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Epigenetic mechanisms in atrial fibrillation: New insights and future directions

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ABSTRACT

Atrial fibrillation (AF) is the most common sustained arrhythmia. AF is a complex disease that results from genetic and environmental factors and their interactions. In recent years, numerous studies have shown that epigenetic mechanisms significantly participate in AF pathogenesis. Even though a poor understanding of the molecular and electrophysiologic mechanisms of AF, accumulated evidence has suggested that the relevance of epigenetic changes in the development of AF. The aim of this review is to describe the present knowledge about the epigenetic regulatory features significantly participates in AF, and look ahead on new perspectives of epigenetic mechanisms research. Epigenetic regulatory features such as DNA methylation, histone modification, and microRNA influence gene expression by epigenetic mechanisms and by directly binding to various factor response elements in the target gene promoters. Given the role of epigenetic alterations in regulating genes, there is potential for the integration of factors-induced epigenetic alterations as informative factors in the risk assessment process. In this review, new insight into the epigenetic mechanisms in AF pathogenesis is discussed, with special emphasis on DNA methylation, histone modification, and microRNA. Further studies are needed to reveal the potential targets of epigenetic mechanisms, and it can be developed as a therapeutic target for AF.

Key words: Atrial fibrillation, Epigenetic, DNA methylation, histone modification, microRNA

Abbreviations: AF, atrial fibrillation, DNMT, DNA methyltransferase, ECM, extracellular matrix, HP1, heterochromatin protein 1, MBD, methyl-binding domain, SOD1, superoxide dismutase 1, IL-18, interleukin-18, HAT, histone acetyltransferase, TIMPs, tissue inhibitors of matrix metalloproteinases, HDACs, histone deacetylases, miRNA, microRNA, 3′-UTRs, 3′-untranslated regions, RISC, RNA-induced silencing complex, SERCA2a, sarcoplasmic reticulum Ca-ATPases, Spry1, sprouty 1, PTEN, phosphatase and tensin homolog, CTGF, connective tissue growth factor.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia seen in clinical practice with prevalence in excess of 33 million worldwide [1,2]. Despite AF being a documented cause of stroke for a long time, until recently, it was still considered a relatively "benign" arrhythmia [3]. AF is a significant contributor to cardiovascular morbidity and mortality [4]. Efforts to increase our understanding of AF and its complications have focused on unraveling the mechanisms of electrical and structural remodeling of the atrial myocardium [5,6]. Yet, it is increasingly recognized that AF is more

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than an atrial disease, being associated with systemic inflammation, endothelial dysfunction, and adverse effects on the structure and function of the left ventricular myocardium that may be prognostically important [7].

However, there is no therapy for AF in general, largely because the underlying basis of AF is unclear. A better mechanistic understanding of the molecular basis of AF may allow for the development of safer and more effective treatment approaches. The mechanisms underlying AF susceptibility are multiple and incompletely understood. The two major determinants of AF maintenance are reentry and ectopic impulse formation [8]. The changes in atrial structure and function that result from heart disease, and indeed AF itself, constitute atrial remodeling and are key elements of the AF substrate [9]. In addition, genetic factors establish electrophysiological substrates that determine individual vulnerability to AF occurrence and maintenance [10]. Particular emphasis is placed on understanding how epigenetic mechanisms play a key role in the etiology of AF.

Epigenetics describes the study of mitotically and meiotically heritable changes in gene expression without mutating the DNA sequence [11]. Epigenetic alterations regulate key events in cellular homeostasis, including transcriptional and translational regulation of gene expression [12]. Epigenetic modifications include three commonly studied alterations: DNA methylation, histone modifications, and microRNAs (miRNA) [13]. Epigenetic regulation of gene expression can be influenced by a variety of environmental factors, and their dysregulations has been implicated in various diseases [14,15]. Emerging data suggest that these epigenetic modifications also impact on the development of AF [16]. Epigenetic modifications have been described as important regulators of AF.

