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Gene Control in Pharmaceutical Synthesis and Delivery

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Abstract

Hepatitis C virus (HCV) RNA replicates its genome on specialized endoplasmic reticulum modified membranes termed membranous web and utilizes lipid droplets for initiating the viral nucleocapsid assembly. HCV maturation and/or the egress pathway requires host sphingolipid synthesis, which occur in the Golgi. Ceramide transfer protein (CERT) and oxysterol-binding protein (OSBP) play a crucial role in sphingolipid biosynthesis. Protein kinase D (PKD), a serine/threonine kinase, is recruited to the trans-Golgi network where it influences vesicular trafficking to the plasma membrane by regulation of several important mediators via phosphorylation. PKD attenuates the function of both CERT and OSBP by phosphorylation at their respective Ser132 and Ser240 residues Here, we investigated the functional role of PKD in HCV secretion. Our studies show that HCV gene expression down-regulated PKD activation. PKD depletion by shRNA or inhibition by pharmacological inhibitor Gö6976 enhanced HCV secretion. Overexpression of a constitutively active form of PKD suppressed HCV secretion. The suppression by PKD was subverted by the ectopic expression of nonphosphorylatable serine mutant CERT S132A or OSBP S240A. These observations imply that PKD negatively regulates HCV secretion/release by attenuating OSBP and CERT functions by phosphorylation inhibition.

Introduction

Drug metabolism is a biological process that involves specific enzyme systems modifying medicinal compounds. Drug metabolism can be affected by changes in the expression of drug-metabolizing enzyme genes. Epigenetic control of drug-metabolizing enzyme genes has recently been identified as a critical mechanism. Heritable factors of genomic modifications that do not include changes in DNA sequence are referred to as epigenetic regulation. DNA methylation, histone modifications, and non-coding RNAs are examples of such modifications[1-15].The impact of epigenetic regulators on genes involved in drug metabolism is examined in this review, which also proposes a network approach to epigenetic regulation. Epigenetic mechanisms have significant therapeutic consequences and may provide insight into effective medication development as well as increase drug therapy safety.

Subjective heading

OSBP is a sterol sensor and facilitates trafficking of cholesterol or hydroxycholesterol from ER to Golgi OSBP binds to both vesicle-associated membrane protein-associated protein (VAP)-subtype A on the ER and phosphatidylinositol 4-phosphate (PI4P) on the Golgi to form a “membrane contact site” (MCS) to facilitate lipid transfer between opposing surfaces . CERT, which shares functional homology with OSBP, regulates the transport of ceramide from ER to the Golgi where the ceramide is converted to sphingolipids OSBP modulates CERT activation and translocation to the Golgi and thereby integrates sterol homeostasis to sphingolipid biosynthesis . We previously showed that OSBP mediates HCV secretion while binding to NS5A and vesicle-associated membrane protein-associated protein (VAP)-subtype A Inhibition of CERT function effectively suppressed HCV release without affecting RNA replication These studies indicate that these lipid transport proteins, CERT, and OSBP directly contribute to HCV morphogenesis/secretion.

Syphilis is an infection caused by Treponema pallidum. Usually, *T.* pallidum is transmitted through sexual intercourse. In addition, syphilis greatly increases the risk of infection and transmission of acquired immune deficiency syndrome . In recent years, the global incidence of syphilis has increased because of the ability of *T.* pallidum to evade host immune defenses and spread from the initial site of infection to other organs and tissues. Hence, it is also termed a “stealth pathogen. How *T.* pallidum overcomes the immune response and damages tissue is incompletely understood. Explaining the pathogenesis and immune mechanism of action of *T.* pallidum has become a key link to controlling syphilis.

Discussion

The metabolic process and therapeutic effect of a medicine are heavily influenced by factors that influence the expression and function of drug-metabolizing enzymes and transporters. Genetic differences in enzymes and transporters have long been known to cause changes in medication responsiveness. There have been numerous genetic polymorphisms discovered in genes encoding drug-metabolizing enzymes and transporters that can be converted into clinical differences. However, genetic influences can only explain a portion of the huge interindividual variability in medication responsiveness. Only 10%–30% of phenotypic variations may be explained by genetic variants in genes encoding drug-metabolizing enzymes and transporters in the majority of cases.

