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Uptake of *Staphylococcus aureus* by keratinocytes is reduced by interferon–fibronectin pathway and filaggrin expression

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Abstract

Staphylococcus aureus (*S. aureus*) is frequently detected in the skin of patients with atopic dermatitis (AD). AD skin-derived strains of *S. aureus* (AD strain) are selectively internalized into keratinocytes (HaCaT cells) compared to standard strains. However, the mechanism of AD strain internalization by keratinocytes and effect of the skin environment on internalization remain unclear. HaCaT cells were exposed to heat-killed AD or standard strains of fluorescently labeled *S. aureus*, with or without interferon (IFN)-γ, interleukin (IL)-4, and IL-13 cytokines, for 24 h. Filaggrin and fibronectin expression in HaCaT cells was knocked down using small interfering RNA. The amount of internalized *S. aureus* was evaluated using a cell imaging system. The effects of INF-γ, IL-4, and *S. aureus* exposure on mRNA expression in HaCaT cells were analyzed using single-cell RNA sequencing. AD strains adhered to HaCaT cells in approximately 15 min and were increasingly internalized for up to 3 h (2361 ± 467 spots/100 cells, mean ± SD), whereas the standard strain was not (991 ± 71 spots/100 cells). In the presence of IFN-γ, both the number of internalized strains and fibronectin expression significantly decreased compared to in the control, whereas Th2 cytokines had no significant effects. The number of internalized AD strains was significantly higher in filaggrin knockdown and lower in fibronectin knockdown HaCaT cells compared to in the control. RNA sequencing revealed that IFN-γ decreased both fibronectin and filaggrin expression. Keratinocyte internalization of the AD strain may be predominantly mediated by the INF-γ-fibronectin pathway and partially regulated by filaggrin expression.

KEYWORDS
atopic dermatitis, cell imaging, keratinocyte, microbiome, *Staphylococcus aureus*

アトピー性皮膚炎におけるケラチノサイトと黄色ブドウ球菌、皮膚免疫との関連について、次世代シークエンサーと画像解析ソフトを用いて解析を行いました。