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Cardiovascular Disorders and Acetylation: Molecular Processes and Clinical Effects

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Abstract

The post-translational modification (PTM) processes that epigenetically regulate gene expression and transcriptional activity include acetylation. Reversible histone acetylation on lysine deposits administers the collaborations among DNA and histones to intercede chromatin rebuilding and quality record. Acetylation of non-histone proteins hinders cellular function, whereas acetylation of important mitochondrial enzymes controls bioenergetic metabolism. The delicate homeostatic regulation of embryonic development, postnatal maturation, cardiomyocyte differentiation, cardiac remodeling and the onset of various cardiovascular diseases like obesity, diabetes mellitus, cardiometabolic diseases, ischemia-reperfusion injury, cardiac remodeling, hypertension and arrhythmias is dependent on the acetylation and deacetylation of functional proteins. Histone acetyltransferase (Caps) and histone deacetylases (HDACs) are fundamental proteins for the most part answerable for the guideline of lysine acetylation levels, accordingly giving conceivable drugable focuses to remedial mediations in the administration of cardiovascular illnesses.

Keywords: Acetylation • Post-translational modifications • SIRT family • Cardiac remodeling • Contractile function

Introduction

In response to cellular stress, protein post-translational modifications (PTM) are an essential molecular regulatory mechanism that takes place rapidly and economically. However, only a few of the hundreds of PTM types, including phosphorylation, methylation, acetylation, ubiquitination and glycosylation, have been thoroughly investigated. Fortunately, since the turn of the century, innovative high-resolution mass spectrometry (MS) and proteomics have made it possible to detect PTMs more effectively and precisely. Acetylation, which refers to the process of adding an acetyl group to lysine residues, was initially regarded as an epigenetic modification of histone and chromatin-related proteins among the various PTMs. Later, it was discovered that chromatin remodeling may be controlled by reversible acetylation of histone lysine residues. By weakening (loosening) the interactions between DNA and histones, lysine acetylation encourages transcription. Non-histone proteins like -tubulin and p53, most of which are linked to metabolic or mitochondrial processes, were found to be acetylated in subsequent research [1].

Histone acetyltransferases (HATs) and histone deacetylases (HDACs), which reversibly transfer acetyl groups between the acetyl-CoA and -amino side chains of lysine residues, are primarily in charge of acetylation. Similar enzymes are referred to as lysine acetyltransferases (KATs) and lysine deacetylases (KDACs) in the context of non-histone acetylation. The GCN5, CBP/p300 and MYST families comprise KATs, while the SIRT family of KDACs is the most prevalent type. Additionally, acetylation can take place in a non-enzymatic manner. Through protein-nucleic acid and protein-protein interactions, chromatin remodeling and DNA transcription are primarily regulated by histone acetylation. Hyperacetylation of histone proteins will loosen euchromatins and increase transcription activity in eukaryotic cells. Hypoacetylation, on the other hand, makes chromatins more tightly packed and, as a result, less active. Reversible acetylation of histone proteins plays a role in the regulation of numerous metabolic or age-related pathological processes, such as obesity, diabetes, cancer and neurodegeneration [2,3].

Literature Review

Gene transcription, the cell cycle, cell division, DNA damage repair, signaling transduction, protein folding, protein aggregation and autophagy are all thought to involve non-histone protein acetylation. Proteins that are related to metabolism and mitochondria frequently exhibit non-histone acetylation. About 60% of mitochondrial proteins have acetylation sites, the majority of which are involved in the metabolism of mitochondrial energy. By and large, acetylation of mitochondrial compounds brings about hindrance of oxidative digestion, the course of which is reversible by the mitochondrial deacetylase SIRT3. Through the induction of SIRT3, dietary fasting and calorie restriction may also facilitate oxidative metabolism of fatty acids and amino acids. Acetyl-CoA levels also make it possible for non-enzyme acetylation. Acetylation levels are influenced by the metabolic processes and levels of essential metabolic metabolites like ATP, NAD+ and acetyl-CoA. Acetyl-CoA fills in as a contributor for acetyl bunches in KAT-subordinate acetylation, while the action of acetyl-CoA synthetase is likewise directed by acetylation. In this mini-review, we will briefly discuss the role of acetylation in cardiovascular diseases due to its crucial role in regulating gene expression and metabolic processes [4].

