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Summary of: Gut microbiota derived bile acid metabolites maintain the homeostasis of gut and system immunity by Xiaomin Su, Yunhuan Gao, and Rongcun Yang

Bile acids (BA’s), derived from cholesterol, play crucial roles in vital physiological functions such as absorbing nutrients, maintaining glucose levels, and regulating energy expenditure. The liver produces primary bile acids such as cholic acid (CA) and chenodeoxycholic acid (CDCA), while secondary bile acids like deoxycholic acid (DCA) and lithocholic acid (LCA) are formed in the intestine with the help of microorganisms. Beyond their physiological functions, bile acids and their by-products influence the development and functions of different cells. These cells include macrophages, dendritic cells, regulatory T cells (Treg), B cells and others. Disturbances in BA’s and their metabolites can contribute to disease like inflammatory bowl diseases. BA’s and their derivatives contribute to maintaining a balance in the gut and the body.

Bile acids and their metabolites are not only abundant in the mammalian gut, but potentially distributed throughout other tissues and organs. In individuals, the immune system comprises both innate (e.g., macrophages, dendritic cells, natural killer cells) and adaptive (e.g., T-cells, B cells) components, along with numerous regulatory cells like T cells (Tregs), Breg cells, and innate immune lymphocytes (ILCs) that maintains immune balance locally and systemically. The gut microbiota produces metabolites such as short-chain fatty acids, tryptophan- derived metabolites, and bile acid derivatives, which regulate the differentiation and functions of these immune cells. Bile acids and their derivatives interact with various receptors expressed in different immune cells, influencing their differentiation and function. The specific affinity of each BAs derivative for its receptor determines its impact on immune cells. This provides insights into disease like inflammatory bowl diseases, metabolic disorders, obesity, and chronic inflammatory conditions. The primary BAs undergo conjugation with glycine, taurine, or other amino acids in hepatocytes and/ or gut microbiota. Then, conjugated BAs are secreted into the intestine, where bacterial enzymes transform them into secondary BAs , such as lithocholic acid and deoxycholic acid.

In humans, four distinct processes include deconjugation, dehydroxylation, oxidation, and epimerization that are all involved in the transformation of BAs, which were extensively reviewed. Primarily BAs, initially conjugated with glycine and taurine in the liver, are released into the intestine via the gallbladder. Recent research indicates that certain gut microbiota, like Clostridium bolteae, can also conjugate BAs with amino acids such as phenylalanine, leucine, and tyrosine. Conjugated bile acids (BAs) produced by the liver can undergo deconjugation in the small intestine through the action of bile salt hydrolases (BSHs). The enzymes are present in various gut microbiota such as Lactobacillus spp, Bifidobacterium spp, Enterococcus spp, Clostridium spp, and Bacteroides spp.

Macrophages (Macs) in the intestine are categorized into two main subpopulations, inflammatory macrophages associated with pro-inflammatory response and immune tolerogenic macrophages associated with immune suppressive responses. In the resting intestine, mature residents Macs derived from inflammatory monocytes Macs express contributing to intestinal homeostasis. The inconsistent effects of BAs on Macs are attributed to different receptors expressed in the cells with the majority of BAs activated receptors like FXR, TGR5, VDR, LXRs, PXR, and S1PR2 being detected in myeloid cells. While elevated cellular concentrations around 100-500 uM of bile acids, particularly hydrophilic secondary BAs, can act as danger-associated molecular pattern molecules (DAMPs), triggering calcium-dependent activation of the NLRP3 infammasome. It occurs when Macs are preactivated after exposure to endotoxin. Hydrophobic primary BAs like CDCA can induce NLRP3 activation and secretion of 1L-1B by promoting reactive oxygen species production and potassium outflow in Macs. BAs, in synergy with ATP, induce prolonged calcium influx and NLRP3 activation. Conjugated BAs like taurocholic acid active S1PR2, promoting immune cell infiltration and inflammation in mouse models. S1PR2 activation leads to caspase-11-dependent Mac pyroptosis and worsens E. coli sepsis, contributing to proinflammatory effects and increased liver damage.

Dendritic cells (DCs) are vital for adaptive immunity and immune regulation. The secondary bile acid deoxycholic acid (DCA) suppresses pro-inflammatory cytokines in DCs, but this effect is reversed by TGR5 deficiency. TGR5 inhibits NF-kB through TGR5-cAMP-PKA signaling, influencing monocyte differentiation into DCs with reduced IL-12 and TNF-a. Vitamin D receptor (VDR) activation inhibits inflammatory cytokines and the differentiation/maturation of DCs.