In this review, we focus on the epigenetic modifications influencing onset and progression of AF (Fig. 1). Firstly, we summarize the state of the art of research on DNA and histone epigenetic modifications in AF; we discuss the biological roles and the molecular functions of known chromatin-associated epigenetic whose expression is deregulated in AF, highlighting that epigenetic regulation should be taken into account for potential therapeutic approaches. We discuss the implications of these findings for preclinical and basic research and provide a current clinical perspective.

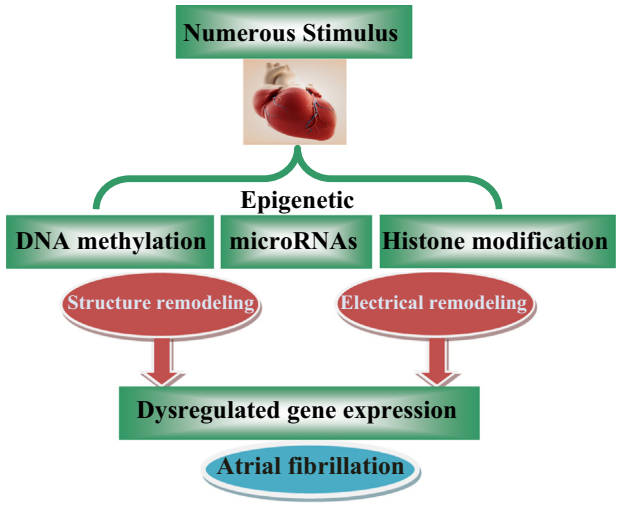

Fig. 1 – Epigenetic modifications play a key role in the development of atrial fibrillation. Important alterations encompassing epigenetic changes are DNA methylation, microRNAs, and histone modifications.

Overview of epigenetic mechanisms

Epigenetics is defined as heritable changes in gene expression that are not due to any alteration in the primary DNA sequence [17]. Epigenetics signifies the way genetic information is organized, maintained, and read [18]. Epigenetic modifications include the best-known and much studied methylation of DNA, modifications of the histone proteins that bind to DNA, the nucleosome positioning along DNA, and miRNAs [19].

DNA methylation

In mammalian DNA, cytosines in the CpG dinucleotide context are commonly methylated [20]. DNA methylation is involved in the normal development and maintenance of cellular homeostasis and functions in adult organisms, particularly for X-chromosome inactivation in females, genomic imprinting, silencing of repetitive DNA elements, regulation of chromatin structure, and control of gene expression [21,22]. The transfer of a methyl group to cytosine forms 5-methyl cytosine (5-mC) in CpG dinucleotides [23]. The DNA methyltransferase (DNMT) family consists of DNMT1, DNMT2, DNMT3A, and DNMT3B [24]. DNMT1 maintains the methylation status once it is established by DNMT3A and DNMT3B through de novo methylation [25,26]. These DNMTs cooperate to maintain a precise DNA methylation pattern. Methyl-binding domain (MBD) proteins including MeCP2, MBD1, MBD2, and MBD4 are readers that recognize and bind to methylated CpG sites and presumably mediate transcription repression or silencing [27].

Approximately 70–90% of CpG dinucleotides in the mammalian genome are methylated; however, CpG sites are not distributed uniformly across the genome and are concentrated in short regions (<4 kb) of DNA with a high G + C content and a high frequency of CpG dinucleotides called "CpG islands" [28]. In normal cells, CpG sites located in CpG islands are unmethylated [29]. In contrast, most of the remaining CpG sites of the genome are methylated [30]. Cytosine methylation is a stable modification of the genomic DNA and the pattern of DNA methylation is inherited during DNA replication [31]. The role of DNA methylation in vivo and provide the foundations for deciphering how environment can impact on the epigenetic regulation of genes in general [32].

Histone modifications

Histone modifications provide another important mechanism of epigenetic regulation [33]. Histones package and order DNA into basic structural units called nucleosomes [34]. The N-terminal tails of histones can undergo various post-translational modifications, including acetylation, methylation, phosphorylation, ubiquitylation, and sumoylation [35]. These post-translational modifications of histone proteins