked by two CARG elements in the promoters of contractile genes, including *MYH11* and *TAGLN*. In addition, KLF4 recruits HDACs, reducing histone acetylation in the promoters. Consequently, it diminishes SRF binding and the expression of contractile genes [86]. In the mouse atherosclerosis model, SMC-specific KLF4 knockout showed less mesenchymal-stem-cell- and macrophage-like cells derived from SMC, along with less lesion and increased fibrous cap thickness, underscoring significant roles of KLF4 in the cardiovascular diseases [9].

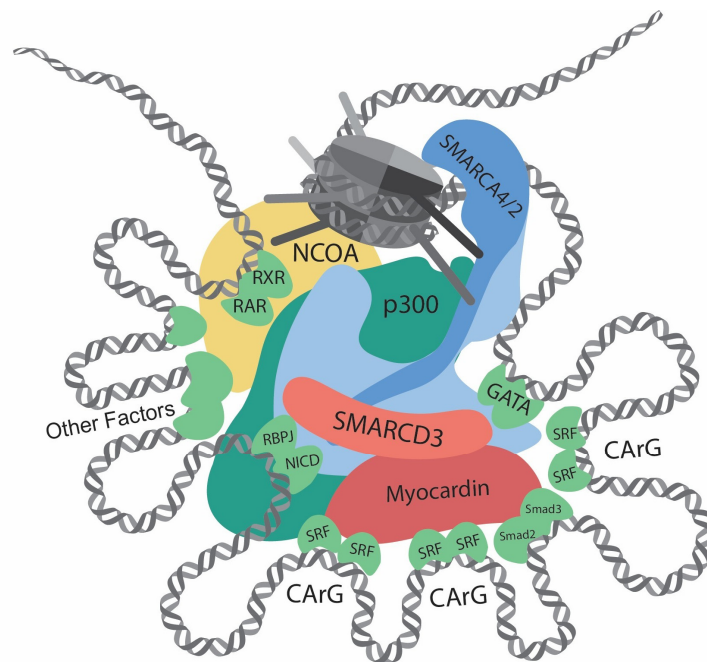


Figure 1. Transcriptional regulation at the CREs (cis-regulatory elements) of VSMC contractile genes. This diagram showcases the intricate network of interactions involving transcription regulators, such as chromatin remodelers, histone modifiers, transcription factors, and cofactors, at the CREs of the VSMC contractile genes. Chromatin remodelers that expose DNA regions by unwinding nucleosomes are central to the regulation. Several CArG elements, present at promoters and introns, bind to two SRFs and interact with myocardin. Within this region, there are binding sites for Smad2/3, NICD/RBPJ, and GATA. Retinoic acid signaling, crucial for VSMC differentiation, facilitates interactions between RAR/RXR and the SMARCD subunit of the SWI/SNF complexes. Other key contributors to VSMC differentiation include Prx1, Nkx3-2, PITX2, MEF2, and PIAS1. In addition, chromatin remodelers and transcription factors interact with histone modifiers, such as p300 and members of the NCOA family. Such complex interactions determine delicate and complicated regulation of contractile genes.

As we delve deeper into the research on the transcriptional regulation of contractile genes, epigenetic regulation gains increasing interest [87,88]. Structural investigations revealed that SRF does not bind to nucleosomal DNA [89–91], implying its exclusive binding to open DNA regions. Meanwhile, several factors affect the binding activity of SRF to the CArG elements [80,86,88]. These findings shed light on the significance of chromatin conformation in the transcriptional regulation of contractile genes. McDonald et al. discovered that H3K4me₂, H3K79me₂, H3K9Ac, and H4Ac are enriched in the CArG elements in the SMC but not in the non-SMC [86]. In addition, H3K4me₂ tethers with SRF and myocardin, and this modification persists even after VSMC dedifferentiation [92]. Loss of H3K4me₂ at the CArG elements causes a decrease in contractile gene expression through the reduced TET2 (ten-eleven translocation-2)-mediated DNA demethylation [77,93]. In contrast, in embryonic stem cells or other non-SMCs, H3K9me₃ and H3K27me₃ govern the repression of contractile gene expression [91]. Lysine demethylase 3A (KDM3A), previously known as JMJD1a, interacts with myocardin and demethylates H3K9me₃, thus promoting the expression of contractile genes [69]. In addition, numerous histone modifiers have been identified to regulate contractile genes, including PR/SET domain 6 (PRDM6), SET and MYND domain containing 2 (SMYD2), SUV39H1, polycomb repressive complexes 2 (PRC2), and protein arginine methyltransferase 5 (PRMT5) (Table 1; Figures 1 and 2) [68,71–75,78]. Although previous studies elucidated the intricate regulation of transcription and histone modification, the specific roles of chromatin remodelers in directly executing chromatin transformations require further investigation.

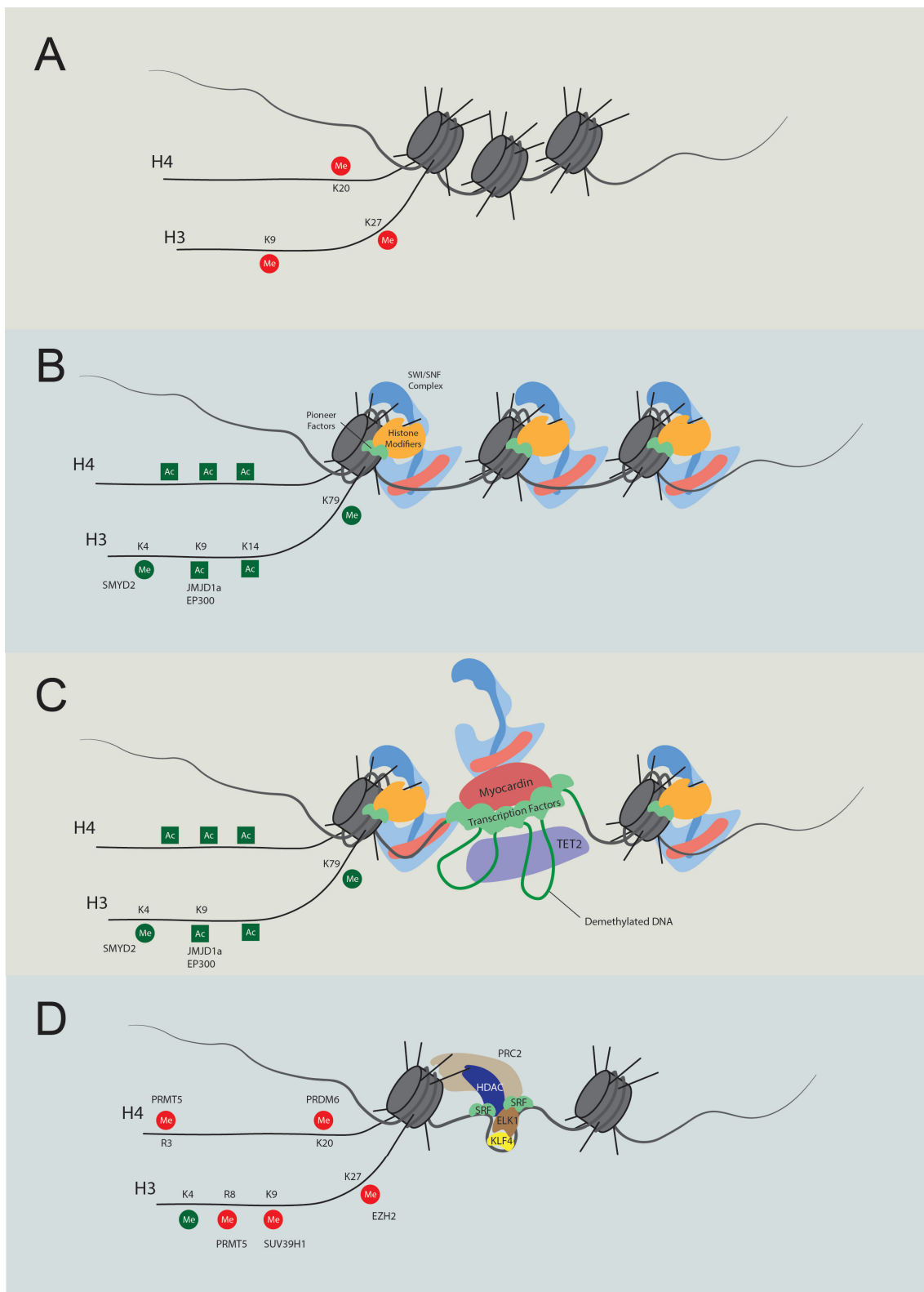


Figure 2. Temporal regulation of VSMC contractile gene expression. **(A)** Stem cell chromatin state: specific DNA regions are tightly wrapped into nucleosomes in stem cells. These regions are marked by repressive histone modifications, notably H4K20me₃, H3K9me₃, and H3K27me₃, which play pivotal roles in maintaining gene silencing. **(B)** Activation of chromatin regions: during the transition to an active chromatin state, repressive histone marks are displaced, and active modifications emerge, such as H4Ac, H3K4Me₂, H3K9Ac, H3K14Ac, and H3K79Me. Key players in this process include

JMJD1a (H3K9me removal), SMYD2 (H3K4Me induction), and p300 (H3Ac and H4Ac induction). As histone acetylation weakens histone-DNA binding, pioneer factors can bind with nucleosomal DNA, subsequently recruiting either chromatin remodelers like the SWI/SNF complex or additional histone modifiers. (C) Transcription: the SWI/SNF complex introduces nucleosome-free regions, enabling TET2 to demethylate DNA. As a result, specific transcription factors bind to their respective elements. Subsequently, cofactors, including myocardin and CSRP, are recruited, promoting interactions between transcription regulators to promote transcription. (D) Dedifferentiation and transcriptional inactivation: in response to dedifferentiation signals like platelet-derived growth factor BB (PDGF-BB), the transcription of contractile genes was suppressed. In this situation, KLF4 binds to the G/C elements, while SRF partners with Elk1 rather than myocardin. Concurrently, HDACs and PRC are also recruited to deacetylate and induce methylation of H3K27. Additionally, PRDM6, PRMT5, and SUV39H1 mediate methylation at H4K20, H4R3 and H3R8, and H3K9, respectively. The loss of required transcription factors and DNA accessibility cease contractile gene transcription.

4. Chromatin Remodeling and SWI/SNF Complexes

In eukaryotic cells, DNA wraps around histones, forming the basic structural unit: a nucleosome [94]. In a rigid and delicate manner, DNA accessibility is highly regulated for complex activities, including replication, repair, and transcription. Chromatin remodeling involves altering interactions between histones and DNA, including assembly and disorganization of nucleosomes. Transcription requires DNA free from histones to interact with proteins such as polymerase II and transcription factors. Studies have shown that chromatin remodelers are essential in controlling pluripotency, cell fate, and differentiation [95–97]. Four prominent remodeler families have spiked the most study interest to date, including SWI/SNF, Imitation switch (ISWI), chromodomain helicase DNA-binding (CHD), and INOitol requiring 80/SWI2/SNF2-Related 1 (INO80/SWR1) [98,99]. This review focuses on the SWI/SNF complexes.

The SWI/SNF chromatin remodeling complexes were first discovered in *Saccharomyces cerevisiae*. SWI stands for ‘switch’ as the relevant genes regulate the *HO* gene, which is crucial for mating type switching [100]. Similarly, SNF denotes ‘sucrose nonfermenting’ since these genes control the *SUC2* gene responsible for sucrose catabolism [101]. Subsequent research has found that some genes from these two screenings overlap, forming a complex that regulates chromatin structure [102]. SWI/SNF complexes use energy from ATP hydrolysis to mediate nucleosome sliding or ejection [103]. The mammalian SWI/SNF complex was purified in 1996 [104]. In mammals, either Brg1 or Brm serves as the ATPase of the complex; the SWI/SNF complex is also named the BRG1/BRM-associated factor (BAF). The initially isolated complex was termed canonical BAF (cBAF) [104]. Subsequent research has identified two more types of SWI/SNF assemblies: polybromo-associated BAF (PBAF) [105] and non-canonical BAF (ncBAF) [106–108]. These complexes are assembled by 9–16 subunits, and some subunits consist of several paralogs (Figure 3 and Table 2) [109]. Each subunit conveys unique functions for chromatin remodeling [110]. More than 1000 unique combinations of SWI/SNF subunits form diverse complexes with varied functions [111,112].

