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Review

Immune oxysterols: Role in mycobacterial infection and inflammation

Saikou Y. Bah[a,c,*], Paul Dickinson[a], Thorsten Forster[a], Beate Kampmann[c,d], Peter Ghazal[a,b,*]

[a] Division of Infection and Pathway Medicine, University of Edinburgh Medical, Edinburgh EH16 4SB, United Kingdom
[b] SynthSys at Edinburgh University, The Kings Buildings, Edinburgh, United Kingdom
[c] Vaccines and Immunity Theme, MRC Unit, Gambia
[d] Centre of International Child Health, Department of Medicine, Imperial College London, United Kingdom

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ABSTRACT

Infection remains an important cause of morbidity and mortality. Natural defenses to infection are mediated by intrinsic/innate and adaptive immune responses. While our understanding is considerable it is incomplete and emerging areas of research such as those related to the *immune-metabolic axis* are only beginning to be appreciated. There is increasing evidence showing a connection between immune signalling and the regulation of sterol and fatty acid metabolism. In particular, metabolic intermediates of cholesterol biosynthesis and its oxidized metabolites (oxysterols) have been shown to regulate adaptive immunity and inflammation and for innate immune signalling to regulate the dynamics of cholesterol synthesis and homeostasis. The side-chain oxidized oxysterols, 25-hydroxycholesterol (25HC) and vitamin D metabolites (vitamin D_3 and vitamin D_2), are now known to impart physiologically profound effects on immune responses. Macrophages play a frontline role in this process connecting immunity, infection and lipid biology, and collaterally are a central target for infection by a wide range of pathogens including viruses and bacteria, especially intracellular bacteria such as mycobacteria. Clinical manifestations of disease severity in the infected host are likely to pay tribute to perturbations of the metabolic-immune phenomena found in lymphocytes and myeloid cells. Historically and consistent with this notion, vitamin D based oxysterols have had a long association with promoting clinical improvements to patients infected with *Mycobacterium tuberculosis*. Hence understanding the role of *early* metabolic mediators of inflammatory responses to infection in particular oxysterols, will aid in the development of urgently needed host directed therapeutic and diagnostic design innovation to combat adverse infection outcomes and antibiotic resistance.

Contents

Abbreviations: 25HC, 25 hydroxycholesterol; BCG, Bacillus Calmette Guerin; IFN-γ, interferon gamma; TLR, toll like receptor; IL, interleukin; TNF-α, tumor necrosis factor alpha; TGF-β, tumor growth factor beta; igr, intracellular growth operon; ACAD, acyl-CoA dehydrogenases; KstD, ketosteroid dehydrogenase; HMCGR, 3-hydroxy-3-methylglutarly CoA reductase; MDM, monocytes derived English; BMDM, bone marrow derived macrophages; CH25H, cholesterol 25 hydroxylase; CYP, cytochrome P450; VDR, vitamin D receptor; RXR, retinoid acid receptor; VDRE, vitamin D receptor element; CAMP, cathelicidin antimicrobial peptides; CD, cluster of differentiation; M-CSF, monocytes colony stimulating factor; PPAR-γ, peroxisome proliferator-activated receptor gamma; SREBP, sterol regulatory element binding protein; TACO, tryptophan aspartate containing coat protein.

* Corresponding authors at: Division of Infection and Pathway Medicine, University of Edinburgh Medical, Edinburgh EH16 4SB, United Kingdom
E-mail addresses: sabah@mrc.gm (S.Y. Bah), p.ghazal@ed.ac.uk (P. Ghazal).

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1. Introduction

Cholesterol constitutes about 20% of lipids in the plasma membrane playing a key role in the maintenance of membrane integrity and fluidity, which impacts on a variety of cellular physiology. For example, cholesterol rich microdomains, known as lipid rafts, form a platform for interaction between membrane bound receptors and their ligands to instigate signal transduction [1]. Moreover, the cholesterol biosynthesis pathway has multiple branches generating intermediate molecules, such as isoprenoids and oxysterols that are vital for a diverse range of biochemical and physiological processes such as in vesicular trafficking, steroid hormone production, protein prenylation and as metabolite based effectors and regulators of the immune response [2].