Histone H3 acetylation is an important epigenetic modification regarding the ability for genes to be transcribed. Acetylation has the most potential to unfold chromatin, because it neutralizes the basic charge of the lysine residual and loosens the interaction between histone and DNA. Acetylation is generally associated with activation of transcription. Several histone acetyltransferase have been identified as transcription co-activators. In contrast, histone deacetylation

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is generally associated with repression of transcription. Histone deacetylases have been identified as transcriptional co-repressors

Because genetic information can be expressed differently in different people throughout time and space, and even monozygotic twins do not necessarily have the same phenotype, epigenetic factors are now thought to be a major part of the molecular control of gene expression4. The general idea of epigenetics will be briefly discussed in this review, as will its influence on genes encoding proteins involved in drug metabolism and transport. We'll also look at epigenetic mechanisms as a regulatory network and talk about how epigenetic research affects medication.

Property of epigenetics

Epigenetics is the study of heritable changes in gene expression that are not driven by DNA sequence changes. Epigenetic control results in generally stable alterations that can be influenced by a variety of different factors, including age, diet, lifestyle, disease, and environment. DNA methylation, histone modifications, and non-coding RNAs are only a few examples of epigenetic regulatory systems that can influence gene expression without affecting the underlying DNA sequences. DNA methylation

In a dinucleotide setting, DNA methylation usually refers to the insertion of a methyl group to the cytosine pyrimidine ring at position DNA methyltransferases (DNMTs) and demethylases keep track of a site's methylation status, which can be passed down via cell divisions. For optimal gene regulation, chromosomal integrity, and parental imprinting, DNA methylation is required. It is vital in the long-term silencing of transcription and the development of heterochromatin.

Protein kinase D (PKD), a serine/threonine kinase, is recruited to the trans-Golgi network where it influences vesicular trafficking to the plasma membrane by regulation of several important mediators via phosphorylation. PKD attenuates the function of both CERT and OSBP by phosphorylation at their respective Ser^{132} and Ser^{240} residues Here, we investigated the functional role of PKD in HCV secretion. Our studies show that HCV gene expression down-regulated PKD activation. PKD depletion by shRNA or inhibition by pharmacological inhibitor Gö6976 enhanced HCV secretion. Overexpression of a constitutively active form of PKD suppressed HCV secretion. The suppression by PKD was subverted by the ectopic expression of nonphosphorylatable serine mutant CERT S132A or OSBP S240A. These observations imply that PKD negatively regulates HCV secretion/release by attenuating OSBP and CERT functions by phosphorylation inhibition.

OSBP is a sterol sensor and facilitates trafficking of cholesterol or hydroxycholesterol from ER to Golgi OSBP binds to both vesicle-associated membrane protein-associated protein (VAP)-subtype A on the ER and phosphatidylinositol 4-phosphate (PI4P) on the Golgi to form a "membrane contact site" (MCS) to facilitate lipid transfer between opposing surfaces CERT, which shares functional homology with OSBP, regulates the transport of ceramide from ER to the Golgi where the ceramide is converted to sphingolipids OSBP modulates CERT activation and translocation to the Golgi and thereby integrates sterol homeostasis to sphingolipid biosynthesis We previously showed that OSBP mediates HCV secretion while binding to NS5A and vesicle-associated membrane protein-associated protein subtype Inhibition of CERT function effectively suppressed HCV release without affecting RNA replication These studies indicate that these lipid transport proteins, CERT, and OSBP directly contribute to HCV morphogenesis/secretion.

Histone modifications

Histone proteins in the nucleosome, surrounded by 146 bp DNA, play a dominant role in the regulation of gene expression. Several covalent modifications on the N-termini of histone proteins have been discovered, many of which contain distinct regulatory functions and are transmissible through cell divisions Histone modifications can be divided into those that correlate with activation or repression of gene expression Histone H3 acetylation is an important epigenetic modification regarding the ability for genes to be transcribed. Acetylation has the most potential to unfold chromatin, because it neutralizes the basic charge of the lysine residual and loosens the interaction between histone and DNA. Acetylation is generally associated with activation of transcription. Several histone acetyltransferase have been identified as transcription co-activators. In contrast, histone deacetylation is generally associated with repression of transcription. Histone deacetylases have been identified as transcriptional co-repressors

Conclusion

In summary, epigenetic regulation of drug-metabolizing genes and transporters is a critical factor in control of drug metabolism and transport as schematically illustrated. Epigenetic mechanism is an important source of interindividual variability in drug metabolism and transport. Combining the current understanding with further studies about the network of epigenetic regulations in drug metabolism may help to improve the safety and effectiveness of drug therapy.

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Conflict of Interest

The authors declare that they are no conflict of interest.

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