Recent advancements have significantly illuminated the structure of SWI/SNF complexes [113–116]. These findings further deepen our understanding of the chromatin remodeling mechanism of SWI/SNF complexes and the function of their subunits. According to Chen et al., SWI/SNF complexes can be divided into three modules: the motor module, actin-related protein (ARP) module, and substrate recruitment module (SRM) [117]. SRM can be further divided into nucleosome binding lobe (NBL), DNA binding lobe (DBL), and histone-tail binding lobe (HBL) [117]. The central motor module is the ATPase, SMARCA4 (BRG1), and SMARCA2 (BRM), which directly hydrolyze ATP to translocate DNA [118]. The ARP module comprises actin beta (ACTB), BCL7, and actin-like 6 (ACTL6). They serve the dual function of connecting ATPase with SRM and regulating the ATPase activity. Within the nucleosome binding lobe, SMARCB1, coupled with double PHD fingers (DPF)

and SMARCC, attaches directly to the nucleosome acidic patch via the C-terminal domain (CTD) [119]. The DNA binding lobe interacts with extranucleosomal linker DNA and various factors. This lobe consists of several DNA binding domains like the HMG-box domain on SMARCE1 and polybromo 1 (PBRM1) [120], AT-rich interaction domain (ARID) on ARID1A/B, and ARID2 [121].

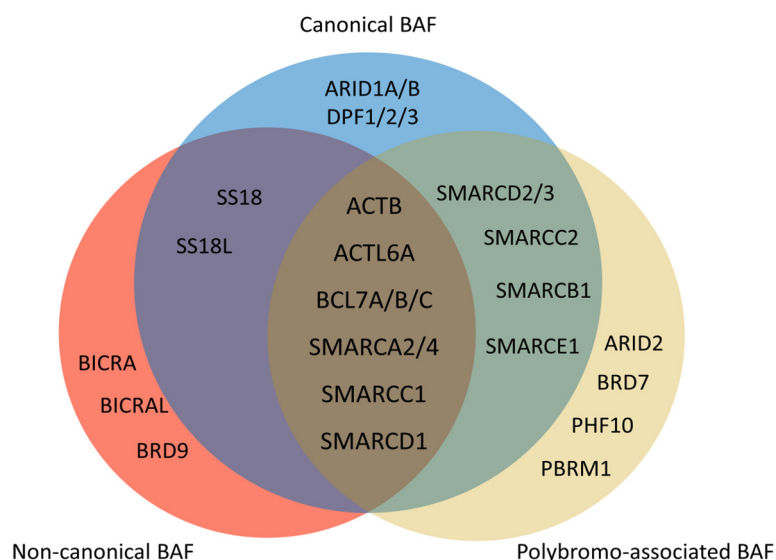


Figure 3. Composition of mammalian SWI/SNF complexes. The mammalian SWI/SNF chromatin remodeling complexes exist in three distinct types of assemblies: canonical BAF (cBAF), non-canonical BAF (ncBAF), and polybromo-associated BAF (PBAF). All three share several common subunits, such as the ATPase SMARCA2/4 and the ARP module (which includes ACTB, ACTL6A, and BCL7A/B/C). There are several differences between three types of assemblies. ARID1A/B and DPF1/2/3 only exist in cBAF. There are ARID2, BRD7, PHF10, and PBRM1 but no SS18/SS18L in PBAF. Non-canonical BAF possesses BICRA, BICRAL, and BRD9, and lacks SMARCC2, SMARCD2/3, SMARCB1, and SMARCE1.

Table 2. SWI/SNF complex subunit HUGO name and common name.

HUGO Name	Common Name
SMARCC1	BAF155, SRG3
SMARCC2	BAF170
SMARCD1/2/3	BAF60A/B/C
SMARCB1	BAF47, INI1
SMARCE1	BAF57
ARID1A/B	BAF250A/B
ARID2	BAF200
PHF10	BAF45A
DPF1/2/3	BAF45B/D/C
BICRA/BICRAL	GLTSCR1/GLTSCR1L
SMARCA4	BRG1
SMARCA2	BRM
ACTL6A/B	BAF53A/B
PBRM1	BAF180

Of note, multiple interactors of SWI/SNF complexes exist to orchestrate gene transcription (some interactions validated by the GST pull-down assay are listed in Table 3). The SMARCD family, including SMARCD1, SMARCD2, and SMARCD3, are reported to mediate the interactions between the SWI/SNF complex and various factors, such as PPARγ coactivator 1α (PGC1α) and CCAAT enhancer binding protein ε (CEBPε) [122,123].

Recently, Wolf et al. [124] fused TurboID [125] with SMARCD1 and revealed close associations of the SWI/SNF complex with various transcription factors and epigenetic machinery, including lysine-specific methyltransferase 2 (KMT2) family, nuclear receptor coactivator (NCOA) family and histone acetyltransferases (HATs). The SWI/SNF complex can also recognize histone modifications. The bromodomains within its subunit BRD7/9, SMARCA4, SMARCA2, and PBRM1 facilitate their binding to acetylated histones [126]. The chromodomains on the subunit SMARCC1 and SMARCC2 recognize methylated H3 [127]. Given their sophisticated structure and interactors, it is speculated that the whole complexes remodel the chromatin at precise locations and accurate time points.

Table 3. SWI/SNF subunit-interacting proteins validated by GST pull-down assay.

Interactor	SWI/SNF Subunit	Reference
AR	SMARCC1	[128]
CBP	SMARCA4	[129]
ER α	SMARCD1	[130]
ER α	SMARCD3	[131]
FOS	SMARCD1	[132]
JUN	SMARCD1	[132]
JUN	SMARCD3	[131]
MYC	SMARCA2	[133]
MYC	SMARCA4	[133]
MYC	SMARCB1	[133]
MYC	SMARCE1	[133]
Myocardin	SMARCD3	[134]
NCOA1	ARID1	[135]
NCOA1	SMARCC1	[128]
NCOA1	SMARCE1	[135,136]
Nkx2-5	SMARCD3	[134]
NR3C1/GR	SMARCD1	[130]
NR3C1/GR	SMARCE1	[130]
PCG1 α	SMARCD1	[123]
PPAR γ	SMARCD1	[123]
PPAR γ	SMARCD3	[131]
PRMT5	SMARCB1	[133]
PRMT5	SMARCE1	[133]
RAR	SMARCD3	[135]
RBP-J	SMARCD3	[137]
ROR α	SMARCD3	[131]
RXR	SMARCD3	[131,135]
SREBP1 α	SMARCD3	[131]
Tbx5	SMARCD3	[134,137]

5. SWI/SNF Complex in Cardiovascular Development

Coffin–Siris syndromes (CSSs) represent congenital disorders predominantly linked to mutations in the subunits of SWI/SNF complexes and are characterized by mental retardation [138]. *ARID1B* is responsible for CSS1, with *ARID1A* for CSS2, *SMARCB1* for CSS3, *SMARCA4* for CSS4, *SMARCE1* for CSS5, *ARID2* for CSS6, *DPF2* for CSS7, *SMARCC2* for CSS8, *SMARCD1* for CSS11, and *BICRA* for CSS12. Recently, more phenotypes in the cardiovascular system have been noticed in CSS patients [139]. Among fetuses, 67% of patients present cardiac anomalies, and 53% of patients present vascular anomalies [140]. For instance, one case study has reported that one fetus with *SMARCC2* deficiency was diagnosed with tetralogy of Fallot, a rare congenital disease caused by a combination of four heart defects [141]. Considering the lethality of cardiovascular anomaly and the higher possibility of termination due to poor prognosis, the actual incidence of cardiovascular complications in CSS might be underestimated.

Over decades of research on the mammalian SWI/SNF complex, numerous animal models have been developed. In the mouse model, *SMARCA4* null embryo dies at day three

due to the arrest of differentiation [142], while *SMARCA2* knockout mice are viable [143]. This indicates that the roles of *SMARCA4* and *SMARCA2* differ in development. As an essential subunit in the SWI/SNF complex, *DPF3* is highly expressed in the heart and skeletal muscle and serves as a histone modification reader. *DPF3* possesses 2 plant homeodomains (PHDs), which facilitate its binding with acetylated H3 and H4, and H3K4me1/2. Knockdown *dpf3* in the zebrafish leads to irregular cardiac morphology and muscular fiber disarray [144]. Constitutive knockout of *BIRCA* (*BRD4 interacting chromatin remodeling complex associated protein*) (also known as *GLTSCR1* (*glioma tumor suppressor candidate region gene 1*)) results in embryonic lethality and cardiac defects, including ventricular septal defect, double outlet right ventricle and a thinner ventricular wall [145]. These results indicate the indispensable roles of the SWI/SNF complex in the development of the cardiovascular system.

6. *SMARCA4* and *SMARCA2* in VSMC Biology and Cardiovascular Diseases

SMARCA4 and *SMARCA2* (also called *Brg1* and *Brm*, respectively) are the two mutually exclusive ATPase subunits of the SWI/SNF complex, which hydrolyze ATP to provide energy for the complex to remodel chromatin. Emerging evidence from early cardiovascular studies illuminates the potential significance of the *SMARCA* family in VSMC. In 2003, Chang et al. [54] found that SMC-enriched protein cysteine and glycine-rich protein (*CSRP*) 1/2 bridge SRF with *GATA4/5/6* to promote SMC contractile protein expression in pluripotent 10T1/2 fibroblasts, while skeletal-muscle-enriched *CSRP3* inhibits this transition to VSMC. Further study in 2007 [55] found that *CSRP2* overexpression in adult cardiomyocytes promotes SMC-specific marker gene expression. At VSMC marker promoters, such as *MYH11* and *Calponin* (*CNN1*), an interplay of SRF, p300, and varying histone modifications was observed. Notably, *SMARCA4* and *SMARCB1*, but not *SMARCA2*, were recruited, underlining the significance of the SWI/SNF complex in SMC marker gene expression in adult cardiomyocytes. Interestingly, the interaction between *CSRP* and the SWI/SNF complex is also captured via *SMARCD1*-TurboID in the abovementioned study [124].

Following Chang's work, Herring and his colleagues conducted a series of studies investigating the roles of *SMARCA4* in VSMCs. They employed a special cell line called B22 cells derived from NIH-3T3 fibroblast, which express a dominant-negative *SMARCA4* (DN-*SMARCA4*) induced by tetracycline withdrawal [146]. In this system, the increase in contractile genes via overexpression of myocardin-related transcription factor (MRTFA) is attenuated by DN-*SMARCA4*. Notably, MRTFA promotes contractile protein expression in cervical cancer HeLa cells but not in adrenal carcinoma SW13 cells, as the latter lacks *SMARCA4* or *SMARCA2*. When *SMARCA4* or *SMARCA2* is overexpressed in SW13, the ability of MRTFA to promote contractile protein expression is restored. Furthermore, DN-*SMARCA4* led to a decrease in contractile protein expression in primary colon SMCs. Through in vitro investigations, it was proved that *SMARCA4* directly binds with MRTFA but not with SRF. DN-*SMARCA4* significantly interferes with SRF binding [42]. Similarly, *SMARCA4* interacts with myocardin and permits its effect on contractile proteins [43]. *SMARCA4* also regulates miR-143 and miR-145 expression in conjunction with myocardin or MRTFA. Only when *SMARCA4* and myocardin or MRTFA are coexpressed in the SW13 cells can SRF be recruited to CArG elements in the promoter of miR-143/145 [147]. Among all the SRF targets, *ACTA2* is a special case that offers profound insight, as it appears to be less susceptible to the influence of *SMARCA* loss. *ACTA2* is already highly expressed in the B22 cells, and SRF binding at its promoters is much higher than that of *MYLK* and *TAGLN*. When MRTFA or myocardin is induced, SRF binding at the *ACTA2* promoter and *ACTA2* expression are increased. DN-*SMARCA4* did not attenuate the effect of MRTFA or myocardin for *ACTA2*. This indicates a possibility that the *ACTA2* promoter in B22, fibroblasts, and SMCs remains accessible for SRF binding. The loss of *SMARCA4* does not close this region, and MRTFA or myocardin can still effectively promote *ACTA2* expression.

Herring and his colleagues further specifically knocked out *Smarca4* with or without *Smarca2* in SMCs using SMMHC-Cre. About 33% of SMC-*Smarca4* knockout mice demonstrate cardiopulmonary abnormalities, including defects in the cardiac outflow tract, patent ductus arteriosus (PDA), and ventricular septal defect (VSD). Those defects are coupled with cyanosis and elevated neonatal mortality rates. In addition, striking phenotypes are noticed in the gastrointestinal (GI) tract. They found that SMC-*Smarca4*/*Smarca2* double knockout mice died within two weeks after birth, with dilated intestines. While SMC-*Smarca4* knockout mice consistently showed enlarged intestines, the SMC-*Smarca2* knockout mice demonstrated relatively fewer aberrations. Consistently, contractile proteins are significantly decreased in the SMC derived from surviving SMC-*Smarca4* knockout and double knockout mice, including telokin, Myh11, Cnn1, Tagln, and Acta2. Moreover, SMCs exhibited increased apoptosis and decreased proliferation [148].

