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Review

Epigenetic regulation of oxysterol formation

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ABSTRACT

Oxysterols are oxygenated derivatives of cholesterol that may be formed by either enzymatic or non-enzymatic mechanisms. Expression of the genes responsible for oxysterol synthesis (GROS) is known to be restricted across different tissues and cell types. Regulation of the transcription of GROS and the activity of their enzyme transcripts has been the subject of intense activity for many years. Recent studies have sought to decipher the mechanism(s) that underpin the restricted expression of the GROS. Available data indicates that epigenetic mechanisms have an important role to play in the control of the expression of GROS. In the current review we summarize the available evidence for the epigenetic regulation of these genes.

1. Introduction

Oxysterols are C27 derivatives of cholesterol that contain one or more oxygen function(s) in addition to the 3β-hydroxy group present in cholesterol. Oxysterols may be formed by two processes – non-enzymatic mechanisms mediated by reactive chemical species such as reactive oxygen species (ROS) [1] and enzymatic processes [2,3]. With one exception (24S,25-epoxycholesterol) all oxysterols are formed either directly from cholesterol, or from oxysterols derived from cholesterol [4]. The enzymes regulating the formation of oxysterols (i.e. GROS) are not universally present in different tissues and cells, with the consequence that particular organs are enriched with particular oxysterols, typically in relation the relative expression of the appropriate GROS [5]. For example,

Abbreviations: 24S-OHC, 24S-hydroxycholesterol; 5-Aza, 5-azacitidine; ASCOM, activating signal cointegrator-2 containing coactivator complex; ATF3, activating transcription factor-3; BAF, Brg-1 associated factors; Brg-1, Brahma-related gene-1; CBP, cAMP responsive element binding protein 1-binding protein; CH25H, Cholesterol 25-hydroxylase; CTCF, CCCTC-binding transcription factor; CYP27A1, sterol 27-hydroxylase; CYP39A1, 24-hydroxycholesterol 7α-hydroxylase; CYP3A4, cytochrome P450, family 3, subfamily A, polypeptide 4; CYP46A1, cholesterol 24-hydroxylase; CYP7A1, cholesterol 7α-hydroxylase; CYP7B1, oxysterol 7α-hydroxylase; DMNT, DNA methyltransferase; DZA, 5-aza-2′-deoxycitidine; ERK, extracellular signal-regulated kinase-1/mitogen-activated protein kinase 3; FGF-1, fibroblast growth factor-1; FXR, farnesoid X receptor; G9a, histone-lysine N-methyltransferase; GABP, GA-binding protein; GROS, genes responsible for oxysterol synthesis; H1, histone protein H1; H2A, histone protein H2A; H2B, histone protein H2B; H3, histone protein H3; H4, histone protein H4; HD, Huntington's disease; HDAC, histone deacetylase (number indicates family member); HDACi, histone deacetylase inhibitor; HNF1, hepatocyte nuclear factor-1; HPRT, hypoxanthine-guanine phosphoribosyltransferase; LRH-1, liver receptor homolog-1; LDLD, low-density lipoprotein-receptor; LXR, liver X receptor; MEK, mitogen-activated protein kinase kinase-1; mSin3A, transcriptional regulator, SIN3A; NHR, nuclear hormone receptor; p300, histone acetylase p300; PPARα, peroxisome proliferator-activated receptor-α; PRMT1, protein arginine methyltransferase-1; PXR, pregnane X receptor; REST, restrictive elelement-1 silencing transcription factor; ROS, reactive oxygen species; RUNX2, Runt-related transcription factor 2; RXR, retinoid X receptor; SHP, small heterodimer partner; SP, specificity protein (number indicates family member); STAT1, signal transducer and activator of transcription-1; TLR4, toll like receptor-4; TSA, trichostatin A.

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the brain contains relatively high amounts of 24S-hydroxycholesterol (24S-OHC) and its generative enzyme, cholesterol 24-hydroxylase (CYP46A1), is highly expressed in CNS neurons [6].

Over the last two decades many investigators have explored the mechanisms by which different GROS are regulated at the transcriptional level [7]. These studies have highlighted a role for numerous different transcription factors, in particular the nuclear hormone receptor (NHR) family of proteins, as well as several different intracellular signalling pathways in the transcriptional regulation of GROS. While it is beyond the scope of the current review to detail these mechanisms, it should be emphasized that studies on the role of epigenetics in the regulation of GROS typically emerges from the limitations of classical mechanisms to explain certain regulatory features. For details of these studies the reader is directed to [7,8] for recent reviews. In this paper we review the studies to date on the role of epigenetics in regulation of GROS and summarise the evidence for this (Table 1).

2. Epigenetic regulation of gene expression

The organisation of the genome in eukaryotes is based on nucleosomes, nucleoprotein complexes that consist of 147 bp of DNA wound around an octameric complex made up of two copies of the histone proteins H2A, H2B, H3 and H4 [9]. Histone protein H1 binds to a 20 bp linker region that connects nucleosomes together. Further organisation of nucleosomes leads to the formation of solenoids, chromatin and chromosomes. While packaging the genome in this manner is crucial to permit it to fit into the cell nucleus, it also has profound effects on gene expression. Highly packed regions of the genome (i.e. heterochromatin) are transcriptionally silent while more open regions of the genome (i.e. euchromatin) are accessible to the basal transcriptional machinery and are thus active. Changes in the structural organisation of the genome are thus considered important determinants of gene expression [10].