Structurally, a cholesterol molecule consists of four steroid rings with a hydroxyl group attached on the A-ring and a hydrophobic 8-carbon side-chain. Cholesterol biosynthesis uses Acetyl-CoA as the primary building block, leading to the production of isoprenoids and sterols from the mevalonate and lanosterol pathways, respectively. Notably, in the Kandutch-Russell pathway of the sterol biosynthesis branch, 7-dehydrocholesterol is also used for the synthesis of vitamin D_3 (Fig. 1). Furthermore, essential metabolites are generated downstream from cholesterol itself and include, bile acids, steroid hormones

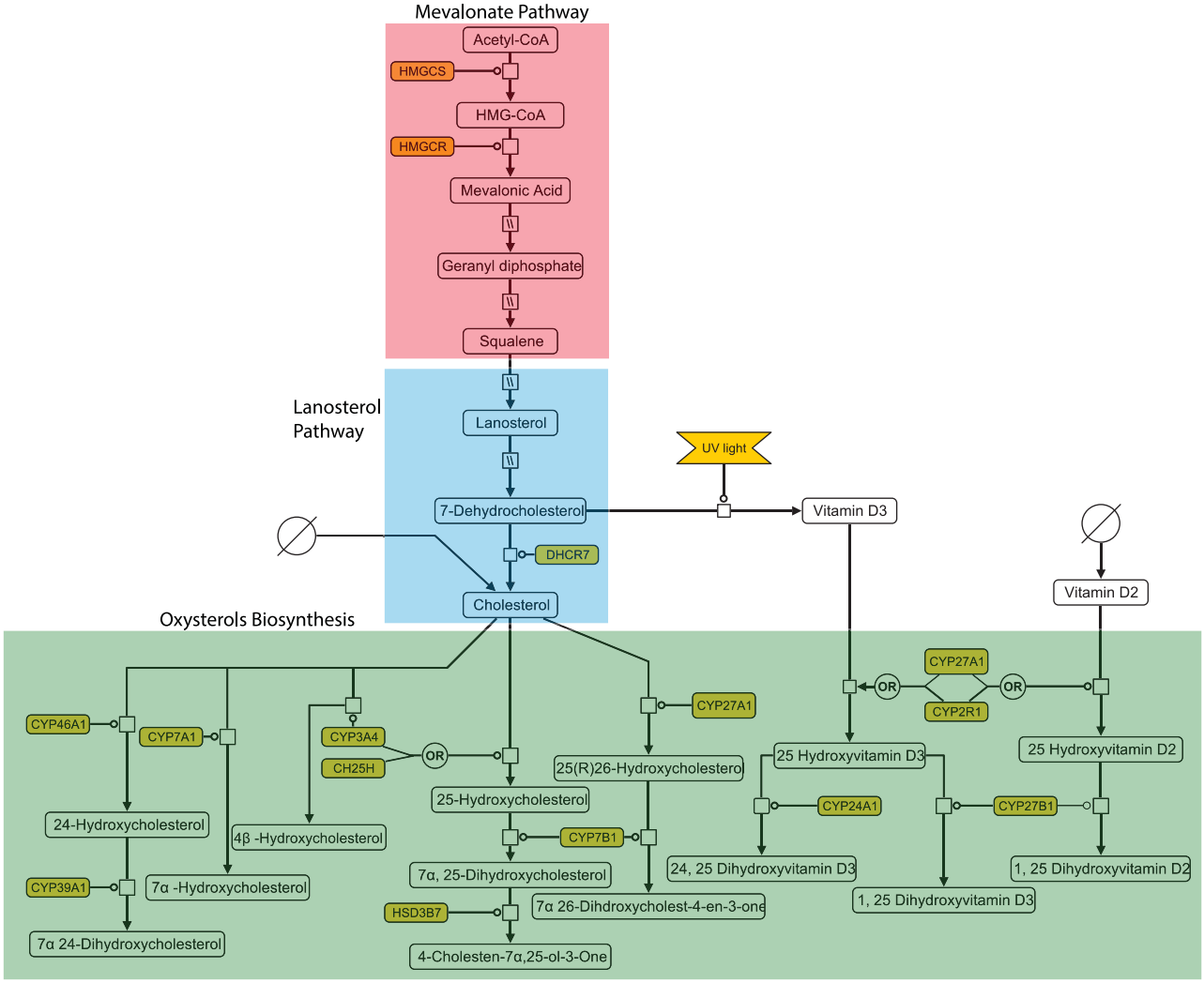

Fig. 1. Cholesterol and oxysterols synthesis pathway. The mevalonate pathway starts with Acetyl-CoA and produces Lanosterol. Lanosterol is converted into 7-dehydroxycholesterol, which is a substrate for cholesterol and vitamin D3. The source symbol on vitamin D2 indicates dietary source. Cholesterol is hydroxylated into different types of oxysterols. Enzymes involved in the synthesis are shown in light red colours. NB; 25(R)26-hydroxycholesterol is also commonly called 27-hydroxycholesterol. The source/sink glyph Ø indicates dietary source. See Table 1 for glyph notation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)