Additionally, compelling evidence suggests that SMARCA4 and SMARCA2 regulate VSMC proliferation and inflammation. Endothelin 1 (ET-1) enhances VSMC contraction, proliferation, and inflammation in VSMCs, playing multifaceted roles in CVD [149]. ET-1 was found to increase the expression of *SMARCA4* in rat aortic smooth muscle cells, while this can be attenuated by NaHS. Overexpression of *Smarca4* promotes VSMC proliferation and the expression of *Ntf3*, *Pcna*, and *Pdgfra*. *Smarca4* binds at the promoters of those genes and modulates DNA accessibility [150]. SMARCA4 and SMARCA2 are critical for activating inflammatory genes, including *IL6*, *IL1β*, and *CCL2*, particularly when stimulated by ET-1 in VSMCs. A luciferase assay revealed that the binding of SMARCA4 and SMARCA2 at the promoters of those genes is increased in VSMC in response to ET-1 [151].

Additional evidence further indicates the roles of SMARCA4 in CVD. Several groups have reported an increase in SMARCA4 in the human standard type A aortic dissection specimens [152–154]. To mimic different types of heritable thoracic aortic aneurysm (TAA), two pathologic variants, *TGFR2*^{G357W} and *ACTA2*^{R179H}, were, respectively, overexpressed in human aortic VSMC. Consistent with the patient's specimen carrying that allele, contractile genes, including *smoothelin-1* (*SMTN1*), *CNN1*, *vinculin* (*VCL1*), and *Tagln*, are decreased, while HDAC9 is increased, especially in the nucleus. In this model, SMARCA4 is indispensable for HDAC9 and EZH2 binding at the promoters of contractile genes, which are then repressed [155]. In the ligation-induced carotid artery model, *SMARCA4* is also significantly increased in the adventitial SCA1⁺ smooth muscle cells (AdvSca1-SM). Oral administration of SMARCA4/SMARCA2 inhibitor PFI-3 can rescue ligation-induced vascular remodeling and inflammatory cell infiltration. Perivascular administration of SMARCA4 shRNA attenuates adventitial expansion and vascular fibrosis. Under normal or TGFβ-stimulated conditions, PFI-3 decreases Myh11, Cnn1, and Acta2 expression, indicating essential roles of SMARCA4/SMARCA2. The cleavage under targets and release using nuclease (CUT&RUN) assay reveals that, in the presence of PFI-3, the binding of SMARCA4 and the level of H3K27Ac at the *Acta2* promoter are reduced [156].

A prevailing controversy exists that SMARCA4 augments the expression of contractile proteins in vitro, but SMARCA4 increases with contraction protein decrease in human TAA samples. Since SMARCA4 and SMARCA2 constitute all SWI/SNF complexes, they might collaborate with diverse factors to activate and repress genes [157]. SMARCA may serve as a universal subunit for different regulations in the process of vascular diseases.

7. Roles of the SMARCD Family in VSMC

The human SMARCD family was first cloned and identified in 1996, with specific tissue distributions observed. Of note, SMARCD1 is universally distributed, SMARCD2 is predominantly expressed in the pancreas, and SMARCD3 is primarily found in the heart and skeletal muscle [158]. All three SWI/SNF complexes contain only one of the three SMARCD subunits: ncBAF only has SMARCD1, whereas cBAF and PBAF can contain any one of the three SMARCD members. SMARCD1-3 is one of the core subunits in the SWI/SNF complex. Knockout of SMARCDs disrupts the engagement of the ARID family and ATPase to the complex core [109].

The roles of the SMARCD family in myogenesis are extensively documented [159]. *Smarcd3* participates in the early myogenesis in zebrafish [160]. Myoblast determination protein 1 (MyoD) stands as a pioneering transcription factor in myogenesis, initiating muscular cell differentiation, binding to closed chromatin, and aiding subsequent binding of other transcription factors. SMARCD3 and SMARCA4 interact with MyoD and bind at the promoter of myogenin, a muscle-specific transcription factor. The binding of MyoD at the promoter of Myogenin is facilitated by SMARCD3. SMARCD3 phosphorylation mediated by p38 α is indispensable for SMARCA4 recruitment and muscle subsequent differentiation [161].

The roles of SMARCD3 in cardiovascular development were first reported in 2004 [162]. Bruneau and his colleague found that SMARCD3 is expressed in the early stages of cardiac development. *Smarcd3* KO causes abnormal cardiac development, including shortened outflow tract, hypoplastic atrium and ventricle, and left–right asymmetry [137,162]. In zebrafish, *Smarcd3* cooperates with Gata5 (a functional homolog of mammalian Gata4) and T-box transcription factor 5 (Tbx5) to promote cardiac development [163]. Cardiac defects are found in both *Smarcd3* constitutive KO and cardiac-specific KO models driven by *Nkx2-5* or *Myh6* Cre [134].

SMARCD3 interacts with transcription factors to regulate cardiac developmental markers. Knockdown of *Smarcd3* reduces natriuretic peptide A (NPPA), a cardiac differentiation marker. Additionally, NPPA–luciferase reporter is synergistically transactivated by TBX5, NKX2-5, GATA4, and SMARCD3, and this activation is blocked when SMARCA4 is depleted. Moreover, the interaction between SMARCA4 and either TBX5 or NKX2-5 is critically dependent on SMARCD3. This aligns with other studies suggesting that SMARCD3 facilitates the interaction between transcription factors and the SWI/SNF complex [162]. Transient induction of *Smarcd3* along with *Tbx5*, *Nkx2-5*, and *Gata4* in the mouse embryo induces ectopic expression of cardiac marker *actin alpha cardiac muscle 1 (Actc1)*, *myosin light chain 2 (Myl2)*, *troponin T2 (TNNT2)* in the mesoderm non-cardiac cells [164]. Furthermore, ectopic cardiac myocytes are found to be beating, which indicates the existence of a full contraction machinery. Notably, Gata4 and *Smarcd3* interaction can induce the expression of *Actc1*, although the beating phenomenon is not observed. The addition of Tbx5 is required for the ectopic cardiac myocyte to beat. Moreover, *Smarcd3* is essential for guiding Gata4 to its subsequent targets [164].

Although several studies have demonstrated the critical roles of SMARCD3 in developing skeletal muscle and cardiomyocytes, its contribution to VSMC biology was first reported in 2012. Sohni et al. [165] used rat multipotent adult progenitor cells (rMAPCs) as a platform. These cells exhibit the capability to differentiate into SMCs in MAPC basal medium supplemented with TGF β 1 and PDGFBB without the presence of Fetal bovine serum (FBS). During this differentiation process, the expression of *Smarcd3* and *Myocardin* is increased, along with the increase in contractile markers, including *Cnn1*, *Tagln*, *Smtn*, *Acta2*, and *Myh11*. They found that *Smarcd3* is indispensable for the expression of *Tagln* and *Acta2*. Moreover, the elevation of *Smarcd3* induced by TGF β 1 in rMAPC can be subdued by the Smad3-specific inhibitor and TGF β receptor inhibitor. When the Smad3 binding element (SBE) upstream of *Smarcd3* is mutated, TGF β can no longer promote *Smarcd3*-luciferase activity, indicating that *Smarcd3* is indeed regulated by TGF β via Smad3 signaling. Moreover, *Smarcd3* can interact with Srf and CARG elements in the promoters of *Acta2* and *Tagln*. This interaction indicates that SMARCD3 serves as a coactivator for SRF to promote the expression of contractile proteins.

Another SMARCD family member, SMARCD1, is also identified in the vascular system [166]. In primary rat VSMCs, free fatty acid (FFA, mixture of oleic acid, and palmitic acid) decreases *Smarcd1* in a dose- and time-dependent manner. With gain- and loss-of-function approaches, *Smarcd1* was found to promote the expression of clock genes, including *Bmal1* (*basic helix-loop-helix ARNT like 1*), *Clock*, and *Dbp* (*D-box binding PAR bZIP transcription factor*). Notably, both overexpression and knockdown of *Smarcd1* only modulate the basal expression levels of these clock genes without affecting their circadian

patterns. ROR α has been identified to bind with *Smarcd1*, mediating the expression of *Bmal1*. Overexpression of *Smarcd1* results in increased levels of H3Ac and H3K4me3 and decreased H3K9me2 at the ROR-binding sites (RORE). Furthermore, overexpression of *SMARCD1* inhibits FFA-induced Erk phosphorylation and prevents VSMC proliferation and migration [166]. In 2020, we found that *SMARCD1* is significantly upregulated in the human abdominal aortic aneurysm (AAA) specimen and AAA tissues from the mouse model [167]. SMC-specific *Smarcd1* knockout mice exhibit a dramatic decrease in AAA incidence and maximal diameter in both AAA models induced by elastase and Angiotensin II with hypercholesterolemia. Extracellular matrix (ECM) degradation and related proteases, including cathepsin S, matrix metalloproteinase-2 (MMP2), and MMP9, are significantly reduced in the *Smarcd1*^{SMKO} AAA specimen. We also observed reduced infiltration of Mac2⁺ macrophages and decreased levels of MCP-1 and IL-6 in the serum. Knockdown and overexpression of *SMARCD1* in the human aortic smooth muscle cell (HASMC) demonstrates that NF- κ B downstream inflammatory genes, including *TNF α* , *IL1 α* , and *IL1 β* , are modulated by *SMARCD1*. ChIP-seq data showed reduced *SMARCA4* binding at the TSS of NF- κ B downstream genes, accompanied by decreased active histone markers, H3K9Ac and H3K27Ac. Interaction between p300 and *SMARCA4* is also decreased when *SMARCD1* is knocked down.

Of note, *SMARCD3* exhibits the opposite effects in AAA pathogenesis in mouse models [44]. Microarray data indicate that *SMARCD3* is significantly reduced in human AAA samples [168]. In the scRNAseq analysis of the mouse AAA model, *Smarcd3* decreased specifically in VSMC [169]. SMC-specific *Smarcd3* knockout (*Smarcd3*^{SMKO}) mice showed higher AAA incidence and larger maximal diameters, accompanied by significant increases in ECM degradation, lymphocyte, and macrophage infiltration in the aortic wall [44]. Consistent with previous studies [165], *SMARCD3* is essential for contractile gene expression in the VSMC. SRF and *SMARCA4* binding at the promoters and H3K9Ac and H3K27Ac at the TSS of contractile genes are all regulated by *SMARCD3*. *SMARCD3* is also required for interaction among SWI/SNF complex, SRF, and p300.

In addition, *SMARCD3* knockdown increases VSMC apoptosis [44]. Knockdown of *SMARCD3* decreases the expression of the anti-apoptotic gene *BCL2*. ChIP-seq and the ChIP assay demonstrate decreased *SMARCA4*, H3K9ac, and H3K27Ac binding at the *KLF5* binding region within the promoter of *BCL2*. Knockdown of *SMARCD3* also reduces *KLF5* binding at the promoter and its interaction with *SMARCA4*. In human pulmonary artery smooth muscle cells, prostate cancer cells, and colorectal cancer cells, *KLF5* was found to serve as a protector against apoptosis, which induces antiapoptotic genes, including *BCL2*, *baculoviral IAP repeat containing 5 (BIRC5)* and repress pro-apoptotic genes like *BCL2 associated X (BAX)* [170–172]. Our study uniquely highlights the pivotal role of *SMARCD3* and the SWI/SNF complex in regulating VSMC apoptosis through *KLF5* [44]. In alignment with our findings, *SMARCD3* has been identified as a crucial factor for the survival of pancreatic ductal adenocarcinoma (PDAC) stem cells. We speculate that those cancer cells hijack the *SMARCD3/KLF5* pathway to resist apoptosis [173].

8. Concluding Remarks and Future Directions

Research on VSMCs has evolved from studying physiological functions and contractile machinery to exploring transcription and epigenetic regulation. With its intricate plasticity mechanisms, this unique cell type likely holds the therapeutic potential for CVD.

The SWI/SNF complex has been identified as a target for an increasing number of drugs in cancer research [174]. For instance, Xiao et al. [175] found that androgen receptor (AR) and forkhead box A1 (FOXA1)-positive prostate cancer cells are sensitive to proteolysis-targeting chimera (PROTAC) degrader against *SMARCA4* and *SMARCA2*. In VSMCs, however, *SMARCA4* is essential for simultaneously expressing contractile proteins and inflammatory genes. Therefore, *SMARCA4* and *SMARCA2* are not ideal targets for cardiovascular disease treatment. Of note, the knockout of *SMARCD1* in VSMC prevents inflammation and AAA formation [167]. Several studies have also highlighted the role

of BRD9 in inflammation in β cells [176] and macrophages [177–179]. BRD9 is a unique subunit in ncBAF, while SMARCD1 is the only SMARCD family member in ncBAF. Since both BRD9 and SMARCD1 promote inflammation, we speculate that ncBAF plays an important role in inflammation in VSMC. Inhibitors targeting BRD9 or SMARCD1 hold promising potential for mitigating inflammation and addressing associated CVD.

