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REVIEW

A Lipidomic Perspective on Intermediates in Cholesterol Synthesis as Indicators of Disease Status

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ABSTRACT

Lipidomics is increasingly becoming a viable method for researchers to routinely identify the various sterols present in samples, beyond just measuring cholesterol itself. In particular, the measurement of intermediates in cholesterol synthesis can shed new insights into not only the flux through the pathway, but also numerous disease states where levels of sterol intermediates are drastically altered. In this review, we indicate several intermediates that are relevant to disease, and discuss the challenges for analysing them, including the need for standardised methodology or universal controls across the lipidomics field.

KEYWORDS: Cholesterol; Intermediates; Lipidomics

INTRODUCTION

The lipidome has a staggering complexity, estimated to comprise a million or more individual lipid species, dwarfing the genome and proteome combined. The major challenge for lipidomics research is to try to capture as many of these diverse lipid species as possible.

Possessing diverse functions, sterols are an important class of lipids involved in a multitude of cellular processes. As such, they should be comprehensively covered in any lipidomic analysis. However, the literature to date suggests only a few specialised laboratories routinely measure more than a handful of sterols. All natural mammalian sterols are derived from cholesterol or its precursors (Liebisch et al., 2013). There are also plant sterols like β-sitosterol and campesterol, which originate from the diet and are routinely used as markers of cholesterol absorption (Miettinen et al., 1989). Oxysterols contain one or more extra oxygen-containing functional groups and can have many potent biological effects (Gill et al., 2008; Brown and Jessup, 2009). They can be found in food or generated by free radicals *in vivo*, e.g., 7-ketocholesterol (Brown and Jessup, 2009). Alternatively, oxysterols can be derived enzymically from cholesterol (e.g., 27-hydroxycholesterol) or *via* a shunt pathway in cholesterol synthesis (e.g., 24(*S*),25-epoxycholesterol). Moreover, oxysterols may be formed from intermediates of cholesterol synthesis (Xu et al., 2013). It should be remembered that intermediates before the cyclisation step (catalysed by lanosterol synthase), are non-sterols, such as the isoprenoid squalene. Here, we focus on mostly sterol intermediates of the cholesterol synthesis pathway (Fig. 1).

Our aim is to provide a useful companion to lipidomics researchers who are interested in some background for the various intermediates, such as which ones to measure and why. This review mainly focuses on levels of intermediates in serum/plasma, but also makes some mention of intermediates found in other fluids [e.g., cerebrospinal fluid (CSF)] and tissues (e.g., brain).

WHY LOOK AT INTERMEDIATES IN CHOLESTEROL SYNTHESIS?

As will be discussed, several intermediates of cholesterol synthesis have been demonstrated to be indicators of diseases,

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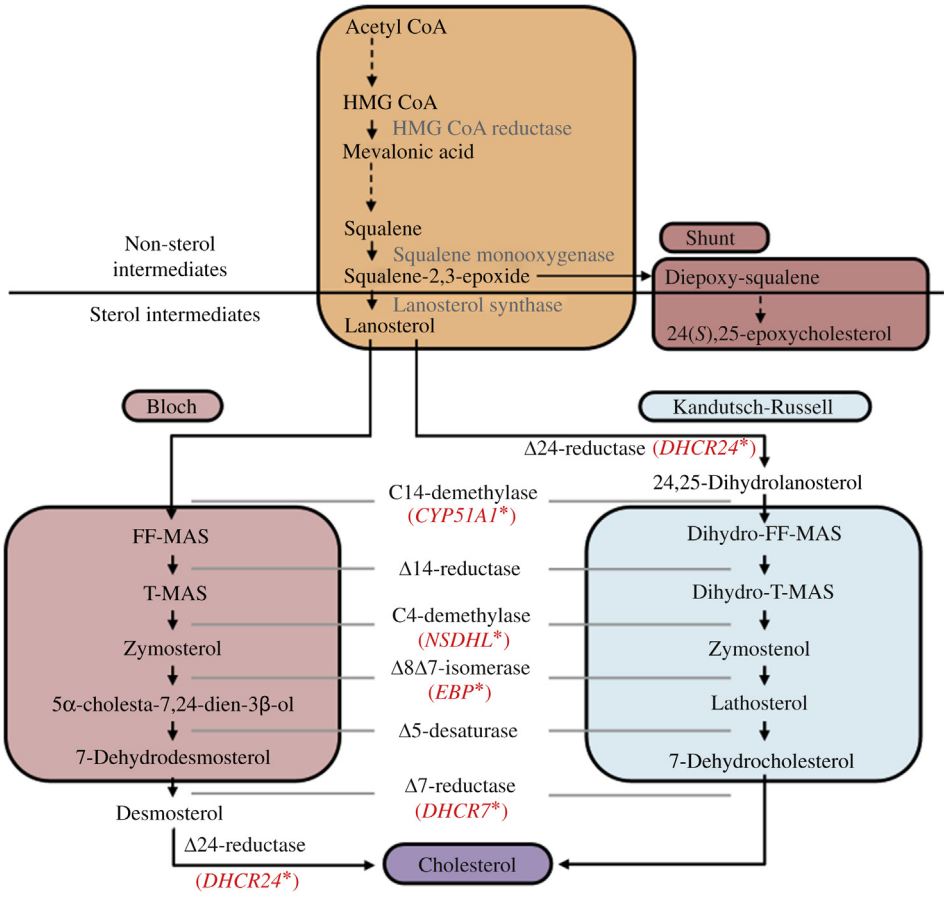

