Perspective

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The role of bile acids in human aging

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Abstract: Bile acids are recognized as important signaling molecules that enable fine-tuned inter-communication from the liver, through the intestine, to virtually any organ, thus encouraging their pleiotropic physiological effects. Aging is a complex natural process defined as a progressive decline in cellular and organismal functions. A causal link between bile acids and the aging process is emerging. However, there are gaps in our understanding of the molecular mechanisms and precise targets responsible for the alteration of bile acid profiles and their role in the aging process. Intestinal barrier dysfunction leads to endotoxemia, systemic inflammation, insulin resistance, diabetes, lipid accumulation, obesity and fatty liver diseases, and health decline and death. In fact, intestinal barrier dysfunction is suggested to be an evolutionarily conserved hallmark of aging. Bile acids may modulate the aging process by regulating intestinal barrier integrity.

Keywords: age; bile acid; gut microbiota; enterohepatic circulation; intestinal barrier

In 2022, almost 10 % of the global population was 65 years or older. This segment has been growing at an increasing rate. It is expected to reach 16 % in 2050 and 24 % by 2100. Alarmingly, 90 % of individuals within this age group are grappling with age-associated dysfunctions. There is still a need to develop effective safe treatments that address the underlying causes of aging and provide a path to healthier aging. A better understanding of the causes and consequences of age-onset intestinal barrier dysfunction has relevance to the development of interventions to improve healthspan. Beyond nutrient digestion and absorption, bile acids (BAs) play a crucial role in various physiological functions, such as metabolism and cancer, as signaling molecules. However, BAs have been ignored in terms of age-associated conditions.

The current understanding of the relationship between BAs and aging

Reciprocal regulation between BAs and gut microbiota

BAs are synthesized from cholesterol in the liver through oxidation catalyzed by hepatic cytochrome P450 (CYP) and conjugation catalyzed by bile acid-CoA synthase (BACS) and bile acid-CoA: amino acid N-acyltransferase (BAAT). Subsequently, BAs are secreted into the intestine, where BAs undergo transformation into secondary or tertiary BAs via de-hydroxylation and/or de-conjugation facilitated by enzymes in the gut microbiota. In turn, BAs influence the composition of the intestinal microbiota by exhibiting antimicrobial activity and activating signaling pathways crucial for maintaining gut homeostasis. The interaction between BAs and gut microbiota is a dynamic equilibrium. Disruption of this balance could lead to metabolic diseases, inflammation, and cancer, and accelerate the aging process.

Gut microbiota and aging

The gut microbiota plays a crucial role in both the development and maintenance of the host immune system and the functionality of the intestinal barrier. When fecal microbiota is transplanted from young mice to aged counterparts, the recipients exhibit significant extension in healthspan [1]. This effect was attributed to the correction of aging-associated intestinal dysbiosis and the restoration of secondary bile acids. Gut microbes, including *Akkermansia muciniphila* (*A. muciniphila*), which comprise 3–5 %

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of the intestinal microbial community in humans, have contributed to extending healthspan and lifespan in mice. In mice, the introduction of exogenous *A. muciniphila* to the intestine improved barrier integrity, reduced endotoxin induction and inflammation, protected against metabolic disorders and inflammatory bowel disease (IBD), and modulated the aging process [2]. These findings underscore a role for the gut microbiota in aging.