It is crucial to comprehensively investigate the functions of specific SWI/SNF subunits or complexes in VSMC. There are three major complexes, encompassing 9–16 subunit families with over 1000 potential combinations. The diversity of the SWI/SNF complex determines the diversity of its targets and functions. As mentioned above, we have demonstrated the opposite functions of SMARCD1 and SMARCD3 in VSMC and AAA formation [44,167]. Contradicting functions between SMARCD1 and SMARCD3 have also been reported in skeletal muscle differentiation and metabolism regulation [180–182]. However, the role of the remaining family member, SMARCD2, in VSMC remains to be elucidated. It has been reported that SMARCD2, but not SMARCD1, partially functions as SMARCD3 in cardiomyocyte differentiation [164]. Interestingly, during in vitro differentiation of VSMC and cardiomyocyte, there is a decrease in SMARCD1 and SMARCD2, along with an increase in SMARCD3 [183,184]. It is still unknown whether SMARCD2 shares similar functions with SMARCD3 or SMARCD1 or possesses unique functions in VSMC biology. Further studies are essential for advancing our understanding of the intricate epigenetic regulation governing VSMC biology and associated vascular diseases.

Funding: This research was funded by National Institutes of Health grants, grant numbers HL153710 and HL138139 (J.Z.), HL109946 and HL162294 (Y.E.C.), HL172832 (G.Z.); grants from the American Heart Association, 936135 (G.Z.).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Pease, D.C.; Paule, W.J. Electron microscopy of elastic arteries; the thoracic aorta of the rat. *J. Ultrastruct. Res.* **1960**, *3*, 469–483. [[CrossRef](#)] [[PubMed](#)]
2. Geer, J.C.; McGill, H.C.; Strong, J.P. The fine structure of human atherosclerotic lesions. *Am. J. Pathol.* **1961**, *38*, 263–287. [[PubMed](#)]
3. Still, W.J.; O’Neal, R.M. Electron microscopic study of experimental atherosclerosis in the rat. *Am. J. Pathol.* **1962**, *40*, 21–35. [[PubMed](#)]
4. Parker, F. An Electron Microscopic Study of Experimental Atherosclerosis. *Am. J. Pathol.* **1960**, *36*, 19–53.
5. Basatemur, G.L.; Jorgensen, H.F.; Clarke, M.C.H.; Bennett, M.R.; Mallat, Z. Vascular smooth muscle cells in atherosclerosis. *Nat. Rev. Cardiol.* **2019**, *16*, 727–744. [[CrossRef](#)] [[PubMed](#)]
6. Bennett, M.R.; Sinha, S.; Owens, G.K. Vascular Smooth Muscle Cells in Atherosclerosis. *Circ. Res.* **2016**, *118*, 692–702. [[CrossRef](#)] [[PubMed](#)]
7. Landerholm, T.E.; Dong, X.R.; Lu, J.; Belaguli, N.S.; Schwartz, R.J.; Majesky, M.W. A role for serum response factor in coronary smooth muscle differentiation from proepicardial cells. *Development* **1999**, *126*, 2053–2062. [[CrossRef](#)]
8. Wang, D.; Chang, P.S.; Wang, Z.; Sutherland, L.; Richardson, J.A.; Small, E.; Krieg, P.A.; Olson, E.N. Activation of cardiac gene expression by myocardin, a transcriptional cofactor for serum response factor. *Cell* **2001**, *105*, 851–862. [[CrossRef](#)]
9. Shankman, L.S.; Gomez, D.; Cherepanova, O.A.; Salmon, M.; Alencar, G.F.; Haskins, R.M.; Swiatlowska, P.; Newman, A.A.; Greene, E.S.; Straub, A.C.; et al. KLF4-dependent phenotypic modulation of smooth muscle cells has a key role in atherosclerotic plaque pathogenesis. *Nat. Med.* **2015**, *21*, 628–637. [[CrossRef](#)]
10. Owens, G.K. Regulation of differentiation of vascular smooth muscle cells. *Physiol. Rev.* **1995**, *75*, 487–517. [[CrossRef](#)]
11. Brozovich, F.V.; Nicholson, C.J.; Degen, C.V.; Gao, Y.Z.; Aggarwal, M.; Morgan, K.G. Mechanisms of Vascular Smooth Muscle Contraction and the Basis for Pharmacologic Treatment of Smooth Muscle Disorders. *Pharmacol. Rev.* **2016**, *68*, 476–532. [[CrossRef](#)] [[PubMed](#)]
12. Milewicz, D.M.; Trybus, K.M.; Guo, D.C.; Sweeney, H.L.; Regalado, E.; Kamm, K.; Stull, J.T. Altered Smooth Muscle Cell Force Generation as a Driver of Thoracic Aortic Aneurysms and Dissections. *Arterioscler. Thromb. Vasc. Biol.* **2017**, *37*, 26–34. [[CrossRef](#)] [[PubMed](#)]
13. Isselbacher, E.M.; Lino Cardenas, C.L.; Lindsay, M.E. Hereditary Influence in Thoracic Aortic Aneurysm and Dissection. *Circulation* **2016**, *133*, 2516–2528. [[CrossRef](#)] [[PubMed](#)]
14. Pinard, A.; Jones, G.T.; Milewicz, D.M. Genetics of Thoracic and Abdominal Aortic Diseases. *Circ. Res.* **2019**, *124*, 588–606. [[CrossRef](#)]
15. Sibinga, N.E.; Foster, L.C.; Hsieh, C.M.; Perrella, M.A.; Lee, W.S.; Endege, W.O.; Sage, E.H.; Lee, M.E.; Haber, E. Collagen VIII is expressed by vascular smooth muscle cells in response to vascular injury. *Circ. Res.* **1997**, *80*, 532–541. [[CrossRef](#)]

16. Niklason, L.E.; Lawson, J.H. Bioengineered human blood vessels. *Science* **2020**, *370*, eaaw8682. [[CrossRef](#)]
17. Cook, C.L.; Weiser, M.C.; Schwartz, P.E.; Jones, C.L.; Majack, R.A. Developmentally timed expression of an embryonic growth phenotype in vascular smooth muscle cells. *Circ. Res.* **1994**, *74*, 189–196. [[CrossRef](#)]
18. Pan, H.; Xue, C.; Auerbach, B.J.; Fan, J.; Bashore, A.C.; Cui, J.; Yang, D.Y.; Trignano, S.B.; Liu, W.; Shi, J.; et al. Single-Cell Genomics Reveals a Novel Cell State During Smooth Muscle Cell Phenotypic Switching and Potential Therapeutic Targets for Atherosclerosis in Mouse and Human. *Circulation* **2020**, *142*, 2060–2075. [[CrossRef](#)]
19. Wirka, R.C.; Wagh, D.; Paik, D.T.; Pjanic, M.; Nguyen, T.; Miller, C.L.; Kundu, R.; Nagao, M.; Collier, J.; Koyano, T.K.; et al. Atheroprotective roles of smooth muscle cell phenotypic modulation and the TCF21 disease gene as revealed by single-cell analysis. *Nat. Med.* **2019**, *25*, 1280–1289. [[CrossRef](#)]
20. Chappell, J.; Harman, J.L.; Narasimhan, V.M.; Yu, H.; Foote, K.; Simons, B.D.; Bennett, M.R.; Jørgensen, H.F. Extensive Proliferation of a Subset of Differentiated, yet Plastic, Medial Vascular Smooth Muscle Cells Contributes to Neointimal Formation in Mouse Injury and Atherosclerosis Models. *Circ. Res.* **2016**, *119*, 1313–1323. [[CrossRef](#)]
21. Mizrak, D.; Zhao, Y.; Feng, H.; Macaulay, J.; Tang, Y.; Sultan, Z.; Zhao, G.; Guo, Y.; Zhang, J.; Yang, B.; et al. Single-Molecule Spatial Transcriptomics of Human Thoracic Aortic Aneurysms Uncovers Calcification-Related CARTPT-Expressing Smooth Muscle Cells. *Arterioscler. Thromb. Vasc. Biol.* **2023**, *43*, 2285–2297. [[CrossRef](#)] [[PubMed](#)]
22. Allahverdian, S.; Chehroudi, A.C.; McManus, B.M.; Abraham, T.; Francis, G.A. Contribution of intimal smooth muscle cells to cholesterol accumulation and macrophage-like cells in human atherosclerosis. *Circulation* **2014**, *129*, 1551–1559. [[CrossRef](#)] [[PubMed](#)]
23. Wang, Y.; Dubland, J.A.; Allahverdian, S.; Asonye, E.; Sahin, B.; Jaw, J.E.; Sin, D.D.; Seidman, M.A.; Leeper, N.J.; Francis, G.A. Smooth Muscle Cells Contribute the Majority of Foam Cells in ApoE (Apolipoprotein E)-Deficient Mouse Atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **2019**, *39*, 876–887. [[CrossRef](#)] [[PubMed](#)]
24. Majesky, M.W.; Horita, H.; Ostriker, A.; Lu, S.; Regan, J.N.; Bagchi, A.; Dong, X.R.; Poczobutt, J.; Nemenoff, R.A.; Weiser-Evans, M.C. Differentiated Smooth Muscle Cells Generate a Subpopulation of Resident Vascular Progenitor Cells in the Adventitia Regulated by Klf4. *Circ. Res.* **2017**, *120*, 296–311. [[CrossRef](#)]
25. Rong, J.X.; Shapiro, M.; Trogan, E.; Fisher, E.A. Transdifferentiation of mouse aortic smooth muscle cells to a macrophage-like state after cholesterol loading. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 13531–13536. [[CrossRef](#)] [[PubMed](#)]
26. Feil, S.; Fehrenbacher, B.; Lukowski, R.; Essmann, F.; Schulze-Osthoff, K.; Schaller, M.; Feil, R. Transdifferentiation of vascular smooth muscle cells to macrophage-like cells during atherogenesis. *Circ. Res.* **2014**, *115*, 662–667. [[CrossRef](#)]
27. Davies, J.D.; Carpenter, K.L.H.; Challis, I.R.; Figg, N.L.; McNair, R.; Proudfoot, D.; Weissberg, P.L.; Shanahan, C.M. Adipocytic differentiation and liver x receptor pathways regulate the accumulation of triacylglycerols in human vascular smooth muscle cells. *J. Biol. Chem.* **2005**, *280*, 3911–3919. [[CrossRef](#)] [[PubMed](#)]
28. Durham, A.L.; Speer, M.Y.; Scatena, M.; Giachelli, C.M.; Shanahan, C.M. Role of smooth muscle cells in vascular calcification: Implications in atherosclerosis and arterial stiffness. *Cardiovasc. Res.* **2018**, *114*, 590–600. [[CrossRef](#)]
29. Proudfoot, D.; Skepper, J.N.; Shanahan, C.M.; Weissberg, P.L. Calcification of human vascular cells in vitro is correlated with high levels of matrix Gla protein and low levels of osteopontin expression. *Arterioscler. Thromb. Vasc. Biol.* **1998**, *18*, 379–388. [[CrossRef](#)]
30. Sorokin, V.; Vickneson, K.; Kofidis, T.; Woo, C.C.; Lin, X.Y.; Foo, R.; Shanahan, C.M. Role of Vascular Smooth Muscle Cell Plasticity and Interactions in Vessel Wall Inflammation. *Front. Immunol.* **2020**, *11*, 599415. [[CrossRef](#)]
31. Miano, J.M.; Fisher, E.A.; Majesky, M.W. Fate and State of Vascular Smooth Muscle Cells in Atherosclerosis. *Circulation* **2021**, *143*, 2110–2116. [[CrossRef](#)] [[PubMed](#)]
32. Allahverdian, S.; Chaabane, C.; Boukais, K.; Francis, G.A.; Bochaton-Piallat, M.L. Smooth muscle cell fate and plasticity in atherosclerosis. *Cardiovasc. Res.* **2018**, *114*, 540–550. [[CrossRef](#)] [[PubMed](#)]
33. Grootaert, M.O.J.; Bennett, M.R. Vascular smooth muscle cells in atherosclerosis: Time for a re-assessment. *Cardiovasc. Res.* **2021**, *117*, 2326–2339. [[CrossRef](#)]
34. Chen, Y.E. Vascular cell lineage determination and differentiation. *Arterioscler. Thromb. Vasc. Biol.* **2011**, *31*, 1467–1468. [[CrossRef](#)]
35. Mack, C.P. Signaling mechanisms that regulate smooth muscle cell differentiation. *Arterioscler. Thromb. Vasc. Biol.* **2011**, *31*, 1495–1505. [[CrossRef](#)] [[PubMed](#)]
36. Alexander, M.R.; Owens, G.K. Epigenetic control of smooth muscle cell differentiation and phenotypic switching in vascular development and disease. *Annu. Rev. Physiol.* **2012**, *74*, 13–40. [[CrossRef](#)] [[PubMed](#)]
37. Xie, C.; Ritchie, R.P.; Huang, H.; Zhang, J.; Chen, Y.E. Smooth muscle cell differentiation in vitro: Models and underlying molecular mechanisms. *Arterioscler. Thromb. Vasc. Biol.* **2011**, *31*, 1485–1494. [[CrossRef](#)] [[PubMed](#)]
38. Minty, A.; Kedes, L. Upstream regions of the human cardiac actin gene that modulate its transcription in muscle cells: Presence of an evolutionarily conserved repeated motif. *Mol. Cell. Biol.* **1986**, *6*, 2125–2136. [[CrossRef](#)]
39. Sartorelli, V.; Kurabayashi, M.; Kedes, L. Muscle-specific gene expression. A comparison of cardiac and skeletal muscle transcription strategies. *Circ. Res.* **1993**, *72*, 925–931. [[CrossRef](#)]
40. Boxer, L.M.; Prywes, R.; Roeder, R.G.; Kedes, L. The sarcomeric actin CARG-binding factor is indistinguishable from the c-fos serum response factor. *Mol. Cell. Biol.* **1989**, *9*, 515–522. [[CrossRef](#)]
41. Wang, Z.; Wang, D.Z.; Hockemeyer, D.; McAnally, J.; Nordheim, A.; Olson, E.N. Myocardin and ternary complex factors compete for SRF to control smooth muscle gene expression. *Nature* **2004**, *428*, 185–189. [[CrossRef](#)] [[PubMed](#)]