Epigenetics is defined as 'the study of heritable changes in gene expression that occur independent of changes in the primary DNA sequence' [11]. These changes are mediated by alteration in the structural organisation of the genome, typically as a result of developmental, nutritional, microbial, toxic or pharmacological challenge, that influence the expression of genes in a cell-, tissue- and organ-specific manner [12]. Such structural organisation is driven by post-translational modifications of histone proteins, DNA methylation and/or modification of nucleosome position along the genome which ultimately leads to a more open genomic organisation [12]. The heritability of these changes enables cells to manifest distinct identities even though they contain the same basal genomic sequence.

Table 1
Summary of literature on epigenetic regulation of GROS.

Gene	Evidence for epigenetic regulation	CTCF	RE-1
CYP7A1	Li, 2012; Li, 2010; Kim, 2009; Knutson, 2008; Fang, 2008; Gilardi, 2007; Mitro, 2007; Gobinet, 2005; Kemper, 2004	✓	X
CYP7B1	Shafaati, 2009; Leuenberger, 2007; Olsson, 2007	✓	✓
CYP27A1	Shafaati, 2009; Chittur, 2008; Escher, 2005	✓	X
CYP46A1	Milagre, 2012; Milagre, 2010; Nunes, 2010; Shafaati, 2009; Ballas, 2005	✓	✓
CYP39A1	Shafaati, 2009; Tepyluk, 2008	✓	X
CYP3A4	Kim, 2004; Ahn, 2004; Xie, 2009	✓	X
CH25H	Gold, 2012; Park, 2012	✓	X

Note that the columns for CTCF and RE-1 sites are based on bioinformatics analysis and data mining and have not been experimentally verified for these genes.

The N-terminal tail region of hastened proteins can be modified post-transcriptionally by acetylation, methylation, phosphorylation, sumoylation, ubiquitylation and citrullination [13]. These modifications either directly alter the genomic structure, or facilitate recruitment (or occlusion) of other effector proteins, e.g. Histone Deacetylases (HDAC) [13]. In general, hyperacetylation of histone proteins is associated with gene activation and hypo/deacetlytation is associated with gene repression. In contrast, the effects of histone tail methylation are strongly linked to the position and type of methylation. For example, trimethylation of lysine 4 of histone H3 is a mark of transcriptionally active regions, while trimethylation of lysine 9 of histone H3 is a mark of transcriptional repression [12].

DNA methylation is a result of the addition of a methyl group to cytosine present in a CpG unit by the action of either so-called de novo or maintenance DNA methyltransferases (DNMT) which establish methylation patterns during early development or cellular division, respectively [14]. As with histone post-translational modifications, DNA methylation can influence the recruitment or occlusion of other regulatory proteins or methyl-CpG binding proteins. These changes typically result in transcriptional repression.

The position of nucleosomes on a gene sequence also influences gene expression and nucleosome-free regions are often present at the putative promoter region where they are believed to provide a platform for assembly of the basal transcriptional machinery [9]. ATP-dependent remodelling of nucleosome organisation can also regulate access to regulatory regions which may be wound around the histone octamer, thereby permitting (or preventing) regulation of gene expression (See [15] for a recent review of nucleosome remodelling).

3. CYP7A1

CYP7A1 encodes the cholesterol 7α-hydroxylase enzyme which is the initial and rate limiting step in the classical pathway for bile acid formation [2]. It is highly expressed in the hepatocytes of the liver but virtually absent from all other tissues [5]. The regulation of CYP7A1 expression has been extensively studied and sophisticated regulatory pathways have been characterised. In short, cholesterol stimulates while bile acids, the terminal products of the bile acid biosynthetic pathway, inhibit the expression of *CYP7A1*. The precise details of these regulatory loops are species-dependent, e.g. activation of CYP7A1 by the liver X receptor (LXR) occurs in the mouse but not in man (the reader is directed to [7] for a recent review of this area). Many other transcription factors and intracellular signalling pathways have been implicated in the regulation of CYP7A1, at least in some species [7]. The regulatory mechanisms involved in the control of CYP7A1 defined a paradigm for the investigation of the transcriptional regulation of other GROS.

Feedback repression of CYP7A1 expression by bile acids occurs in an indirect mechanism, whereby the farnesoid X receptor (FXR), a nuclear hormone receptor which is activated by bile acids and which forms a heterodimer with the retinoid X receptor (RXR), binds to the promoter of the small heterodimer protein (SHP). Binding of the FXR:RXR heterodimer increases transcription of the SHP gene, which then interacts with the liver receptor homolog-1 (LRH-1) at the CYP7A1 promoter, leading to transcriptional repression of the gene. Studies initiated in 2004 by Kemper et al. ([16]and elegantly summarised by Smith in Ref. [17]) have characterised the mechanisms by which FXR and SHP lead to activation and repression, respectively, and have identified a crucial role for post-translational modifications of histone proteins and dynamic chromatin remodelling in these processes. In particular, SHP has emerged as a central coordinator of chromatin modifying factors and has been shown to interact with dozens of different nuclear receptors, transcription factors and co-regulators (See [18] for a review of these interactions).