Role of BAs in the intestinal barrier

Intestinal barrier dysfunction was suggested to be an evolutionarily conserved hallmark of aging. Alterations in the gastrointestinal environment can impact the integrity of the intestinal barrier. For example, the presence of deoxycholic acid (DCA) in drinking water disrupted the mucosal barrier and induced intestinal inflammation in mice [3]. DCA inhibits mucosal healing, while ursodeoxycholic acid (UDCA) promotes it [4]. Additionally, DCA and cholic acid (CA) reduced the expression of α-defensins in cultured ileum *in vitro* [5]. Cytochrome P450 family 8 subfamily B member 1 (*Cyp8b1*) knockout mice, characterized by an altered BA profile with a decreased ratio of 12α-hydroxylated (12α-OH) BAs to non-12α-OH BAs, exhibited elevated levels of antimicrobial peptides, such as regenerating islet-derived protein type 3 (Reg3). Reg3 promoted the self-renewal of the intestinal lining and modified the growth of gut microbes [6]. Conversely, exogenous CA or liver CYP8B1 overexpression exacerbated intestinal injury by suppressing the renewal of intestinal stem cells (ISC) and reducing the levels of antimicrobial peptides [7]. Therefore, dysregulation of enterohepatic circulating BAs may alter the function of the intestinal barrier by influencing ISC renewal (physical barrier), immune cell differentiation (immunological barrier), and commensal bacterial dysbiosis (biochemical barrier).

Alteration of BA profile with age

Aging is associated with a decline in BA levels and alteration in BA profile [8]. Existing information hinted at a potential connection between BAs and the aging process, exemplified by the anti-aging effects of lithocholic acid (LCA) in yeast and the enrichment of LCA derivative (e.g., isoallo-LCA) in centenarians [9]. Additionally, UDCA and its derivatives play a role in protecting against neurodegenerative disorders [10]. Bile acid sequestrants can be used to treat conditions such as hypercholesterolemia and dyslipidemia, which impact healthspan. Notably, regular exercise and diet modulation can change the profiles of BAs and gut microbiota, and have a pronounced effect on intestinal barrier function, impacting aging and lifespan. These findings suggest that an altered BA profile and/or specific BAs may contribute to the age-related neural decline and longevity.

Perspectives

Targeting BA receptors

BA receptors help maintain the intestinal barrier function. Beyond the role in maintaining cholesterol and BA balance in the liver, farnesoid X receptor (FXR) is vital for the inflammatory response and preservation of the intestinal barrier function. FXR ligands demonstrated therapeutic efficacy in IBD by enhancing the intestinal barrier [11]. Similarly, activation of Takeda G protein-coupled receptor 5 (TGR5) is closely associated with anti-inflammatory effects and the reinforcement of the intestinal barrier. Dietary supplementation with tauroursodeoxycholic acid (TUDCA) reduced the incidence of diarrhea in weaned piglets by enhancing intestinal barrier function and immunity mediated by TGR5 [12]. Vitamin D receptor (VDR) is highly expressed in the intestine and is activated by specific BAs such as LCA. As a transcription factor, VDR regulates the expression of several tight junction genes, including those that encode for Claudins and ZOs, in intestinal epithelial cells [13]. Conjugated BAs activate sphingosine-1-phosphate receptor 2 (S1PR2), and the inhibition of S1PR2 alleviated colonic damage in mice with ulcerative colitis [14]. Given that intestinal barrier dysfunction is recognized as an evolutionarily conserved hallmark of aging, any modulation that redirects BA receptor signaling pathways towards protecting the intestinal barrier holds the potential to extend health and lifespan (Figure 1).

Targeting BA–gut microbiota

Inflammation and immunosenescence are prevalent features of aging and compromised intestinal barrier may drive the aging process. Multiple cellular and matric layers compose the intestinal barrier. In this regard, the commensal gut microbiota serves as a biological barrier responsible for colonization resistance. Beyond *A. muciniphila*, numerous bacteria demonstrate protective effects on the intestinal barrier. For example, *Clostridia*, a dominant class of commensal microbes, stimulates the generation of colonic regulatory T cells. These cells suppress inflammatory and allergic responses by producing butyrate and other

