

Title	高親和性IgA中和抗体産生を増強する大豆粉由来因子の探索
Sub Title	Soybean flour-derived factors enhance high-affinity IgA antibodies against commensal microbiota
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Abstract	食事は腸内細菌叢の重要な修飾因子であり、実際に離乳期に固形食の摂食とともに腸内細菌叢が成熟を始める。離乳期に異なるタイプの食餌を与え、異なる細菌叢をもつマウスを作成することで、Tfh細胞の分化誘導を行う腸内細菌叢の探索が容易になると考えた。はじめに離乳期のマウスに非精製飼料CE-2及び精製飼料AIN-93Gを摂食させ、パイエル板のTfh細胞を解析した。その結果AIN-93G摂食群ではCE-2摂食群と比較して顕著にTfh細胞やGCB細胞が割合、数ともに減少し、糞便中分泌型IgA量もAIN-93G摂食群ではCE-2摂食群の1/3程度にまで減少した。またAIN-93G摂食群におけるTfh細胞やGCB細胞の減少は小腸近位部と比較して、小腸遠位パイエル板で顕著であった。次にCE-2に含有される原材料のうち、小腸遠位パイエル板Tfh細胞数の維持に寄与する原材料を探索したところ、AIN-93Gに大豆粉を添加した群でCE-2摂食群と同程度にまでTfh細胞やGCB細胞の数と割合、糞便中IgA量が回復した。以上の結果から大豆粉がTfh細胞の分化誘導を介して高親和性IgA産生誘導を行うことが示唆された。 大豆粉の摂食によるTfh細胞の増加はスペクトラムの異なる3種類の抗菌剤の単剤投与でそれぞれキャンセルされた。これら3剤の抗菌剤への感受性や大豆粉摂食群で特徴的に増加している腸内細菌を統合的に解析した結果、Muribaculum intestinaleとLactobacillus reuteriの2菌をTfh細胞誘導細菌の候補とした。これら2菌を無菌マウスに定着させたノトバイオートマウスのパイエル板では、無菌マウスと比較してTfh細胞やGCB細胞が割合、数ともに増加し、糞便中IgA量も増加した。さらにGCB細胞の割合、数や糞便中IgAは、M. intestinaleとL. reuteriそれぞれ単菌のノトバイオートマウスと比較しても2菌のノトバイオートマウスで有意に高い値を示したことから、この2菌が協働してTfh-GCB細胞応答を増強していることが示唆された。 Diet is an important modifier of the gut microbiota, and indeed the gut microbiota begins to mature with the feeding of solid food during weaning. We thought that by feeding different types of diets during weaning and creating mice with different microbiota composition, it would be easier to search for the gut microbiota that induces Tfh cell differentiation. First, we fed the weaned mice with a non-purified diet CE-2 and purified diet AIN-93G and analyzed Peyer's patches of Tfh, GCB cells. The results showed that the number and percentage of Tfh cells and GCB cells were significantly decreased in the AIN-93G-fed group compared to the CE-2-fed group, and the amount of secretory IgA in the feces of the AIN-93G-fed group was about 1/3 that of the CE-2-fed group. The decrease in Tfh cells and GCB cells in the AIN-93G-fed group was more pronounced in the distal Peyer's patches of the small intestine than in the proximal small intestine. Next, we searched for raw materials contained in CE-2 that contribute to the maintenance of the number of Tfh cells in the distal Peyer's patches of the small intestine and found that the number and percentage of Tfh and GCB cells and the amount of IgA in feces recovered in the group fed AIN-93G plus soybean flour to the same level as the CE-2 fed group. These results suggest that soybean flour induces high-affinity IgA production via induction of Tfh cell differentiation. The increase in Tfh cells induced by soybean flour feeding was canceled by single-dose administration of three antimicrobial agents with different spectrums. Based on an integrated analysis of the sensitivity to these three antimicrobial agents and the intestinal bacteria characteristically increased in the soybean flour feeding group, two bacteria, Muribaculum intestinale and Lactobacillus reuteri, were selected as candidates for Tfh cell-inducing bacteria. In the Peyer's patches of gnotobiotic mice in which these two bacteria were established in germ-free mice, the percentage and number of Tfh cells and GCB cells were increased, as well as the amount of IgA in the feces, compared to germ-free mice. Furthermore, the percentage and number of GCB cells and fecal IgA were significantly higher in the two-bacteria gnotobiotic mice than in the single-bacteria gnotobiotic mice, suggesting that the two bacteria cooperate to enhance the Tfh-GCB cell response.
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2023年度 学事振興資金（個人研究）研究成果実績報告書

