シンポジウム 2-4

腸内細菌が皮膚生理に及ぼす影響

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【背景と目的】日本では「便秘で肌が荒れる」等，腸内環境が皮膚生理と密接にかかわっていることを自覚する健常女性が少なくない．しかしながら，これらの相互作用の科学的根拠を示す報告は殆どない．そこで我々は，腸内細菌と皮膚生理とのかかわりについて，いくつかのアプローチにより検討を行っている．本講演では，特定の腸内細菌の代謝産物であるフェノール類（フェノール，パラクレゾール）が肌荒れを引き起こす機構について，これまでの研究成果を紹介する．

【結果】
1）ヘアレスマウス（Hos:hr-1）へのチロシン負荷実験において，チロシン負荷飼料投与群では通常飼料投与群よりも，盲腸内容物中，血中，皮膚中のフェノール類量が有意に高いことが示された．また，皮膚は肝臓よりもフェノール類が蓄積されやすいことが示唆された．
2）無菌ヘアレスマウスを用いて，通常ヘアレスマウス糞便中から単離されたフェノール産生菌（*Morganella morganii*: TD4）およびフェノール非産生菌（*Escherichia coli*: D5a）のノトバイオート実験を行った．その結果，TD4定着マウス群ではD5a定着マウス群よりも角質細胞面積が有意に小さく，表皮細胞の分化（角化）に変調をきたしていることが示された．さらに，TD4定着マウス群では皮膚のくすみ（皮膚色b*値の有意な増加）が認められた．
3）ヒト表皮細胞を用いた*in vitro*分化誘導実験において，細胞毒性を示さない20 nmol/mlのフェノール類の添加は，表皮細胞の分化マーカーであるKeratin 10の発現を抑制した．
4）日常的にプロ-/プレ-バイオティクスを摂取する健常女性19名に，3週間のプロ-/プレ-バイオティクス摂取制限後，ガラクトオリゴ糖を含むプレバイオティクス飲料を3週間飲用してもらった．その結果，摂取制限により血中パラクレゾール量の有意な増加，健全な表皮細胞角化状態を示すパラメータおよび角層水分含量の有意な減少が認められ，角化状態が悪化し皮膚が乾燥していることが示唆された．さらにプレバイオティクス飲用により，血中パラクレゾールの有意な減少，角化状態および皮膚乾燥の有意な改善が認められた．
5）健常女性40名を対象に，ガラクトオリゴ糖を含むビフィズス菌発酵乳のプラセボ対照二重盲験並行群間飲用試験を行ったところ，被験飲料に血中パラクレゾール量減少効果および皮膚性状改善効果が認められた．

【考察】以上の結果より，腸内細菌が産生したフェノール類は，吸収され血流を介して皮膚に蓄積し，表皮細胞の正常な分化に変調をきたすことで，皮膚のくすみや乾燥を引き起こすことが示唆された．また，プロバイオティクスおよびプレバイオティクス摂取の，血中パラクレゾール量減少作用を介する皮膚性状改善効果が示された．

Gut Microbiota and Skin Homeostasis

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Among Japanese women, it is commonly believed that persistent constipation leads to skin problems; however, there is little empirical evidence linking the gut environment to skin condition. Our group is actively investigating the relationship between gut microbiota and skin homeostasis using a number of approaches. This presentation focuses on the impact of phenolic metabolites produced by gut bacteria on the host skin condition.

In experiments using hairless mice (Hos:hr-1), a tyrosine-enriched diet caused increased phenol levels (phenol and *p*-cresol) in caecal contents, serum, flank skin and livers. Interestingly, the levels of phenols in skin were much higher than those in livers, indicating that lipid-soluble phenols may preferentially accumulate in skin, which has relatively high lipid content. Gnotobiotic hairless mice challenged with *Morganella morganii* (TD4), a phenol-producing gut bacterium, or *Escherichia coli* (D5a), a phenol-non-producing gut bacterium, both were derived from feces of hairless mice, were also analyzed to examine the effects of microbial phenolic metabolites on skin. Compared to D5a-colonized gnotobiotic mice, the skin of mice challenged with TD4 appeared yellowish dullness (confirmed by high color meter b* values), and exhibited disturbed keratinocyte differentiation, as indicated by measurements of corneocyte size. In *in vitro* experiments using monolayer-cultured keratinocytes, we demonstrated that phenols disrupted the early stage of keratinocyte differentiation at a concentration (20 nmol/ml) which was not toxic to cells. To determine whether the identical phenomenon observed in mice and *in vitro* experiments are also applicable to humans, as well as to evaluate the efficacy of pre- and probiotics, we conducted two human trials. In a prebiotic-beverage administration trial, 19 healthy female volunteers refrained from consuming pro- or prebiotics during an initial 3-week restriction period, and were then administered a daily prebiotic beverage (containing 3.0 g galacto-oligosaccharides) for 3 weeks. Although serum *p*-cresol levels significantly increased during the restriction period, the levels markedly decreased following prebiotic administration. In addition, keratinocyte differentiation, which was evaluated by corneocyte size and cathepsin L-like activity in stratum corneum, and skin conductance, an indicator of skin moisture level, significantly declined during the restriction period, but recovered on prebiotic administration. Finally, in a double-blind, placebo-controlled trial involving 40 healthy women treated with a synbiotic beverage, *Bifidobacterium breve*-fermented milk containing 1.0 g galacto-oligosaccharides, for 4 weeks, the serum *p*-cresol levels of the test group were significantly reduced compared to those of the placebo group. Similar to the prebiotic trial, a tendency of higher cathepsin L-like activity and moisture content of stratum corneum was also observed in the test group.

From the results of the *in vitro* and mice experiments, and our human trials, we conclude that phenols produced by gut bacteria are absorbed in the colon, distributed by the circulation system, and accumulate in skin, where they subsequently cause skin problems, particularly dullness and dryness, through the disruption of normal keratinocyte differentiation. Furthermore, consumption of both probiotics and prebiotics appears to be a promising treatment for maintaining healthy skin via decreasing serum *p*-cresol levels.