

# FEATURES

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## The Epigenetic Regulation of the Opioid System: New Individualized Prompt Prevention and Treatment Strategies

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2419

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The most well-known physiological effect associated with opioid system is their efficacy in pain reduction or analgesia, although their effect on a variety of other physiological and physiopathological functions has become apparent in recent years. This review is an attempt to clarify in more detail the epigenetic regulation of opioid system to understand with more precision their transcriptional and posttranscriptional regulation in multiple physiological and pharmacological contexts. The opioid receptors show an epigenetic regulation and opioid peptide precursors by methylation, chromatin remodeling and microRNA. Although the opioid receptor promoters have similarity between them, they use different epigenetic regulation forms and they exhibit different pattern of expression during the cell differentiation. DNA methylation is also confirmed in opioid peptide precursors, being important for gene expression and tissue specificity. Understanding the epigenetic basis of those physiological and physiopathological processes is essential for the development of individualized prompt prevention and treatment strategies.

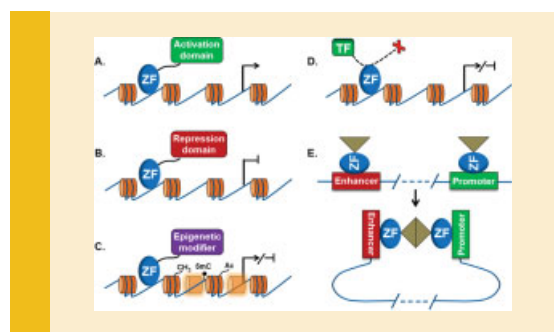
## Artificial Zinc Finger DNA Binding Domains: Versatile Tools for Genome Engineering and Modulation of Gene Expression

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2435

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Genome editing and alteration of gene expression by synthetic DNA binding activities gained a lot of momentum over the last decade. This is due to the development of new DNA binding molecules with enhanced binding specificity. The most commonly used DNA binding modules are zinc fingers (ZFs), TALE-domains, and the RNA component of the CRISPR/Cas9 system. These binding modules are fused or linked to either nucleases that cut the DNA and induce DNA repair processes, or to protein domains that activate or repress transcription of genes close to the targeted site in the genome. This review focuses on the structure, design, and applications of ZF DNA binding domains (ZFDBDs). ZFDBDs are relatively small and have been shown to penetrate the cell membrane without additional tags suggesting that they could be delivered to cells without a DNA or RNA intermediate. Advanced algorithms that are based on extensive knowledge of the mode of ZF/DNA interactions are used to design the amino acid composition of ZFDBDs so that they bind to unique sites in the genome. Off-target binding has been a concern for all synthetic DNA binding molecules. Thus, increasing the specificity and affinity of ZFDBDs will have a significant impact on their use in analytical or therapeutic settings.



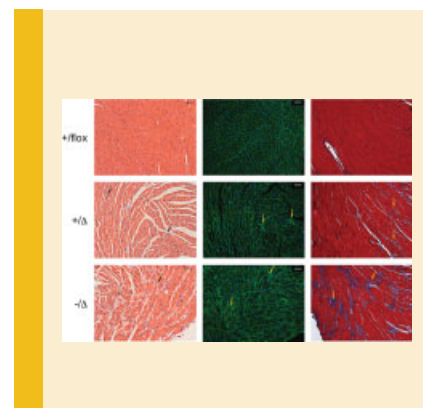
**Cardiac-Specific Disruption of Bin1 in Mice Enables a Model of Stress- and Age-Associated Dilated Cardiomyopathy**

2541

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Non-compensated dilated cardiomyopathy (DCM) leading to death from heart failure is rising rapidly in developed countries due to aging demographics, and there is a need for informative preclinical models to guide the development of effective therapeutic strategies to prevent or delay disease onset. In this study, we describe a novel model of heart failure based on cardiac-specific deletion of the prototypical mammalian BAR adapter-encoding gene *Bin1*, a modifier of age-associated disease. *Bin1* deletion during embryonic development causes hypertrophic cardiomyopathy and neonatal lethality, but there is little information on how *Bin1* affects cardiac function in adult animals. Here we report that cardiomyocyte-specific loss of *Bin1* causes age-associated dilated cardiomyopathy (DCM) beginning by 8–10 months of age. Echocardiographic analysis showed that *Bin1* loss caused a 45% reduction in ejection fraction during aging. Younger animals rapidly developed DCM if cardiac pressure overload was created by transverse aortic constriction. Heterozygotes exhibited an intermediate phenotype indicating *Bin1* is haplo-insufficient to sustain normal heart function. *Bin1* loss increased left ventricle (LV) volume and diameter during aging, but it did not alter LV volume or diameter in hearts from heterozygous mice nor did it affect LV mass. *Bin1* loss increased interstitial fibrosis and mislocalization of the voltage-dependent calcium channel  $Ca_v1.2$ , and the lipid raft scaffold protein caveolin-3, which normally complexes with *Bin1* and  $Ca_v1.2$  in cardiomyocyte membranes. Our findings show how cardiac deficiency in *Bin1* function causes age- and stress-associated heart failure, and they establish a new preclinical model of this terminal cardiac disease.



**Histone Deacetylase Inhibition Impairs Normal Intestinal Cell Proliferation and Promotes Specific Gene Expression**

2695

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Mechanisms that maintain proliferation and delay cell differentiation in the intestinal crypt are not yet fully understood. We have previously shown the implication of histone methylation in the regulation of enterocytic differentiation. In this study, we investigated the role of histone deacetylation as an important epigenetic mechanism that controls proliferation and differentiation of intestinal cells using the histone deacetylase inhibitor suberanilohydroxamic acid (SAHA) on the proliferation and differentiation of human and mouse intestinal cells. Treatment of newly confluent Caco-2/15 cells with SAHA resulted in growth arrest, increased histone acetylation and up-regulation of the expression of intestine-specific genes such as those encoding sucrase-isomaltase, villin and the ion exchanger SLC26A3. Although SAHA has been recently used in clinical trials for cancer treatment, its effect on normal intestinal cells has not been documented. Analyses of small and large intestines of mice treated with SAHA revealed a repression of crypt cell proliferation and a higher expression of sucrase-isomaltase in both segments compared to control mice. Expression of SLC26A3 was also significantly up-regulated in the colons of mice after SAHA administration. Finally, SAHA was also found to strongly inhibit normal human intestinal crypt cell proliferation in vitro. These results demonstrate the important implication of epigenetic mechanisms such as histone acetylation/deacetylation in the regulation of normal intestinal cell fate and proliferation.