42. Zhang, M.; Fang, H.; Zhou, J.; Herring, B.P. A novel role of Brg1 in the regulation of SRF/MRTFA-dependent smooth muscle-specific gene expression. *J. Biol. Chem.* **2007**, *282*, 25708–25716. [[CrossRef](#)]
43. Zhou, J.; Zhang, M.; Fang, H.; El-Mounayri, O.; Rodenberg, J.M.; Imbalzano, A.N.; Herring, B.P. The SWI/SNF chromatin remodeling complex regulates myocardin-induced smooth muscle-specific gene expression. *Arterioscler. Thromb. Vasc. Biol.* **2009**, *29*, 921–928. [[CrossRef](#)] [[PubMed](#)]
44. Zhao, G.; Zhao, Y.; Lu, H.; Chang, Z.; Liu, H.; Wang, H.; Liang, W.; Liu, Y.; Zhu, T.; Rom, O.; et al. BAF60c prevents abdominal aortic aneurysm formation through epigenetic control of vascular smooth muscle cell homeostasis. *J. Clin. Investig.* **2022**, *132*. [[CrossRef](#)] [[PubMed](#)]
45. Zhou, J.; Herring, B.P. Mechanisms responsible for the promoter-specific effects of myocardin. *J. Biol. Chem.* **2005**, *280*, 10861–10869. [[CrossRef](#)] [[PubMed](#)]
46. Wang, D.Z.; Li, S.; Hockemeyer, D.; Sutherland, L.; Wang, Z.; Schratt, G.; Richardson, J.A.; Nordheim, A.; Olson, E.N. Potentiation of serum response factor activity by a family of myocardin-related transcription factors. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 14855–14860. [[CrossRef](#)] [[PubMed](#)]
47. Yoshida, T.; Gan, Q.; Shang, Y.; Owens, G.K. Platelet-derived growth factor-BB represses smooth muscle cell marker genes via changes in binding of MKL factors and histone deacetylases to their promoters. *Am. J. Physiol. Cell Physiol.* **2007**, *292*, C886–C895. [[CrossRef](#)] [[PubMed](#)]
48. Qiu, P.; Ritchie, R.P.; Fu, Z.; Cao, D.; Cumming, J.; Miano, J.M.; Wang, D.-Z.; Li, H.J.; Li, L. Myocardin enhances Smad3-mediated transforming growth factor-beta1 signaling in a CARG box-independent manner: Smad-binding element is an important cis element for SM22alpha transcription in vivo. *Circ. Res.* **2005**, *97*, 983–991. [[CrossRef](#)]
49. Charron, F.; Paradis, P.; Bronchain, O.; Nemer, G.; Nemer, M. Cooperative interaction between GATA-4 and GATA-6 regulates myocardial gene expression. *Mol. Cell. Biol.* **1999**, *19*, 4355–4365. [[CrossRef](#)]
50. Mano, T.; Luo, Z.; Malendowicz, S.L.; Evans, T.; Walsh, K. Reversal of GATA-6 downregulation promotes smooth muscle differentiation and inhibits intimal hyperplasia in balloon-injured rat carotid artery. *Circ. Res.* **1999**, *84*, 647–654. [[CrossRef](#)]
51. Wada, H.; Hasegawa, K.; Morimoto, T.; Kakita, T.; Yanazume, T.; Sasayama, S. A p300 protein as a coactivator of GATA-6 in the transcription of the smooth muscle-myosin heavy chain gene. *J. Biol. Chem.* **2000**, *275*, 25330–25335. [[CrossRef](#)] [[PubMed](#)]
52. Nishida, W.; Nakamura, M.; Mori, S.; Takahashi, M.; Ohkawa, Y.; Tadokoro, S.; Yoshida, K.; Hiwada, K.; Hayashi, K.; Sobue, K. A triad of serum response factor and the GATA and NK families governs the transcription of smooth and cardiac muscle genes. *J. Biol. Chem.* **2002**, *277*, 7308–7317. [[CrossRef](#)] [[PubMed](#)]
53. Kurz, J.; Weiss, A.C.; Lütke, T.H.; Deuper, L.; Trowe, M.O.; Thiesler, H.; Hildebrandt, H.; Heineke, J.; Duncan, S.A.; Kispert, A. GATA6 is a crucial factor for Myocd expression in the visceral smooth muscle cell differentiation program of the murine ureter. *Development* **2022**, *149*. [[CrossRef](#)] [[PubMed](#)]
54. Chang, D.F.; Belaguli, N.S.; Iyer, D.; Roberts, W.B.; Wu, S.P.; Dong, X.R.; Marx, J.G.; Moore, M.S.; Beckerle, M.C.; Majesky, M.W.; et al. Cysteine-rich LIM-only proteins CRP1 and CRP2 are potent smooth muscle differentiation cofactors. *Dev. Cell* **2003**, *4*, 107–118. [[CrossRef](#)]
55. Chang, D.F.; Belaguli, N.S.; Chang, J.; Schwartz, R.J. LIM-only protein, CRP2, switched on smooth muscle gene activity in adult cardiac myocytes. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 157–162. [[CrossRef](#)]
56. Yoshida, T.; Hoofnagle, M.H.; Owens, G.K. Myocardin and Prx1 contribute to angiotensin II-induced expression of smooth muscle alpha-actin. *Circ. Res.* **2004**, *94*, 1075–1082. [[CrossRef](#)] [[PubMed](#)]
57. Shang, Y.; Yoshida, T.; Amendt, B.A.; Martin, J.F.; Owens, G.K. Pitx2 is functionally important in the early stages of vascular smooth muscle cell differentiation. *J. Cell Biol.* **2008**, *181*, 461–473. [[CrossRef](#)] [[PubMed](#)]
58. Kawai-Kowase, K.; Kumar, M.S.; Hoofnagle, M.H.; Yoshida, T.; Owens, G.K. PIAS1 activates the expression of smooth muscle cell differentiation marker genes by interacting with serum response factor and class I basic helix-loop-helix proteins. *Mol. Cell. Biol.* **2005**, *25*, 8009–8023. [[CrossRef](#)]
59. Katoh, Y.; Molkentin, J.D.; Dave, V.; Olson, E.N.; Periasamy, M. MEF2B is a component of a smooth muscle-specific complex that binds an A/T-rich element important for smooth muscle myosin heavy chain gene expression. *J. Biol. Chem.* **1998**, *273*, 1511–1518. [[CrossRef](#)]
60. Nosedá, M.; Fu, Y.; Niessen, K.; Wong, F.; Chang, L.; McLean, G.; Karsan, A. Smooth Muscle alpha-actin is a direct target of Notch/CSL. *Circ. Res.* **2006**, *98*, 1468–1470. [[CrossRef](#)]
61. Tang, Y.; Urs, S.; Boucher, J.; Bernaiche, T.; Venkatesh, D.; Spicer, D.B.; Vary, C.P.; Liaw, L. Notch and transforming growth factor-beta (TGFbeta) signaling pathways cooperatively regulate vascular smooth muscle cell differentiation. *J. Biol. Chem.* **2010**, *285*, 17556–17563. [[CrossRef](#)]
62. Liu, Y.; Sinha, S.; McDonald, O.G.; Shang, Y.; Hoofnagle, M.H.; Owens, G.K. Kruppel-like factor 4 abrogates myocardin-induced activation of smooth muscle gene expression. *J. Biol. Chem.* **2005**, *280*, 9719–9727. [[CrossRef](#)] [[PubMed](#)]
63. Yoshida, T.; Gan, Q.; Owens, G.K. Kruppel-like factor 4, Elk-1, and histone deacetylases cooperatively suppress smooth muscle cell differentiation markers in response to oxidized phospholipids. *Am. J. Physiol. Cell Physiol.* **2008**, *295*, C1175–C1182. [[CrossRef](#)] [[PubMed](#)]
64. Salmon, M.; Gomez, D.; Greene, E.; Shankman, L.; Owens, G.K. Cooperative binding of KLF4, pELK-1, and HDAC2 to a G/C repressor element in the SM22alpha promoter mediates transcriptional silencing during SMC phenotypic switching in vivo. *Circ. Res.* **2012**, *111*, 685–696. [[CrossRef](#)] [[PubMed](#)]

