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NEWS AND VIEWS

# Derived cholesterol metabolites and sIgA production: A novel intriguing link

The importance of diet in dynamically shaping the immune response was introduced a few years ago with the concept of 'Immunonutrition', highlighting the ability of selected dietary factors to directly or indirectly modulate the immune system development and function. The main indirect effects are mediated by the gut microbiome (GM), that being the first organ met dietary factors, is strongly influenced by them. Thus, GM modulated by diet, shapes the immune system development and function.[1,2]

At the gastrointestinal (GI) tract level, the lymphoid tissue discriminates between dangerous and harmless antigens, while the GM drives immune cell differentiation. The result of this dynamic link is a tolerogenic and anti-inflammatory environment protecting against GI infection and influencing GM homeostasis, through the production of secretory immunoglobulin A(sIgA) by resident plasma cells (PCs).[3]

Current evidence suggests that dietary and microbial stimuli promote T-cell and innate lymphoid cell activation in the gut, whereas PCs are generally considered minimally or not influenced by environmental factors, because PCs are terminally differentiated B cells, programmed to secrete a stable Ig concentration.[4] However, recently Penny H.A. et al. showed that sIgA production follows a daily rhythmicity related to the feeding stimuli instead of the cell-intrinsic circadian cycle. This evidence suggests that some dietary compounds may play a role in regulating the PCs metabolisms and sIgA production.[5]

In this perspective, Ceglia and colleagues proposed an innovative view of cholesterol, known only for its detrimental effects on the cardiovascular system.[3] At the GI level, dietary cholesterol is absorbed by duodenal epithelial cells (DECs) via the transmembrane Niemann–Pick C1-like 1 protein (NPC1L1). The immune properties of cholesterol are unknown; by contrast their derived metabolites oxysterols influence immune system at the spleen and lymph nodes levels, but their role in the gut is unknown (Figure 1).[6]

By elegant experiments, the authors demonstrated that environmental changes at GI level, including a sterol-rich environment and pathogens exposure, significantly impaired the sIgA production.[3]

Dietary cholesterol, absorbed by the NPC1L1, and microbial exposure through the toll-like receptor (TLR) recognition, activate the production of oxysterols by DECs. DECs secrete two different oxysterols: 25-hydroxycholesterol(25-HC) and 7α,25-dihydroxycholesterol(7α,25-HC), through the action of cholesterol 25-hydroxylase(CH25H) and cytochrome P450(CYP7B1) enzymes, respectively (Figure 1). The CH25H induction is downstream of the TLR pathway. To explore the TLR signalling in oxysterol production, these researchers demonstrate that DECs isolated from *Myd88*−/− mice showed reduced CH25H and CYP7B1, resulting in reduced levels of both oxysterols, and were partially derived by commensal recognition (Figure 1).[3] The 7α,25-HC receptor is the G-protein-coupled 183 (GPR183) expressed by PCs, tuning its migration. As demonstrated by these experiments, an environment enriched in cholesterol results in increased levels of oxysterols and GPR183 expression on PCs. To evaluate if this mechanism is mediated by dietary cholesterol, authors performed mouse model experiment by blocking cholesterol absorption with ezetimibe (blocking NPC1L1) and production with mevastatin (blocking 3-hydroxy-3-methylglutaryl-CoA reductase). Ezetimibe, but not mevastatin, markedly reduced 7α,25-HC and 25-HC production in DECs, demonstrating the pivotal role of dietary cholesterol in this mechanism.[3] Furthermore, PCs expressing higher levels of GPR183 showed lower CD98 expression and impaired sIgA production, whereas a mouse line lacking CH25H showed low GPR183 and high CD98 expression on PCs, resulting in increased levels of sIgA, analysed by ELISpot (Figure 1). CD98 is marker of PCs producing sIgA, that ensures the supply of amino acids required for mTORC1 activity, directly controlling antibody secretion. CD98 expression is downregulated by GPR183 and by dietary cholesterol. Indeed, it was observed that CD98 expression was increased in IgA+PCs on ezetimibe, but not on mevastatin treatment.[3]

Altogether, this evidence supports the presence of a link that dynamically connects GI luminal stimuli, epithelial cell metabolism and humoral immune response (Figure 1). This innovative perspective on sIgA production opens the way for innovative approaches in