Acetylation influences undeveloped turn of events, development and separation in different organs including the heart through guideline of quality articulation. A lack of SET domain-containing 5 (Setd5), for instance, will result in severe embryonic defects and death through histone acetylation and inappropriate gene transcription. Setd5 is necessary for the formation of the neural tube and the development of the heart in mammals. According to reports, acetylation of VGLL4 at lysine 225 inhibited the TEAD1-YAP interaction and caused TEAD1 degradation, limiting the proliferation of neonatal cardiomyocytes and ultimately leading to a cardiac growth defect. Maternal openness to liquor during incubation has been broadly recognized as a gamble factor for cardiovascular mutations including strange heart improvement and intrinsic heart illnesses (CHD) of babies. Histone hyperacetylation may play a significant role in the pathological process associated with fetal alcoholism. In the fetal heart of a mouse, prenatal alcohol exposure resulted in the overexpression of the cardiac-specific genes DHAND and EHAND and increased histone H3K14 acetylation [5].

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By increasing histone H3 acetylation through the morphogenetic protein (BMP) signal pathway, alcohol treatment in H9c2 cells increased the expression of genes associated with heart development. Reliably, the BMP inhibitor dorsomorphin may smother the occurrence of CHD. In addition, prenatal alcohol exposure resulted in an upregulation of Gata4 and an increase in HAT activity in fetal mouse hearts. Gata4 overexpression was reduced and histone H3K9 acetylation was prevented by anacardic acid. In a similar vein, it was reported that curcumin treatment prevented fetal cardiac injury caused by prenatal alcohol exposure. Curcumin was found to reduce the expression of apoptotic genes like caspase-3, caspase-8 and Bcl-2 and counteract alcohol-induced hyperacetylation of histone H3K9. In addition, curcumin modulated the activity of HATs in fetal hearts, inhibiting H3K14 acetylation, whereas suberoylanilide hydroxamic acid (SAHA) did the opposite. Contrary to this, another independent study demonstrated that treatment with curcumin caused histone hypoacetylation and decreased levels of essential transcription factors, which in turn caused abnormal heart development in mice, as evidenced by a smaller size, thinner ventricular wall and delayed ventricular septum formation [6].

Additionally, cardiomyocyte differentiation from stem cells relies heavily on acetylation. Through histone acetylation, it was demonstrated that Islet-1 (Isl1) specifically induces MSC C3H10T1/2 cell differentiation into cardiomyocyte-like cells. It is possible that GCN5 and Isl1 work together to promote MSC differentiation into cardiomyocytes. Additionally, P19CL6 cell differentiation into cardiomyocytes was facilitated by histone H3K9 acetylation on its promoter, which in turn activates Isl1 via the Wnt/-catenin signaling pathway. Through delicate regulation of histone acetylation, levels of potassium channels were necessary for the formation of functional cardiomyocytes from mESCs. ASCs (adipose stromal cells) have a limited capacity for transdifferentiation into cardiovascular-like cells. HDAC inhibitor SAHA was displayed to lean toward the cardiovascular lenient territory of ASCs by expanding histone acetylation. When histone H3 is acetylated to trigger related gene transcription, TGF-1 can induce the differentiation of vascular smooth muscle cells (VSMC), partly through a p38 MAPK-dependent signaling pathway [7].