研究代表者	所属	薬学部	職名	専任講師	補助額	300千円 (A)
	氏名	高橋 大輔	氏名（英語）	Takahashi Daisuke		
研究課題（日本語）						
高親和性IgA中和抗体産生を増強する大豆粉由来因子の探索						
研究課題（英訳）						
Soybean flour-derived factors enhance high-affinity IgA antibodies against commensal microbiota						
1. 研究成果実績の概要						
食事は腸内細菌叢の重要な修飾因子であり、実際に離乳期に固形食の摂食とともに腸内細菌叢が成熟を始める。離乳期に異なるタイプの食餌を与え、異なる細菌叢をもつマウスを作成することで、Tfh細胞の分化誘導を行う腸内細菌叢の探索が容易になると考えた。はじめに離乳期のマウスに非精製飼料CE-2及び精製飼料AIN-93Gを摂食させ、パリエル板のTfh細胞を解析した。その結果AIN-93G摂食群ではCE-2摂食群と比較して顕著にTfh細胞やGCB細胞が割合、数ともに減少し、糞便中分泌型IgA量もAIN-93G摂食群ではCE-2摂食群の1/3程度にまで減少した。またAIN-93G摂食群におけるTfh細胞やGCB細胞の減少は小腸近位部と比較して、小腸遠位パリエル板で顕著であった。次にCE-2に含有される原材料のうち、小腸遠位パリエル板Tfh細胞数の維持に寄与する原材料を探索したところ、AIN-93Gに大豆粉を添加した群でCE-2摂食群と同程度にまでTfh細胞やGCB細胞の数と割合、糞便中IgA量が回復した。以上の結果から大豆粉がTfh細胞の分化誘導を介して高親和性IgA産生誘導を行うことが示唆された。大豆粉の摂食によるTfh細胞の増加はスペクトラムの異なる3種類の抗菌剤の単剤投与でそれぞれキャンセルされた。これら3剤の抗菌剤への感受性や大豆粉摂食群で特徴的に増加している腸内細菌を統合的に解析した結果、Muribaculum intestinaleとLactobacillus reuteriの2菌をTfh細胞誘導細菌の候補とした。これら2菌を無菌マウスに定着させたノトパイオートマウスのパリエル板では、無菌マウスと比較してTfh細胞やGCB細胞が割合、数ともに増加し、糞便中IgA量も増加した。さらにGCB細胞の割合、数や糞便中IgAは、M. intestinaleとL. reuteriそれぞれ単菌のノトパイオートマウスと比較しても2菌のノトパイオートマウスで有意に高い値を示したことから、この2菌が協働してTfh-GCB細胞応答を増強していることが示唆された。						
2. 研究成果実績の概要（英訳）						
Diet is an important modifier of the gut microbiota, and indeed the gut microbiota begins to mature with the feeding of solid food during weaning. We thought that by feeding different types of diets during weaning and creating mice with different microbiota composition, it would be easier to search for the gut microbiota that induces Tfh cell differentiation. First, we fed the weaned mice with a non-purified diet CE-2 and purified diet AIN-93G and analyzed Peyer's patches of Tfh, GCB cells. The results showed that the number and percentage of Tfh cells and GCB cells were significantly decreased in the AIN-93G-fed group compared to the CE-2-fed group, and the amount of secretory IgA in the feces of the AIN-93G-fed group was about 1/3 that of the CE-2-fed group. The decrease in Tfh cells and GCB cells in the AIN-93G-fed group was more pronounced in the distal Peyer's patches of the small intestine than in the proximal small intestine. Next, we searched for raw materials contained in CE-2 that contribute to the maintenance of the number of Tfh cells in the distal Peyer's patches of the small intestine and found that the number and percentage of Tfh and GCB cells and the amount of IgA in feces recovered in the group fed AIN-93G plus soybean flour to the same level as the CE-2 fed group. These results suggest that soybean flour induces high-affinity IgA production via induction of Tfh cell differentiation. The increase in Tfh cells induced by soybean flour feeding was canceled by single-dose administration of three antimicrobial agents with different spectrums. Based on an integrated analysis of the sensitivity to these three antimicrobial agents and the intestinal bacteria characteristically increased in the soybean flour feeding group, two bacteria, Muribaculum intestinale and Lactobacillus reuteri, were selected as candidates for Tfh cell-inducing bacteria. In the Peyer's patches of gnotobiotic mice in which these two bacteria were established in germ-free mice, the percentage and number of Tfh cells and GCB cells were increased, as well as the amount of IgA in the feces, compared to germ-free mice. Furthermore, the percentage and number of GCB cells and fecal IgA were significantly higher in the two-bacteria gnotobiotic mice than in the single-bacteria gnotobiotic mice, suggesting that the two bacteria cooperate to enhance the Tfh-GCB cell response.						
3. 本研究課題に関する発表						
発表者氏名 (著者・講演者)		発表課題名 (著書名・演題)		発表学術誌名 (著書発行所・講演学会)	学術誌発行年月 (著書発行年月・講演年月)	

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