65. Liu, Y.; Sinha, S.; Owens, G. A transforming growth factor-beta control element required for SM alpha-actin expression in vivo also partially mediates GSKF-dependent transcriptional repression. *J. Biol. Chem.* **2003**, *278*, 48004–48011. [[CrossRef](#)] [[PubMed](#)]
66. Cao, D.; Wang, Z.; Zhang, C.L.; Oh, J.; Xing, W.; Li, S.; Richardson, J.A.; Wang, D.Z.; Olson, E.N. Modulation of smooth muscle gene expression by association of histone acetyltransferases and deacetylases with myocardin. *Mol. Cell. Biol.* **2005**, *25*, 364–376. [[CrossRef](#)] [[PubMed](#)]
67. Chakraborty, R.; Ostriker, A.C.; Xie, Y.; Dave, J.M.; Gamez-Mendez, A.; Chatterjee, P.; Abu, Y.; Valentine, J.; Lezon-Geyda, K.; Greif, D.M.; et al. Histone Acetyltransferases p300 and CBP Coordinate Distinct Chromatin Remodeling Programs in Vascular Smooth Muscle Plasticity. *Circulation* **2022**, *145*, 1720–1737. [[CrossRef](#)] [[PubMed](#)]
68. Zhou, Y.; Sharma, S.; Sun, X.; Guan, X.; Hou, Y.; Yang, Z.; Shi, H.; Zou, M.H.; Song, P.; Zhou, J.; et al. SMYD2 regulates vascular smooth muscle cell phenotypic switching and intimal hyperplasia via interaction with myocardin. *Cell. Mol. Life Sci.* **2023**, *80*, 264. [[CrossRef](#)]
69. Lockman, K.; Taylor, J.M.; Mack, C.P. The histone demethylase, Jmjd1a, interacts with the myocardin factors to regulate SMC differentiation marker gene expression. *Circ. Res.* **2007**, *101*, e115–e123. [[CrossRef](#)]
70. Gan, Q.; Thiébaud, P.; Thézé, N.; Jin, L.; Xu, G.; Grant, P.; Owens, G.K. WD repeat-containing protein 5, a ubiquitously expressed histone methyltransferase adaptor protein, regulates smooth muscle cell-selective gene activation through interaction with pituitary homeobox 2. *J. Biol. Chem.* **2011**, *286*, 21853–21864. [[CrossRef](#)]
71. Li, N.; Subrahmanyam, L.; Smith, E.; Yu, X.; Zaidi, S.; Choi, M.; Mane, S.; Nelson-Williams, C.; Behjati, M.; Kazemi, M.; et al. Mutations in the Histone Modifier PRDM6 Are Associated with Isolated Nonsyndromic Patent Ductus Arteriosus. *Am. J. Hum. Genet.* **2016**, *98*, 1082–1091. [[CrossRef](#)] [[PubMed](#)]
72. Davis, C.A.; Haberland, M.; Arnold, M.A.; Sutherland, L.B.; McDonald, O.G.; Richardson, J.A.; Childs, G.; Harris, S.; Owens, G.K.; Olson, E.N. PRISM/PRDM6, a transcriptional repressor that promotes the proliferative gene program in smooth muscle cells. *Mol. Cell. Biol.* **2006**, *26*, 2626–2636. [[CrossRef](#)] [[PubMed](#)]
73. Chatterjee, P.; Chakraborty, R.; Xie, Y.; Sizer, A.; Hwa, J.; Martin, K.A. The Histone Methyl Transferase (SUV39H1) Promotes Smooth Muscle Cell Dedifferentiation. In *Arteriosclerosis, Thrombosis, and Vascular Biology*; 2022.
74. Liang, J.; Li, Q.; Cai, W.; Zhang, X.; Yang, B.; Li, X.; Jiang, S.; Tian, S.; Zhang, K.; Song, H.; et al. Inhibition of polycomb repressor complex 2 ameliorates neointimal hyperplasia by suppressing trimethylation of H3K27 in vascular smooth muscle cells. *Br. J. Pharmacol.* **2019**, *176*, 3206–3219. [[CrossRef](#)] [[PubMed](#)]
75. Lino Cardenas, C.L.; Kessinger, C.W.; MacDonald, C.; Jassar, A.S.; Isselbacher, E.M.; Jaffer, F.A.; Lindsay, M.E. Inhibition of the methyltransferase EZH2 improves aortic performance in experimental thoracic aortic aneurysm. *JCI Insight* **2018**, *3*. [[CrossRef](#)] [[PubMed](#)]
76. Ostriker, A.C.; Xie, Y.; Chakraborty, R.; Sizer, A.J.; Bai, Y.; Ding, M.; Song, W.L.; Huttner, A.; Hwa, J.; Martin, K.A. TET2 Protects Against Vascular Smooth Muscle Cell Apoptosis and Intimal Thickening in Transplant Vasculopathy. *Circulation* **2021**, *144*, 455–470. [[CrossRef](#)] [[PubMed](#)]
77. Liu, R.; Jin, Y.; Tang, W.H.; Qin, L.; Zhang, X.; Tellides, G.; Hwa, J.; Yu, J.; Martin, K.A. Ten-eleven translocation-2 (TET2) is a master regulator of smooth muscle cell plasticity. *Circulation* **2013**, *128*, 2047–2057. [[CrossRef](#)] [[PubMed](#)]
78. Zhu, N.; Guo, Z.-F.; Kazama, K.; Yi, B.; Tongmuang, N.; Yao, H.; Yang, R.; Zhang, C.; Qin, Y.; Han, L.; et al. Epigenetic regulation of vascular smooth muscle cell phenotypic switch and neointimal formation by PRMT5. *Cardiovasc. Res.* **2023**, *119*, 2244–2255. [[CrossRef](#)] [[PubMed](#)]
79. Shah, N.M.; Groves, A.K.; Anderson, D.J. Alternative neural crest cell fates are instructively promoted by TGFbeta superfamily members. *Cell* **1996**, *85*, 331–343. [[CrossRef](#)]
80. Hautmann, M.B.; Madsen, C.S.; Owens, G.K. A transforming growth factor beta (TGFbeta) control element drives TGFbeta-induced stimulation of smooth muscle alpha-actin gene expression in concert with two CARG elements. *J. Biol. Chem.* **1997**, *272*, 10948–10956. [[CrossRef](#)]
81. Janknecht, R.; Wells, N.J.; Hunter, T. TGF-beta-stimulated cooperation of smad proteins with the coactivators CBP/p300. *Genes Dev.* **1998**, *12*, 2114–2119. [[CrossRef](#)]
82. Narita, N.; Heikinheimo, M.; Bielinska, M.; White, R.A.; Wilson, D.B. The gene for transcription factor GATA-6 resides on mouse chromosome 18 and is expressed in myocardium and vascular smooth muscle. *Genomics* **1996**, *36*, 345–348. [[CrossRef](#)] [[PubMed](#)]
83. Yap, C.; Mieremet, A.; de Vries, C.J.M.; Micha, D.; de Waard, V. Six Shades of Vascular Smooth Muscle Cells Illuminated by KLF4 (Kruppel-Like Factor 4). *Arterioscler. Thromb. Vasc. Biol.* **2021**, *41*, 2693–2707. [[CrossRef](#)] [[PubMed](#)]
84. Adam, P.J.; Regan, C.P.; Hautmann, M.B.; Owens, G.K. Positive- and negative-acting Kruppel-like transcription factors bind a transforming growth factor beta control element required for expression of the smooth muscle cell differentiation marker SM22alpha in vivo. *J. Biol. Chem.* **2000**, *275*, 37798–37806. [[CrossRef](#)] [[PubMed](#)]
85. Yoshida, T.; Kaestner, K.H.; Owens, G.K. Conditional deletion of Kruppel-like factor 4 delays downregulation of smooth muscle cell differentiation markers but accelerates neointimal formation following vascular injury. *Circ. Res.* **2008**, *102*, 1548–1557. [[CrossRef](#)]
86. McDonald, O.G.; Wamhoff, B.R.; Hoofnagle, M.H.; Owens, G.K. Control of SRF binding to CARG box chromatin regulates smooth muscle gene expression in vivo. *J. Clin. Investig.* **2006**, *116*, 36–48. [[CrossRef](#)]

87. Manabe, I.; Owens, G.K. Recruitment of serum response factor and hyperacetylation of histones at smooth muscle-specific regulatory regions during differentiation of a novel P19-derived in vitro smooth muscle differentiation system. *Circ. Res.* **2001**, *88*, 1127–1134. [[CrossRef](#)]
88. Yoshida, T.; Sinha, S.; Dandré, F.; Wamhoff, B.R.; Hoofnagle, M.H.; Kremer, B.E.; Wang, D.Z.; Olson, E.N.; Owens, G.K. Myocardin is a key regulator of CARG-dependent transcription of multiple smooth muscle marker genes. *Circ. Res.* **2003**, *92*, 856–864. [[CrossRef](#)]
89. Pellegrini, L.; Tan, S.; Richmond, T.J. Structure of serum response factor core bound to DNA. *Nature* **1995**, *376*, 490–498. [[CrossRef](#)]
90. Luger, K.; Mader, A.W.; Richmond, R.K.; Sargent, D.F.; Richmond, T.J. Crystal structure of the nucleosome core particle at 2.8 Å resolution. *Nature* **1997**, *389*, 251–260. [[CrossRef](#)]
91. McDonald, O.G.; Owens, G.K. Programming smooth muscle plasticity with chromatin dynamics. *Circ. Res.* **2007**, *100*, 1428–1441. [[CrossRef](#)]
92. Gomez, D.; Shankman, L.S.; Nguyen, A.T.; Owens, G.K. Detection of histone modifications at specific gene loci in single cells in histological sections. *Nat. Methods* **2013**, *10*, 171–177. [[CrossRef](#)]
93. Liu, M.; Espinosa-Diez, C.; Mahan, S.; Du, M.; Nguyen, A.T.; Hahn, S.; Chakraborty, R.; Straub, A.C.; Martin, K.A.; Owens, G.K.; et al. H3K4 di-methylation governs smooth muscle lineage identity and promotes vascular homeostasis by restraining plasticity. *Dev. Cell* **2021**, *56*, 2765–2782.e10. [[CrossRef](#)] [[PubMed](#)]
94. Richmond, T.J.; Davey, C.A. The structure of DNA in the nucleosome core. *Nature* **2003**, *423*, 145–150. [[CrossRef](#)]
95. de la Serna, I.L.; Ohkawa, Y.; Imbalzano, A.N. Chromatin remodelling in mammalian differentiation: Lessons from ATP-dependent remodelers. *Nat. Rev. Genet.* **2006**, *7*, 461–473. [[CrossRef](#)] [[PubMed](#)]
96. Lessard, J.A.; Crabtree, G.R. Chromatin regulatory mechanisms in pluripotency. *Annu. Rev. Cell Dev. Biol.* **2010**, *26*, 503–532. [[CrossRef](#)]
97. Singhal, N.; Graumann, J.; Wu, G.; Araúzo-Bravo, M.J.; Han, D.W.; Greber, B.; Gentile, L.; Mann, M.; Schöler, H.R. Chromatin-Remodeling Components of the BAF Complex Facilitate Reprogramming. *Cell* **2010**, *141*, 943–955. [[CrossRef](#)] [[PubMed](#)]
98. Cairns, B.R. The logic of chromatin architecture and remodelling at promoters. *Nature* **2009**, *461*, 193–198. [[CrossRef](#)]
99. Clapier, C.R.; Cairns, B.R. The biology of chromatin remodeling complexes. *Annu. Rev. Biochem.* **2009**, *78*, 273–304. [[CrossRef](#)]
100. Stern, M.; Jensen, R.; Herskowitz, I. Five SWI genes are required for expression of the HO gene in yeast. *J. Mol. Biol.* **1984**, *178*, 853–868. [[CrossRef](#)]
101. Neigeborn, L.; Carlson, M. Genes affecting the regulation of SUC2 gene expression by glucose repression in *Saccharomyces cerevisiae*. *Genetics* **1984**, *108*, 845–858. [[CrossRef](#)]
102. Winston, F.; Carlson, M. Yeast SNF/SWI transcriptional activators and the SPT/SIN chromatin connection. *Trends Genet.* **1992**, *8*, 387–391. [[CrossRef](#)] [[PubMed](#)]
103. Kwon, H.; Imbalzano, A.N.; Khavari, P.A.; Kingston, R.E.; Green, M.R. Nucleosome disruption and enhancement of activator binding by a human SWI/SNF complex. *Nature* **1994**, *370*, 477–481. [[CrossRef](#)]
104. Wang, W.; Côté, J.; Xue, Y.; Zhou, S.; Khavari, P.A.; Biggar, S.R.; Muchardt, C.; Kalpana, G.V.; Goff, S.P.; Yaniv, M.; et al. Purification and biochemical heterogeneity of the mammalian SWI-SNF complex. *EMBO J.* **1996**, *15*, 5370–5382. [[CrossRef](#)] [[PubMed](#)]
105. Lemon, B.; Inouye, C.; King, D.S.; Tjian, R. Selectivity of chromatin-remodelling cofactors for ligand-activated transcription. *Nature* **2001**, *414*, 924–928. [[CrossRef](#)] [[PubMed](#)]
106. Alpsy, A.; Dykhuizen, E.C. Glioma tumor suppressor candidate region gene 1 (GLTSCR1) and its paralog GLTSCR1-like form SWI/SNF chromatin remodeling subcomplexes. *J. Biol. Chem.* **2018**, *293*, 3892–3903. [[CrossRef](#)] [[PubMed](#)]
107. Michel, B.C.; D’Avino, A.R.; Cassel, S.H.; Mashtalir, N.; McKenzie, Z.M.; McBride, M.J.; Valencia, A.M.; Zhou, Q.; Bocker, M.; Soares, L.M.M.; et al. A non-canonical SWI/SNF complex is a synthetic lethal target in cancers driven by BAF complex perturbation. *Nat. Cell Biol.* **2018**, *20*, 1410–1420. [[CrossRef](#)] [[PubMed](#)]
108. Wang, X.; Wang, S.; Troisi, E.C.; Howard, T.P.; Haswell, J.R.; Wolf, B.K.; Hawk, W.H.; Ramos, P.; Oberlick, E.M.; Tzvetkov, E.P.; et al. BRD9 defines a SWI/SNF sub-complex and constitutes a specific vulnerability in malignant rhabdoid tumors. *Nat. Commun.* **2019**, *10*, 1881. [[CrossRef](#)] [[PubMed](#)]
109. Mashtalir, N.; D’Avino, A.R.; Michel, B.C.; Luo, J.; Pan, J.; Otto, J.E.; Zullo, H.J.; McKenzie, Z.M.; Kubiak, R.L.; St Pierre, R.; et al. Modular Organization and Assembly of SWI/SNF Family Chromatin Remodeling Complexes. *Cell* **2018**, *175*, 1272–1288.e20. [[CrossRef](#)]
110. Tang, L.; Nogales, E.; Ciferri, C. Structure and function of SWI/SNF chromatin remodeling complexes and mechanistic implications for transcription. *Prog. Biophys. Mol. Biol.* **2010**, *102*, 122–128. [[CrossRef](#)]
111. Wu, J.I.; Lessard, J.; Crabtree, G.R. Understanding the words of chromatin regulation. *Cell* **2009**, *136*, 200–206. [[CrossRef](#)]
112. Otto, J.E.; Ursu, O.; Wu, A.P.; Winter, E.B.; Cuoco, M.S.; Ma, S.; Qian, K.; Michel, B.C.; Buenroostro, J.D.; Berger, B.; et al. Structural and functional properties of mSWI/SNF chromatin remodeling complexes revealed through single-cell perturbation screens. *Mol. Cell* **2023**, *83*, 1350–1367.e7. [[CrossRef](#)]
113. Mashtalir, N.; Suzuki, H.; Farrell, D.P.; Sankar, A.; Luo, J.; Filipovski, M.; D’Avino, A.R.; St Pierre, R.; Valencia, A.M.; Onikubo, T.; et al. A Structural Model of the Endogenous Human BAF Complex Informs Disease Mechanisms. *Cell* **2020**, *183*, 802–817.e24. [[CrossRef](#)] [[PubMed](#)]
114. He, S.; Wu, Z.; Tian, Y.; Yu, Z.; Yu, J.; Wang, X.; Li, J.; Liu, B.; Xu, Y. Structure of nucleosome-bound human BAF complex. *Science* **2020**, *367*, 875–881. [[CrossRef](#)] [[PubMed](#)]