Fig. 1. The mevalonate or cholesterol synthesis pathway.
A simplified version of the cholesterol synthesis pathway including the Bloch, Kandutsch-Russell and shunt pathways. The positions of the intermediates mentioned in this review are shown. * indicates genes for particular enzymes that are defective in inborn errors of the metabolism, as listed in Table 1.

both rare inborn errors of the metabolism (e.g., desmosterolosis) and widespread chronic diseases [e.g., cardiovascular disease (CVD)]. Such diseases are characterised by aberrant sterol profiles, including both cholesterol and its intermediates. Intermediates of cholesterol synthesis are therefore important indicators of diseases, providing an alternative or complementing other analyses such as protein expression or gene analysis (Chevy et al., 2005).

Cholesterol intermediates also have potent biological effects that are not shared by cholesterol (Table 1). For example, 24,25-dihydrolanosterol mediates 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMGCR) inactivation (Song et al., 2005; Lange et al., 2008). Levels of 24,25-dihydrolanosterol are elevated in Antley-Bixler syndrome sufferers (Kelley et al., 2002). In addition, desmosterol is an activator of the liver-X receptors (LXR) (Yang et al., 2006), which coordinate expression of genes involved in reverse cholesterol transport and anti-inflammatory responses (Spann et al., 2012). Desmosterolosis, caused by a defect in 3β-hydroxysterol Δ24-reductase (DHCR24), is characterised by elevated levels of desmosterol in plasma and tissues (FitzPatrick et al., 1998).

Mechanism(s) underlying relative accumulation of particular cholesterol precursors probably involve altered flux through the pathway, and there is a growing appreciation that there are control points beyond the well-recognised rate-limiting enzyme HMGCR. For example, squalene monooxygenase (SM) represents a control point downstream of HMGCR. SM is post-transcriptionally regulated, with cholesterol itself accelerating its degradation (Gill et al., 2011). Importantly, SM acts after the branch point directing intermediates to isoprenoid or sterol synthesis. Hence, unlike HMGCR, inhibition of SM allows continued synthesis of isoprenoids from cholesterol precursors while preventing the synthesis of cholesterol itself. We have also found that DHCR24, catalysing the ultimate step in cholesterol synthesis, is inhibited by 24(*S*),25-epoxycholesterol (Zerenturk et al., 2012), demonstrating a further feedback mechanism on cholesterol synthesis and intermediates, as DHCR24 inhibition leads to an accumulation of desmosterol.

As highlighted in Table 1, genetic defects can occur at many points in the cholesterol synthesis pathway, leading to abnormal levels of cholesterol and its intermediates. Given that there are more than 20 steps in this pathway, methods to accurately screen for each of these many intermediates should be developed in order to properly characterise or diagnose diseases associated with their abnormal levels. Furthermore, analysing these intermediates will give us a better

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