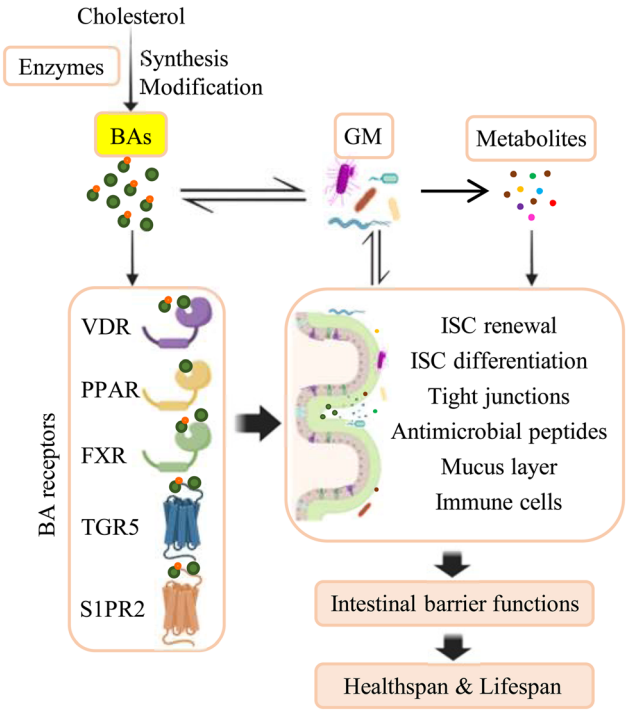

Figure 1: Illustration of potential pathways for BAs in regulating the intestinal barrier functions that impact healthspan and lifespan. Bile acids (BAs) undergo synthesis and modification by hepatic and gut enzymes. These BAs, through a network of receptors (e.g., nuclear receptors VDR, PPAR, and FXR, and G protein-coupled receptors TGR5 and S1PR2), play pivotal roles in regulating various aspects of the intestinal barrier functions. These include the modulation of the renewal and differentiation of intestinal stem cells (ISC), the expression of tight junction and mucus layer proteins, the secretion of antimicrobial peptides, and the function of immune cells. Furthermore, BAs influence these functions by shaping the profiles of gut microbiota (GM) and their metabolites. By strategically targeting upstream enzymes or downstream receptors and modulating gut microbiota to alter the BA pool towards a beneficial profile, which in turn may extend healthspan and lifespan by enhancing the integrity and functions of the intestinal barrier. VDR, vitamin D receptor; PPAR, peroxisome proliferator-activated receptor; FXR, farnesoid X receptor; TGR5, Takeda G protein-coupled receptor 5; S1PR2, sphingosine-1-phosphate receptor 2.

short chain fatty acids, thereby preserving the intestinal barrier [15]. Conversely, certain gut microbiota produce toxins that enter the circulation and contribute to diseases. For instance, *Muribaculaceae* bacterium produces lipopolysaccharides (LPS) while abundance of *Muribaculaceae* negatively correlates with mucus layer thickness and positively correlated with increased intestinal permeability and liver inflammation [16]. As mentioned, BAs are determinants of microbiota abundance, diversity, and metabolic activity. Targeting the interplay between BAs and gut microbiota to fortify the function of the intestinal barrier may provide a means to extend healthspan and lifespan (Figure 1).

Targeting enzymes for BA synthesis and modification

Beyond the downstream targets of BAs, the upstream enzymes that are responsible for BA synthesis and modification are essential for modifying the BA profiles that ultimately regulate the animal physiology. For instance, age is linked to reduced BA synthesis, possibly related to decreased expression of cholesterol 7 alpha-hydroxylase (CYP7A1). Deficiency in 12 alpha-hydroxylase (CYP8B1) significantly lowers the levels of 12α-OH BAs, leading to improved metabolism and reduced inflammation in humans and rodents. Animals with silenced *Cyp8b1* gene, such as naked mole-rats, exhibit favorable metabolic characteristics and longer lifespan. Moreover, the conjugation pattern of BAs, predominantly regulated by hepatic BAAT and BACS and gut bile salt hydroxylase (BSH), undergoes changes with age. Given these facts, modifying the enzymes involved in BA synthesis and modification could provide yet another strategy to extend healthspan and lifespan (Figure 1).

In conclusion, maintaining the intestinal barrier integrity is crucial for the overall wellbeing of the organism across its lifespan. Strategically targeting the BAs profile and related pathways to enhance the functionality of the intestinal barrier represents a promising strategy to prevent or delay age-associated conditions.

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