Titin-truncating variants (TTNtv), one of the most common genetic causes of dilated cardiomyopathy, impair cardiac metabolism and autophagy in rats, possibly through hyperacetylation of mitochondrial proteins. The acetylation level of p53 was raised as a result of coronary microembolization, which is one of the most significant causes of cardiac dysfunction. By triggering SIRT1-mediated deacetylation of p53, resveratrol reduced coronary microembolization and the resulting cardiomyocyte apoptosis. One more review showed that the downregulation of intensity shock protein 25 (HSP25) irritated doxorubicin-actuated apoptosis in H9c2 cells through repressing the collaboration somewhere in the range of SIRT1 and p53 and subsequently expanding the acetylation level of p53 at lysine 379. A case-control study with 342 patients found a strong correlation between the long-term clinical outcomes of patients without coronary artery disease (CAD) and the acetylation level of serum glycoprotein. Glycoprotein acetylation levels may raise the risk of major adverse events and cardiovascular diseases [8].

Discussion

In the hearts of type 2 diabetics, protein acetylation also controls the transport of insulin-stimulated glucose. It has been shown that metabolic substrates like fatty acids, branched-chain amino acids and ketones bodies can cause cardiac metabolic inflexibility, disrupt glucose transport and increase protein acetylation. Robotically, leucine was displayed to increment protein acetylation and stifle insulin-actuated glucose take-up in kind 2 diabetic hearts by repressing the movement of glucose carrier 4 (GLUT4) to the plasma layer. Restraint of acetyltransferases safeguarded leucine's suppressive job on GLUT4 movement and heart glucose take-up. Despite the need for additional research before its clinical application, acetylation has the potential to become new therapeutic targets for diabetic cardiomyopathy, which is not surprising [9].

Many proteins used as pathogenic markers in cardiovascular and neurodegenerative diseases were promoted and inhibited phosphorylation by the antiplatelet drug aspirin. Another normal medication Nonsteroidal calming drugs (NSAIDS) contends and cooperates with ibuprofen, influencing its cardiovascular security. An MS assay was developed by a group of researchers to quantify distinct NSAIDS that cause drug-drug interactions by measuring the level of acetylation of cyclooxygenase-1 (COX-1). Additionally, aspirin-mediated acetylation of platelet COX-1 at serine 529 decreased with hyperglycemia, resulting in a poor aspirin response in diabetic patients [10].

Conclusion

Post-translational modification is an essential gene regulation mechanism that quickly responds to various forms of cellular stress. PTM has been broadly analyzed politeness of the development in high-goal MS examination and proteomics. Reversible acetylation, which occurs on both histone and non-histone proteins and is a significant type of PTM, has complicated crosstalk with other types of PTM, such as phosphorylation. Gene expression is controlled and open, transcriptionally active chromatin is made possible by histone hyperacetylation. Additionally, non-histone acetylation is prevalent, particularly in mitochondrial and metabolic proteins. As a result, we briefly discuss how acetylation is involved in the pathogenesis of various cardiovascular diseases and how it regulates gene expression, cell proliferation, energy metabolism and enzymatic activity.

Due to its significance in regulating gene expression and metabolism, acetylation modification is now emerging as a novel therapeutic approach to treat various cardiovascular diseases. Defective cardiac embryonic development and delayed maturation in fatty acid oxidation and energy metabolism were caused by inappropriate acetylation levels. Additionally, acetylation of particular lysine residues aided in the differentiation of stem-cell-derived cardiomyocytes. In cardiometabolic diseases, hyperacetylation caused metabolic inflexibility, whereas most studies demonstrated that HDAC inhibitors protected the heart from I/R injury and cardiac hypertrophy. Many other cardiovascular diseases, such as hypertension, cardiac arrhythmias, atherosclerosis, an abdominal aortic aneurysm, sepsis and doxorubicin-induced myocardial dysfunction, were also regulated by lysine acetylation. By regulating HDAC enzymatic activity and histone acetylation, many drugs protect the heart.

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Conflicts of Interest

None.

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