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Targeting hidradenitis suppurativa inflammation with dairy-derived lactic acid bacteria: potential immunomodulatory effects

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Introduction

Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic inflammatory skin disorder marked by recurrent abscesses, painful nodules and scarring in various areas of the body, often rich in apocrine glands. Recent studies have implicated keratinocytes (KCs) as active participants in HS lesions indicating that dysfunction in these cells may contribute to the production of proinflammatory cytokines within and around the affected tissue, along with increased immune cell infiltration. In this context, the present study aimed to evaluate the production of proinflammatory cytokines in HaCaT cells, an immortalized human keratinocyte line, following stimulation with either tumor necrosis factor (TNF), a multifunctional cytokine implicated in HS, leading to further induction of other mediators, or lipopolysaccharide (LPS), a commonly used model for general inflammatory responses. Using both stimulation models, 32 lactic acid bacteria (LAB), isolated from dairy products, and previously characterized for their probiotic potential, were assessed for their ability to reduce proinflammatory cytokine levels induced/expressed by HaCaT with the goal of identifying candidates with potential anti-inflammatory effects against HS or other immune-mediated skin disorders.

Methods

LAB strains used in the present study

		Genus/Species	ACA-DC Number	Isolation product
Isolates with probiotic potential	1	*Lactiplantibacillus plantarum*	146	Feta cheese
(1st group of LAB stains)	2	*Lactiplantibacillus plantarum*	201	Kasseri cheese
	3	*Lactiplantibacillus plantarum*	805	Soured sheep milk
	4	*Lactiplantibacillus plantarum*	2640	Feta cheese
	5	*Lactiplantibacillus plantarum*	4039	Kasseri cheese
	6	*Lactobacillus delbrueckii* subsp. *bulgaricus*	87	Yogurt
	7	*Leuconostoc mesenteroides*	1738	Melichloro cheese
	8	*Levilactobacillus brevis*	1705	Melichloro cheese
	9	*Limosilactobacillus fermentum*	179	Kasseri cheese
	10	*Streptococcus thermophilus*	26	Sheep milk yogurt
	11	*Streptococcus thermophilus*	835	Yogurt
Fiji-Milk isolates	1	*Lactiplantibacillus plantarum/paraplantarum/pentosus*	1462	Fermented cow milk
(2nd group of LAB strains)	2	*Lactiplantibacillus plantarum/paraplantarum/pentosus*	1463	Fermented cow milk
	3	*Lactiplantibacillus plantarum/paraplantarum/pentosus*	1470	Fermented cow milk
	4	*Lactiplantibacillus plantarum/paraplantarum/pentosus*	1473	Fermented cow milk
	5	*Lactococcus lactis*	1476	Fermented cow milk
	6	*Lactococcus lactis*	1477	Fermented cow milk
	7	*Leuconostoc lactis*	1480	Fermented cow milk
	8	*Leuconostoc holzapfelii*	1482	Fermented cow milk
	9	*Lacticaseibacillus casei/paracasei/zeae*	1484	Fermented cow milk
	10	*Lactiplantibacillus plantarum/paraplantarum/pentosus*	1486	Fermented cow milk
	11	*Lactiplantibacillus plantarum/paraplantarum/pentosus*	1489	Fermented cow milk
Fiji-Yogurt isolates	1	*Lactiplantibacillus plantarum/paraplantarum/pentosus*	1495	Home made yogurt
(3rd group of LAB strains)	2	*Lactiplantibacillus plantarum/paraplantarum/pentosus*	1497	Home made yogurt
	3	*Lactiplantibacillus plantarum/paraplantarum/pentosus*	1526	Home made yogurt
	4	*Lactiplantibacillus plantarum/paraplantarum/pentosus*	1528	Home made yogurt
	5	*Lacticaseibacillus casei/paracasei/zeae*	1536	Home made yogurt
	6	*Lactiplantibacillus plantarum/paraplantarum/pentosus*	1540	Home made yogurt
	7	*Lactiplantibacillus plantarum/paraplantarum/pentosus*	1541	Home made yogurt
	8	*Lactiplantibacillus plantarum/paraplantarum/pentosus*	1543	Home made yogurt
	9	*Lactiplantibacillus plantarum/paraplantarum/pentosus*	1549	Home made yogurt
	10	*Lactiplantibacillus plantarum/paraplantarum/pentosus*	1552	Home made yogurt

LAB culture: 32 LAB strains, divided into three groups, were initially cultured for 24 h at 30 °C or 37 °C in MRS or M17 medium depending on the species. Bacterial cells were then collected by centrifugation and resuspended in DMEM medium without antibiotics (penicillin/streptomycin) and fetal bovine serum (FBS) at a final concentration of 1 x 10^8 CFU/mL for stimulation experiments.

