

## 質量分析装置による腸内細菌の代謝産物解析を利用した機能性食品の開発

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Development of the functional food thorough analysis of bacterial metabolites using a mass spectrometer

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Mass spectrometry-based metabolomics targeting fecal sample identified a large number of low molecular weight chemicals, which are associated with health and disease, produced by the intestinal microbiome<sup>1</sup>. Polyamines, especially spermidine, which are the bioactive chemicals promote autophagy and suppress inflammation. An extension of lifespan via the oral administration of polyamines, especially spermidine, in model organisms, such as worms, fruit flies, and mice has been reported<sup>2</sup>. We also found that the upregulation of colonic luminal polyamines produced by the intestinal microbiota delays senescence in mice<sup>3</sup>. Recently, it was reported that cardiovascular diseases, including atherosclerosis, can be prevented by spermidine supplementation in rodent experiments<sup>4</sup>. Considering the intestinal microbiome as a manufacturing plant for bioactive substances, by metabolomics using capillary electrophoresis time-of-flight mass spectrometry, we developed a novel polyamine biosynthesis system strategy, in which the simultaneous intake of *Bifidobacterium animalis* subsp. *lactis* LKM512 (*Bifal*) and arginine (Arg) upregulates the production of the putrescine, a precursor of spermidine, in the gut by controlling the bacterial metabolism beyond its vast diversity and inter-individual differences<sup>3,5</sup>. In a clinical trial, healthy individuals with a body mass index near the maximum “healthy” range (25 kg/m<sup>3</sup>; n = 44) were randomized to consume either normal yogurt containing *Bifal* and Arg (*Bifal*+Arg YG) or placebo (normal yogurt) for 12 weeks<sup>6</sup>. The change in reactive hyperemia index determined by EndoPAT from week 0 to 12 in the *Bifal*+Arg YG group was significantly higher than that in the placebo group, indicating that *Bifal*+Arg YG intake improved vascular endothelial function. In addition, the concentrations of fecal putrescine and serum spermidine in the *Bifal*+ Arg YG group were significantly higher than those in the placebo group. These findings suggest that consuming *Bifal*+Arg YG prevents or reduces atherosclerosis risk by upregulating blood spermidine levels, which subsequently induces the suppression of inflammatory reaction and the promotion of autophagy.

**Keywords :** Polyamines; Intestinal microbiome; Metabolomics; Atherosclerosis; Arginine

質量分析装置を用いた糞便メタボロミクスにより、健康／疾病に関与する腸内細菌叢由来の低分子代謝産物の存在が明らかになった<sup>1</sup>。その中の一つであるポリアミン(特にスペルミジン)は、抗炎症作用やオートファジー促進等の生理活性を有し、外因性ポリアミンの供給によるモデル生物で個体レベルでの寿命延伸効果に加え<sup>2,3</sup>、近年、動脈硬化を含む心臓疾患の予防への有効性がマウス実験で報告されている<sup>4</sup>。我々は、CE-TOFMS メタボロミクスを用いて、個体差が大きい腸内細菌叢に安定的にポリアミン(プトレッシン: スペルミジンの前駆体)を作らせる新規技術として、ビフィズス菌 *Bifidobacterium animalis* subsp. *lactis* LKM512 (*Bifal*)とアルギニン(Arg)の併用投

与法を開発した<sup>3,5</sup>。これらを添加したヨーグルト(*Bifal+Arg YG*)を作製し肥満傾向の被験者を対象に無作為化二重盲検試験を実施した結果、糞便のプトレッシンと血清スぺルミジン濃度が増加し、投与前後の血管内皮機能値の変化が *Bifal+Arg YG* 群でプラセボ群と比較して有意に高く改善し、動脈硬化予防効果が認められた<sup>6</sup>。(臨床試験等の詳細は英語参照)。

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