115. Yuan, J.; Chen, K.; Zhang, W.; Chen, Z. Structure of human chromatin-remodelling PBAF complex bound to a nucleosome. *Nature* **2022**, *605*, 166–171. [[CrossRef](#)] [[PubMed](#)]
116. Wang, L.; Yu, J.; Yu, Z.; Wang, Q.; Li, W.; Ren, Y.; Chen, Z.; He, S.; Xu, Y. Structure of nucleosome-bound human PBAF complex. *Nat. Commun.* **2022**, *13*, 7644. [[CrossRef](#)]
117. Chen, K.; Yuan, J.; Sia, Y.; Chen, Z. Mechanism of action of the SWI/SNF family complexes. *Nucleus* **2023**, *14*, 2165604. [[CrossRef](#)]
118. Clapier, C.R.; Iwasa, J.; Cairns, B.R.; Peterson, C.L. Mechanisms of action and regulation of ATP-dependent chromatin-remodelling complexes. *Nat. Rev. Mol. Cell. Biol.* **2017**, *18*, 407–422. [[CrossRef](#)]
119. Valencia, A.M.; Collings, C.K.; Dao, H.T.; St Pierre, R.; Cheng, Y.C.; Huang, J.; Sun, Z.Y.; Seo, H.S.; Mashtalir, N.; Comstock, D.E.; et al. Recurrent SMARCB1 Mutations Reveal a Nucleosome Acidic Patch Interaction Site That Potentiates mSWI/SNF Complex Chromatin Remodeling. *Cell* **2019**, *179*, 1342–1356.e23. [[CrossRef](#)]
120. Stros, M.; Launholt, D.; Grasser, K.D. The HMG-box: A versatile protein domain occurring in a wide variety of DNA-binding proteins. *Cell. Mol. Life Sci. CMLS* **2007**, *64*, 2590–2606. [[CrossRef](#)]
121. Kim, S.; Zhang, Z.; Upchurch, S.; Isern, N.; Chen, Y. Structure and DNA-binding sites of the SWI1 AT-rich interaction domain (ARID) suggest determinants for sequence-specific DNA recognition. *J. Biol. Chem.* **2004**, *279*, 16670–16676. [[CrossRef](#)]
122. Priam, P.; Krasteva, V.; Rousseau, P.; D’Angelo, G.; Gaboury, L.; Sauvageau, G.; Lessard, J.A. SMARCD2 subunit of SWI/SNF chromatin-remodeling complexes mediates granulopoiesis through a CEBPvarepsilon dependent mechanism. *Nat. Genet.* **2017**, *49*, 753–764. [[CrossRef](#)] [[PubMed](#)]
123. Li, S.; Liu, C.; Li, N.; Hao, T.; Han, T.; Hill, D.E.; Vidal, M.; Lin, J.D. Genome-wide coactivation analysis of PGC-1alpha identifies BAF60a as a regulator of hepatic lipid metabolism. *Cell Metab.* **2008**, *8*, 105–117. [[CrossRef](#)] [[PubMed](#)]
124. Wolf, B.K.; Zhao, Y.; McCray, A.; Hawk, W.H.; Deary, L.T.; Sugiarto, N.W.; LaCroix, I.S.; Gerber, S.A.; Cheng, C.; Wang, X. Cooperation of chromatin remodeling SWI/SNF complex and pioneer factor AP-1 shapes 3D enhancer landscapes. *Nat. Struct. Mol. Biol.* **2023**, *30*, 10–21. [[CrossRef](#)] [[PubMed](#)]
125. Branon, T.C.; Bosch, J.A.; Sanchez, A.D.; Udeshi, N.D.; Svinkina, T.; Carr, S.A.; Feldman, J.L.; Perrimon, N.; Ting, A.Y. Efficient proximity labeling in living cells and organisms with TurboID. *Nat. Biotechnol.* **2018**, *36*, 880–887. [[CrossRef](#)] [[PubMed](#)]
126. Haynes, S.R.; Dollard, C.; Winston, F.; Beck, S.; Trowsdale, J.; Dawid, I.B. The bromodomain: A conserved sequence found in human, Drosophila and yeast proteins. *Nucleic Acids Res.* **1992**, *20*, 2603. [[CrossRef](#)] [[PubMed](#)]
127. Jacobs, S.A.; Khorasanizadeh, S. Structure of HP1 chromodomain bound to a lysine 9-methylated histone H3 tail. *Science* **2002**, *295*, 2080–2083. [[CrossRef](#)] [[PubMed](#)]
128. Hong, C.Y.; Suh, J.H.; Kim, K.; Gong, E.-Y.; Jeon, S.H.; Ko, M.; Seong, R.H.; Kwon, H.B.; Lee, K. Modulation of androgen receptor transactivation by the SWI3-related gene product (SRG3) in multiple ways. *Mol. Cell. Biol.* **2005**, *25*, 4841–4852. [[CrossRef](#)] [[PubMed](#)]
129. Naidu, S.R.; Love, I.M.; Imbalzano, A.N.; Grossman, S.R.; Androphy, E.J. The SWI/SNF chromatin remodeling subunit BRG1 is a critical regulator of p53 necessary for proliferation of malignant cells. *Oncogene* **2009**, *28*, 2492–2501. [[CrossRef](#)]
130. Hsiao, P.-W.; Fryer, C.J.; Trotter, K.W.; Wang, W.; Archer, T.K. BAF60a mediates critical interactions between nuclear receptors and the BRG1 chromatin-remodeling complex for transactivation. *Mol. Cell. Biol.* **2003**, *23*, 6210–6220. [[CrossRef](#)]
131. Debril, M.B.; Gelman, L.; Fayard, E.; Annicotte, J.S.; Rocchi, S.; Auwerx, J. Transcription factors and nuclear receptors interact with the SWI/SNF complex through the BAF60c subunit. *J. Biol. Chem.* **2004**, *279*, 16677–16686. [[CrossRef](#)]
132. Ito, T.; Yamauchi, M.; Nishina, M.; Yamamichi, N.; Mizutani, T.; Ui, M.; Murakami, M.; Iba, H. Identification of SWI/SNF complex subunit BAF60a as a determinant of the transactivation potential of Fos/Jun dimers. *J. Biol. Chem.* **2001**, *276*, 2852–2857. [[CrossRef](#)] [[PubMed](#)]
133. Pal, S.; Yun, R.; Datta, A.; Lacomis, L.; Erdjument-Bromage, H.; Kumar, J.; Tempst, P.; Sif, S. mSin3A/histone deacetylase 2- and PRMT5-containing Brg1 complex is involved in transcriptional repression of the Myc target gene cad. *Mol. Cell. Biol.* **2003**, *23*, 7475–7487. [[CrossRef](#)]
134. Sun, X.; Hota, S.K.; Zhou, Y.Q.; Novak, S.; Miguel-Perez, D.; Christodoulou, D.; Seidman, C.E.; Seidman, J.G.; Gregorio, C.C.; Henkelman, R.M.; et al. Cardiac-enriched BAF chromatin-remodeling complex subunit Baf60c regulates gene expression programs essential for heart development and function. *Biol. Open* **2018**, *7*, bio029512. [[CrossRef](#)] [[PubMed](#)]
135. Flajollet, S.; Lefebvre, B.; Cudejko, C.; Staels, B.; Lefebvre, P. The core component of the mammalian SWI/SNF complex SMARCD3/BAF60c is a coactivator for the nuclear retinoic acid receptor. *Mol. Cell Endocrinol.* **2007**, *270*, 23–32. [[CrossRef](#)] [[PubMed](#)]
136. Belandia, B.; Orford, R.L.; Hurst, H.C.; Parker, M.G. Targeting of SWI/SNF chromatin remodelling complexes to estrogen-responsive genes. *EMBO J.* **2002**, *21*, 4094–4103. [[CrossRef](#)] [[PubMed](#)]
137. Takeuchi, J.K.; Lickert, H.; Bisgrove, B.W.; Sun, X.; Yamamoto, M.; Chawengsaksophak, K.; Hamada, H.; Yost, H.J.; Rossant, J.; Bruneau, B.G. Baf60c is a nuclear Notch signaling component required for the establishment of left-right asymmetry. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 846–851. [[CrossRef](#)]
138. Tsurusaki, Y.; Okamoto, N.; Ohashi, H.; Kosho, T.; Imai, Y.; Hibi-Ko, Y.; Kaname, T.; Naritomi, K.; Kawame, H.; Wakui, K.; et al. Mutations affecting components of the SWI/SNF complex cause Coffin-Siris syndrome. *Nat. Genet.* **2012**, *44*, 376–378. [[CrossRef](#)]
139. van der Sluijs, P.J.; Jansen, S.; Vergano, S.A.; Adachi-Fukuda, M.; Alanay, Y.; AlKindy, A.; Baban, A.; Bayat, A.; Beck-Wödl, S.; Berry, K.; et al. The ARID1B spectrum in 143 patients: From nonsyndromic intellectual disability to Coffin-Siris syndrome. *Genet. Med.* **2019**, *21*, 1295–1307. [[CrossRef](#)]

