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The expression of *Apoc3* mRNA is regulated by HNF4α and COUP-TFII, but not acute retinoid treatments, in primary rat hepatocytes and hepatoma cells

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Abstract Vitamin A status regulates obesity development, hyperlipidemia, and hepatic lipogenic gene expression in Zucker fatty (ZF) rats. The development of hyperlipidemia in acne patients treated with retinoic acid (RA) has been attributed to the induction of apolipoprotein C-III expression. To understand the role of retinoids in the development of hyperlipidemia in ZF rats, the expression levels of several selected RA-responsive genes in the liver and isolated hepatocytes from Zucker lean (ZL) and ZF rats were compared using real-time PCR. The *Rarb* and *Srebp-1c* mRNA levels are higher in the liver and isolated hepatocytes from ZF than ZL rats. The *Apoc3* mRNA level is only higher in the isolated hepatocytes from ZF than ZL rats. To determine whether dynamic RA production acutely regulates *Apoc3* expression, its mRNA levels in response to retinoid treatments or adenovirus-mediated overexpression of hepatocyte nuclear factor 4 alpha (HNF4α) and chicken ovalbumin upstream-transcription factor II (COUP-TFII) were analyzed. Retinoid treatments for 2–6 h did not induce the expression of *Apoc3* mRNA. The overexpression of HNF4α or COUP-TFII induced or inhibited *Apoc3* expression, respectively. We conclude that short-term retinoid treatments could not induce *Apoc3* mRNA expression, which is regulated by HNF4α and COUP-TFII in hepatocytes.

Keywords *Apoc3* · HNF4α · COUP-TFII · Retinoids · Liver · Primary hepatocytes · Gene expression

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Introduction

Metabolic disorders, such as obesity and diabetes, are the physiological consequences of alterations in the body's regulation of metabolic substrates or intermediates. The liver plays a critical role in the maintenance of hepatic lipid homeostasis, relying on a delicate balance of lipid uptake, synthesis, catabolism, and excretion. Their alterations will lead to the development of metabolic diseases [1], a phenomenon that has been associated with profound changes in hepatic glucose and lipid metabolism [2]. These changes are often attributed, at least in part, to the expression levels of hepatic genes involved in glucose and lipid metabolism [3, 4].

Vitamin A (VA, retinol) and molecules with similar physiological functions (retinoids) play important physiological roles in vision, embryonic development, immune function, and cellular differentiation [5]. The active metabolite of VA metabolism, retinoic acid (RA), has been used extensively in dermatology and cancer treatments [6, 7]. RA regulates gene expression through activation of two families of nuclear receptors [8], retinoic acid receptors (RARs), and retinoid X receptors (RXRs) [9, 10]. RAR/RXR hetero- or RXR/RXR homodimer binds to the RA responsive element (RARE) at the promoters and activates the transcription of their targeted genes [11, 12].

The homeostasis of triglycerides (TGs) is dynamically regulated by the liver and the adipose tissues in response to nutritional and hormonal signals [13, 14]. Lipoprotein lipase (LPL) hydrolyzes TG in chylomicrons and very low density lipoprotein (VLDL) into free fatty acids (FFAs), monoglycerides and diglycerides for their entry and storage in adipose tissues [15]. Apolipoprotein C-III (Apo-CIII, APOC3 for human, and *Apoc3* for rodent genes) is produced from liver and has been considered an inhibitor of LPL activity [16]. Mice with *Apoc3* gene knockout develop hypotriglyceridemia

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