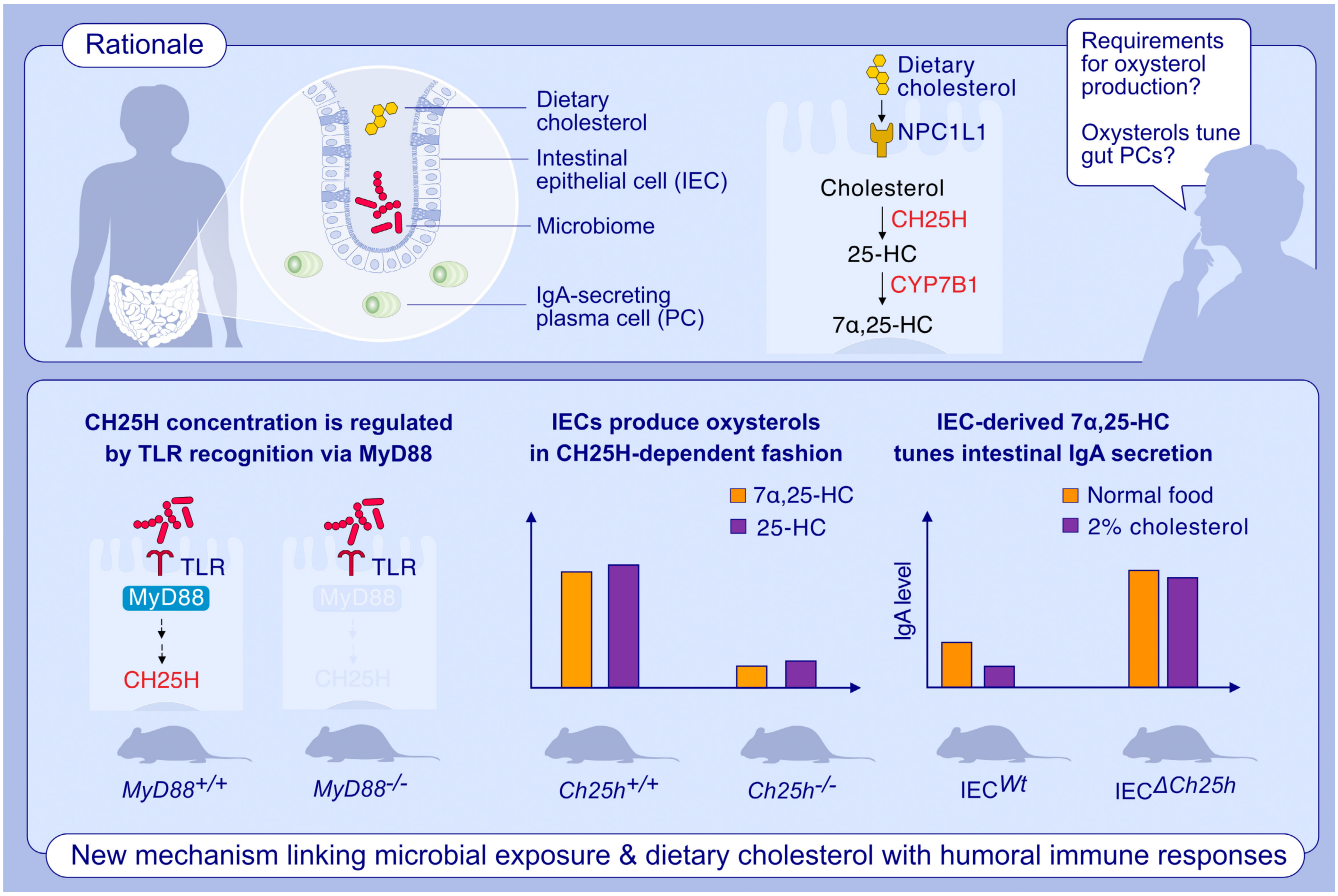


**FIGURE 1** The link between gut luminal stimuli, epithelial metabolism and immune response. In human, gut dietary cholesterol and microbes interact with intestinal epithelial cells (IECs). Dietary cholesterol is absorbed by IECs through the transmembrane protein Niemann–Pick C1-like 1 protein (NPC1L1), and then, by the action of two enzimes: cholesterol 25-hydroxylase(CH25H) and cytochrome P450(CYP7B1), generates the two oxysterols 25-hydroxycholesterol(25-HC) and 7α,25-dihydroxycholesterol(7α,25-HC) respectively. Oxysterols in the spleen and lymphonodes modulate immune system response but their role is still largely unknown at the gut level. One of the dominant lymphocyte populations, playing a pivotal role for protection from enteric pathogens and toxins in the gut, are IgA-secreting plasma cells (PCs). The stimuli influencing PCs IgA secretion are largely undefined. The CH25H induction is downstream of toll-like receptor (TLR) expressed by IECs. TRL is activated by microbe recognition at the gut level, and required *Myd88* signalling for CH25H expression. IECs produce oxysterols in CH25H-dependent fashion. Wild-type mice fed a diet enriched in cholesterol showed impaired sIgA production at gut level compared to mice fed with a normal diet. On the contrary, mice lacking CH25H, irrespective of diet, showed higher levels of sIgA production in the gut. Thus, sIgA secretion is derived from oxysterol levels, which in turn are regulated by CH25H expression.

the immunonutrition field and may also contribute to the dysbiosis development observed in obese patients; but further studies are needed to explore this exciting hypothesis.


## KEYWORDS

antibody, duodenum epithelial cells, oxysterols, plasma cells


## AUTHOR CONTRIBUTIONS

Laura Carucci and Roberto Berni Canani drafted the manuscript. The authors approved the final version of the manuscript as submitted and agreed to be accountable for all aspects of the work.


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## CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

## DATA AVAILABILITY STATEMENT

No original data included.


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