140. van der Sluijs, P.J.; Joosten, M.; Alby, C.; Attié-Bitach, T.; Gilmore, K.; Dubourg, C.; Fradin, M.; Wang, T.; Kurtz-Nelson, E.C.; Ahlers, K.P.; et al. Discovering a new part of the phenotypic spectrum of Coffin-Siris syndrome in a fetal cohort. *Genet. Med.* **2022**, *24*, 1753–1760. [[CrossRef](#)]
141. Sun, H.; Zhang, S.; Wang, J.; Zhou, X.; Zhang, H.; Yang, H.; He, Y. Expanding the phenotype associated with SMARCC2 variants: A fetus with tetralogy of Fallot. *BMC Med. Genom.* **2022**, *15*, 40. [[CrossRef](#)]
142. Bultman, S.; Gebuhr, T.; Yee, D.; La Mantia, C.; Nicholson, J.; Gilliam, A.; Randazzo, F.; Metzger, D.; Chambon, P.; Crabtree, G.; et al. A Brg1 null mutation in the mouse reveals functional differences among mammalian SWI/SNF complexes. *Mol. Cell* **2000**, *6*, 1287–1295. [[CrossRef](#)] [[PubMed](#)]
143. Reyes, J.C.; Barra, J.; Muchardt, C.; Camus, A.; Babinet, C.; Yaniv, M. Altered control of cellular proliferation in the absence of mammalian brahma (SNF2alpha). *EMBO J.* **1998**, *17*, 6979–6991. [[CrossRef](#)] [[PubMed](#)]
144. Lange, M.; Kaynak, B.; Forster, U.B.; Tönjes, M.; Fischer, J.J.; Grimm, C.; Schlesinger, J.; Just, S.; Dunkel, I.; Krueger, T.; et al. Regulation of muscle development by DPF3, a novel histone acetylation and methylation reader of the BAF chromatin remodeling complex. *Genes Dev.* **2008**, *22*, 2370–2384. [[CrossRef](#)] [[PubMed](#)]
145. Han, F.; Yang, B.; Chen, Y.; Liu, L.; Cheng, X.; Huang, J.; Zhou, K.; Zhang, D.; Xu, E.; Lai, M.; et al. Loss of GLTSCR1 causes congenital heart defects by regulating NPPA transcription. *Angiogenesis* **2023**, *26*, 217–232. [[CrossRef](#)] [[PubMed](#)]
146. de La Serna, I.L.; Carlson, K.A.; Hill, D.A.; Guidi, C.J.; Stephenson, R.O.; Sif, S.; Kingston, R.E.; Imbalzano, A.N. Mammalian SWI-SNF complexes contribute to activation of the hsp70 gene. *Mol. Cell. Biol.* **2000**, *20*, 2839–2851. [[CrossRef](#)] [[PubMed](#)]
147. Chen, M.; Herring, B.P. Regulation of microRNAs by Brahma-related gene 1 (Brg1) in smooth muscle cells. *J. Biol. Chem.* **2013**, *288*, 6397–6408. [[CrossRef](#)] [[PubMed](#)]
148. Zhang, M.; Chen, M.; Kim, J.-R.; Zhou, J.; Jones, R.E.; Tune, J.D.; Kassab, G.S.; Metzger, D.; Ahlfeld, S.; Conway, S.J.; et al. SWI/SNF Complexes Containing Brahma or Brahma-Related Gene 1 Play Distinct Roles in Smooth Muscle Development. *Mol. Cell. Biol.* **2011**, *31*, 2618–2631. [[CrossRef](#)]
149. Jankowich, M.; Choudhary, G. Endothelin-1 levels and cardiovascular events. *Trends Cardiovasc. Med.* **2020**, *30*, 1–8. [[CrossRef](#)]
150. Li, L.; Liu, D.; Bu, D.; Chen, S.; Wu, J.; Tang, C.; Du, J.; Jin, H. Brg1-dependent epigenetic control of vascular smooth muscle cell proliferation by hydrogen sulfide. *Biochim. Biophys. Acta* **2013**, *1833*, 1347–1355. [[CrossRef](#)]
151. Yang, Y.; Cheng, X.; Tian, W.; Zhou, B.; Wu, X.; Xu, H.; Fang, F.; Fang, M.; Xu, Y. MRTF-A steers an epigenetic complex to activate endothelin-induced pro-inflammatory transcription in vascular smooth muscle cells. *Nucleic Acids Res.* **2014**, *42*, 10460–10472. [[CrossRef](#)]
152. Yuan, Y.; Wang, C.; Xu, J.; Tao, J.; Xu, Z.; Huang, S. BRG1 overexpression in smooth muscle cells promotes the development of thoracic aortic dissection. *BMC Cardiovasc. Disord.* **2014**, *14*, 144. [[CrossRef](#)] [[PubMed](#)]
153. Liao, W.L.; Tan, M.W.; Yuan, Y.; Wang, G.K.; Wang, C.; Tang, H.; Xu, Z.Y. Brahma-related gene 1 inhibits proliferation and migration of human aortic smooth muscle cells by directly up-regulating Ras-related associated with diabetes in the pathophysiologic processes of aortic dissection. *J. Thorac. Cardiovasc. Surg.* **2015**, *150*, 1292–1301.e2. [[CrossRef](#)] [[PubMed](#)]
154. Wang, S.; Zhang, X.; Yuan, Y.; Tan, M.; Zhang, L.; Xue, X.; Yan, Y.; Han, L.; Xu, Z. BRG1 expression is increased in thoracic aortic aneurysms and regulates proliferation and apoptosis of vascular smooth muscle cells through the long non-coding RNA HIF1A-AS1 in vitro. *Eur. J. Cardiothorac. Surg.* **2015**, *47*, 439–446. [[CrossRef](#)] [[PubMed](#)]
155. Lino Cardenas, C.L.; Kessinger, C.W.; Cheng, Y.; MacDonald, C.; MacGillivray, T.; Ghoshhajra, B.; Huleihel, L.; Nuri, S.; Yeri, A.S.; Jaffer, F.A.; et al. An HDAC9-MALAT1-BRG1 complex mediates smooth muscle dysfunction in thoracic aortic aneurysm. *Nat. Commun.* **2018**, *9*, 1009. [[CrossRef](#)] [[PubMed](#)]
156. Jolly, A.J.; Lu, S.; Dubner, A.M.; Strand, K.A.; Mutryn, M.F.; Pilotti-Riley, A.; Danis, E.P.; Nemenoff, R.A.; Moulton, K.S.; Majesky, M.W.; et al. Redistribution of the chromatin remodeler Brg1 directs smooth muscle-derived adventitial progenitor-to-myofibroblast differentiation and vascular fibrosis. *JCI Insight* **2023**, *8*, e164862. [[CrossRef](#)] [[PubMed](#)]
157. Weber, C.M.; Hafner, A.; Kirkland, J.G.; Braun, S.M.G.; Stanton, B.Z.; Boettiger, A.N.; Crabtree, G.R. mSWI/SNF promotes Polycomb repression both directly and through genome-wide redistribution. *Nat. Struct. Mol. Biol.* **2021**, *28*, 501–511. [[CrossRef](#)] [[PubMed](#)]
158. Wang, W.; Xue, Y.; Zhou, S.; Kuo, A.; Cairns, B.R.; Crabtree, G.R. Diversity and specialization of mammalian SWI/SNF complexes. *Genes Dev.* **1996**, *10*, 2117–2130. [[CrossRef](#)] [[PubMed](#)]
159. Puri, P.L.; Mercola, M. BAF60 A, B, and Cs of muscle determination and renewal. *Genes. Amp Dev.* **2012**, *26*, 2673–2683. [[CrossRef](#)]
160. Ochi, H.; Hans, S.; Westerfield, M. Smarcd3 regulates the timing of zebrafish myogenesis onset. *J. Biol. Chem.* **2008**, *283*, 3529–3536. [[CrossRef](#)]
161. Forcales, S.V.; Albini, S.; Giordani, L.; Malecova, B.; Cignolo, L.; Chernov, A.; Coutinho, P.; Saccone, V.; Consalvi, S.; Williams, R.; et al. Signal-dependent incorporation of MyoD-BAF60c into Brg1-based SWI/SNF chromatin-remodelling complex. *EMBO J.* **2012**, *31*, 301–316. [[CrossRef](#)]
162. Lickert, H.; Takeuchi, J.K.; Von Both, I.; Walls, J.R.; McAuliffe, F.; Adamson, S.L.; Henkelman, R.M.; Wrana, J.L.; Rossant, J.; Bruneau, B.G. Baf60c is essential for function of BAF chromatin remodelling complexes in heart development. *Nature* **2004**, *432*, 107–112. [[CrossRef](#)]
163. Lou, X.; Deshwar, A.R.; Crump, J.G.; Scott, I.C. Smarcd3b and Gata5 promote a cardiac progenitor fate in the zebrafish embryo. *Development* **2011**, *138*, 3113–3123. [[CrossRef](#)]

164. Takeuchi, J.K.; Bruneau, B.G. Directed transdifferentiation of mouse mesoderm to heart tissue by defined factors. *Nature* **2009**, *459*, 708–711. [[CrossRef](#)] [[PubMed](#)]
165. Sohni, A.; Mulas, F.; Ferrazzi, F.; Luttun, A.; Bellazzi, R.; Huylebroeck, D.; Ekker, S.C.; Verfaillie, C.M. TGFbeta1-induced Baf60c regulates both smooth muscle cell commitment and quiescence. *PLoS ONE* **2012**, *7*, e47629. [[CrossRef](#)]
166. Chen, S.; Ding, Y.; Zhang, Z.; Wang, H.; Liu, C. Hyperlipidaemia impairs the circadian clock and physiological homeostasis of vascular smooth muscle cells via the suppression of Smarcd1. *J. Pathol.* **2014**, *233*, 159–169. [[CrossRef](#)] [[PubMed](#)]
167. Chang, Z.; Zhao, G.; Zhao, Y.; Lu, H.; Xiong, W.; Liang, W.; Sun, J.; Wang, H.; Zhu, T.; Rom, O.; et al. BAF60a Deficiency in Vascular Smooth Muscle Cells Prevents Abdominal Aortic Aneurysm by Reducing Inflammation and Extracellular Matrix Degradation. *Arterioscler. Thromb. Vasc. Biol.* **2020**, *40*, 2494–2507. [[CrossRef](#)] [[PubMed](#)]
168. Hinterseher, I.; Erdman, R.; Elmore, J.R.; Stahl, E.; Pahl, M.C.; Derr, K.; Golden, A.; Lillvis, J.H.; Cindric, M.C.; Jackson, K.; et al. Novel pathways in the pathobiology of human abdominal aortic aneurysms. *Pathobiology* **2013**, *80*, 1–10. [[CrossRef](#)]
169. Zhao, G.; Lu, H.; Chang, Z.; Zhao, Y.; Zhu, T.; Chang, L.; Guo, Y.; Garcia-Barrio, M.T.; Chen, Y.E.; Zhang, J. Single-cell RNA sequencing reveals the cellular heterogeneity of aneurysmal infrarenal abdominal aorta. *Cardiovasc. Res.* **2021**, *117*, 1402–1416. [[CrossRef](#)]
170. Shen, X.; Zhang, Y.; Xu, Z.; Gao, H.; Feng, W.; Li, W.; Miao, Y.; Xu, Z.; Zong, Y.; Zhao, J.; et al. KLF5 inhibition overcomes oxaliplatin resistance in patient-derived colorectal cancer organoids by restoring apoptotic response. *Cell Death Dis.* **2022**, *13*, 303. [[CrossRef](#)]
171. Li, X.; He, Y.; Xu, Y.; Huang, X.; Liu, J.; Xie, M.; Liu, X. KLF5 mediates vascular remodeling via HIF-1alpha in hypoxic pulmonary hypertension. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2016**, *310*, L299–L310. [[CrossRef](#)]
172. Li, Y.; Zhang, B.; Xiang, L.; Xia, S.; Kucuk, O.; Deng, X.; Boise, L.H.; Dong, J.T. TGF-beta causes Docetaxel resistance in Prostate Cancer via the induction of Bcl-2 by acetylated KLF5 and Protein Stabilization. *Theranostics* **2020**, *10*, 7656–7670. [[CrossRef](#)] [[PubMed](#)]
173. Ferguson, L.P.; Gatchalian, J.; McDermott, M.L.; Nakamura, M.; Chambers, K.; Rajbhandari, N.; Lytle, N.K.; Rosenthal, S.B.; Hamilton, M.; Albini, S.; et al. Smarcd3 is an epigenetic modulator of the metabolic landscape in pancreatic ductal adenocarcinoma. *Nat. Commun.* **2023**, *14*, 292. [[CrossRef](#)] [[PubMed](#)]
174. Centore, R.C.; Sandoval, G.J.; Soares, L.M.M.; Kadoch, C.; Chan, H.M. Mammalian SWI/SNF Chromatin Remodeling Complexes: Emerging Mechanisms and Therapeutic Strategies. *Trends Genet.* **2020**, *36*, 936–950. [[CrossRef](#)] [[PubMed](#)]
175. Xiao, L.; Parolia, A.; Qiao, Y.; Bawa, P.; Eyunni, S.; Mannan, R.; Carson, S.E.; Chang, Y.; Wang, X.; Zhang, Y.; et al. Targeting SWI/SNF ATPases in enhancer-addicted prostate cancer. *Nature* **2022**, *601*, 434–439. [[CrossRef](#)]
176. Wei, Z.; Yoshihara, E.; He, N.; Hah, N.; Fan, W.; Pinto, A.F.M.; Huddy, T.; Wang, Y.; Ross, B.; Estepa, G.; et al. Vitamin D Switches BAF Complexes to Protect beta Cells. *Cell* **2018**, *173*, 1135–1149.e15. [[CrossRef](#)]
177. Ahmed, N.S.; Gatchalian, J.; Ho, J.; Burns, M.J.; Hah, N.; Wei, Z.; Downes, M.; Evans, R.M.; Hargreaves, D.C. BRD9 regulates interferon-stimulated genes during macrophage activation via cooperation with BET protein BRD4. *Proc. Natl. Acad. Sci. USA* **2022**, *119*, e2110812119. [[CrossRef](#)]
178. Du, J.; Liu, Y.; Wu, X.; Sun, J.; Shi, J.; Zhang, H.; Zheng, A.; Zhou, M.; Jiang, X. BRD9-mediated chromatin remodeling suppresses osteoclastogenesis through negative feedback mechanism. *Nat. Commun.* **2023**, *14*, 1413. [[CrossRef](#)]
179. Wang, L.; Oh, T.G.; Magida, J.; Estepa, G.; Obayomi, S.M.B.; Chong, L.W.; Gatchalian, J.; Yu, R.T.; Atkins, A.R.; Hargreaves, D.; et al. Bromodomain containing 9 (BRD9) regulates macrophage inflammatory responses by potentiating glucocorticoid receptor activity. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2109517118. [[CrossRef](#)]
180. Saccone, V.; Consalvi, S.; Giordani, L.; Mozzetta, C.; Barozzi, I.; Sandona, M.; Ryan, T.; Rojas-Munoz, A.; Madaro, L.; Fasanaro, P.; et al. HDAC-regulated myomiRs control BAF60 variant exchange and direct the functional phenotype of fibro-adipogenic progenitors in dystrophic muscles. *Genes Dev.* **2014**, *28*, 841–857. [[CrossRef](#)]
181. Zhang, P.; Li, L.; Bao, Z.; Huang, F. Role of BAF60a/BAF60c in chromatin remodeling and hepatic lipid metabolism. *Nutr. Metab.* **2016**, *13*, 30. [[CrossRef](#)]
182. Meng, Z.X.; Tao, W.; Sun, J.; Wang, Q.; Mi, L.; Lin, J.D. Uncoupling Exercise Bioenergetics From Systemic Metabolic Homeostasis by Conditional Inactivation of Baf60 in Skeletal Muscle. *Diabetes* **2018**, *67*, 85–97. [[CrossRef](#)] [[PubMed](#)]
183. Patsch, C.; Challet-Meylan, L.; Thoma, E.C.; Urich, E.; Heckel, T.; O’Sullivan, J.F.; Grainger, S.J.; Kapp, F.G.; Sun, L.; Christensen, K.; et al. Generation of vascular endothelial and smooth muscle cells from human pluripotent stem cells. *Nat. Cell Biol.* **2015**, *17*, 994–1003. [[CrossRef](#)] [[PubMed](#)]
184. Hota, S.K.; Johnson, J.R.; Verschueren, E.; Thomas, R.; Blotnick, A.M.; Zhu, Y.; Sun, X.; Pennacchio, L.A.; Krogan, N.J.; Bruneau, B.G. Dynamic BAF chromatin remodeling complex subunit inclusion promotes temporally distinct gene expression programs in cardiogenesis. *Development* **2019**, *146*, dev174086. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.