Different subsets of CD4 T helper (Th) cells, including Treg cells, Th17 cells, Th1 cells, and Th2 cells, are vital for immune homeostasis. Bile acids and their derivatives impact the differentiation and function of these cells. Treg cells, expressing Foxp3, maintain immune tolerance. BAs like isollooLCA and isoDCA promote Treg cell differentiation, with isolloLCA inducing FoxP3 expression through MitoROS production. VDR activation aids T cell maturation and reduces Th17 cell formation. Th17 cells, linked to autoimmunity, are inhibited by BAs such as 3-oxoLCA, isoLCA, and CA-3-S, targeting RORy. Th1 and Th2 cells have been crucial for immune responses and regulated by BAs. The VDR activation shifts Th1 to Th2, and PXR inhibits CD4 T cell proliferation. Innate lymphoid cells reflecting Th cell functions, express BA receptors. RORyt is essential for ILC3 generation, focusing BA role in tissue homeostasis and immune function.

BA derivative NorUDCA reshaped immunometabolism in CD8+ T cells, alleviating hepatic inflammation. TCA hinders the effectiveness of IFNa therapy in chronic hepatitis B patients by suppressing CD8+ T and Natural Killer cell function. Cholestatic mice exhibited a dysfunctional T cell response, with decreased CD4+ and CD8+ cell subpopulations and increased CTLA-4+CD4+ and CD8+subsets. Human CD8+ T lymphocytes express PXR, and its activation inhibits CD8+cell proliferation in vitro.

B cells play a vital role in the immune system contributing to antibody production antigen presentation, and cytokine release. When the bile acid receptor VDR is activated, it lead to various impacts on B lymphocytes, such as decreasing their proliferation, promoting apoptosis in activated B-Cell, and suppressing Ig production. Current studies propose that bile acids might impede vaccine responses, possible by hampering the development of post-class-switched memory B-cells.

NKT cells form a unique subset of T cells recognizing lipids through the non-classical class I molecule CD1D. Comprising type I and II NKT cells, they play a crucial role in tumor immunity, with type I promoting and type II suppressing it. Despite type I NKT cells tumor immunity promotion, they can also induce immunosuppressive Treg cells. Activating the Bile acid receptor FXR in NKT cells inhibits the production osteopontin, a potent pro-inflammatory mediator, that drives NKT cells toward IL-10 secreting type I NKT cells and significantly expand the subset of IL-10 secreting type II NKT cells. Recent research indicates that gut microbiota-mediated bile acid metabolism regulates liver antitumor immunity by influencing NKT cell accumulation.

Metabolic diseases like obesity, type 2 diabetes (T2D), cardiovasucular disease, and non-alcoholic fatty liver disease (NAFLD) are often characterized as chronic inflmamatory conditions. Altered bile acid metabolism is implicated in contributing to these inflammatory disease, and bile acids and their derivatives are considered valuable therapeutic agents. Obesity, driven by imbalances in energy intake and expenditure, leads to metabolic disorders and chronic low-grade inflammation. Interventions such as UDCA supplementation and dietary acetic acid have shown in controlling diet-induced obesity. Bile acid administration in mice increases energy expenditure in brown adipose tissue and preventing obesity and insulin resistance. Studies have suggested that modifying bile acid metabolism can effectively control and prevent these conditions. The relationship between gut microbiota, dietary factors, and bile acid metabolism further highlight the intricate connections between metabolic health and inflammatory diseases.

In conclusion, Bile acids (BAs) exist in various forms, including conjugated and deconjugated primary BAs, secondary BAs like DCA and LCA, and their derivatives. Originating in the liver, primary BAs undergo transformation such as deconjugation, dehydroxylation, and dehydrogenation, and epimerization, by gut microbiota to yield secondary BAs and derivatives. These compounds interact with receptors on immune cells like Macs, MDSCs, DCs,Tregs,Th17, cell, ILCs, CD4 cells, CD8 cells, B cells, and NKT cells, influencing their differentiation and function, thereby impacting both innate and adaptive immune responses for homeostasis. Dysregulation of BA homeostasis is observed in inflammation-associated disorders, including inflammatory bowl disease.