HaCaT culture: HaCaT cells were transferred (1 mL/well) at a density of 3x10^5 cells per well in 12-well cell-culture plates and incubated at 37 °C with 5% CO_2 for 6 days.

Stimulation models: After 6 days of incubation of the 12-well cell-culture plates, medium was removed and HaCaT cells were pre-incubated with each of the 32 LAB strains for 6 h. After 6 h of pre-incubation with LAB strains, and without removing them, stimulants were separately added at final concentrations of 10 ng/mL and 1 µg/mL for TNF and LPS, respectively, and incubation continued for another 18 h. Unstimulated HaCaT cells (control without stimulants) or stimulated cells with TNF or LPS without the presence of LAB strains were used as controls.

Collection of supernatants and quantification of cytokines: At the end of the incubation (24 h), supernatants were collected and cytokines were quantified by ELISA.

Results

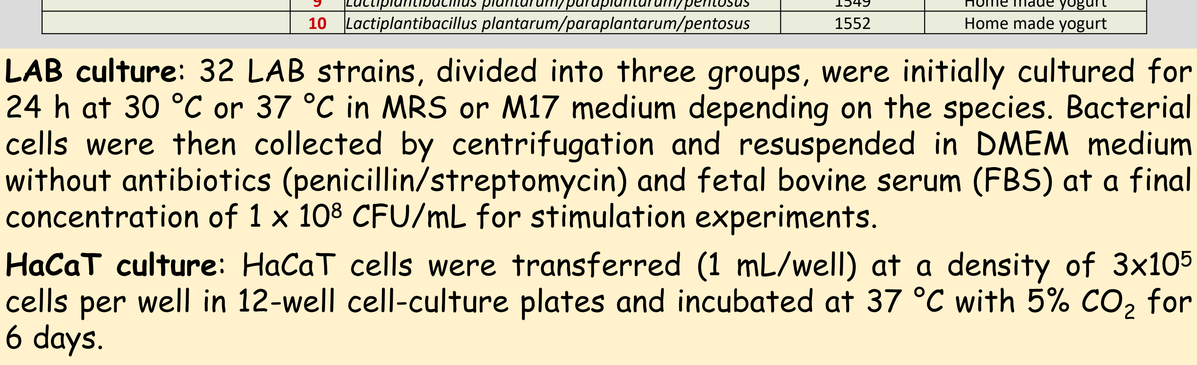

Figure 1. Stimulation of HaCaT cells with TNF or LPS induced IL-6 and IL-8 secretion, whereas IL-1β secretion was not detected

*Secreted IL-6 (A) and IL-8 (B) levels (pg/mL) by HaCaT cells stimulated with TNF or LPS (without the presence of LAB strains) or unstimulated cells (control without stimulants). Cytokines were quantified by ELISA in collected supernatants after 24 h of HaCaT incubation at 37 °C with 5% CO_2. Values are the mean ± standard deviation of three independent experiments (n=3). Statistically significant differences are indicated as *p < 0,05, **p < 0,01, ****p < 0,0001, ns: not significant.*

Conclusions

- Stimulation with either TNF or LPS increased IL-6 and IL-8 secretion in HaCaT cells, with TNF demonstrating a stronger effect
- Pre-incubation of HaCaT cells with LAB strains for 6 h reduced TNF- or LPS-induced IL-6 and IL-8 secretion during the subsequent 18-h stimulation period, with the magnitude of the effect being strain-specific
- The most promising LAB included *Lactiplantibacillus plantarum/paraplantarum/pentosus* and *Leuconostoc mesenteroides* strains
- Overall, the present study highlighted HaCaT cells as an *in vitro* cell model to be utilised as a screening tool of keratinocyte-driven inflammation
- LAB strains, isolated from dairy products, reduced induction of pro-inflammatory cytokines by keratinocytes and can be selected for further investigation in more complex *in vitro* and *in vivo* models associated with HS and possibly other inflammatory skin disorders

Results

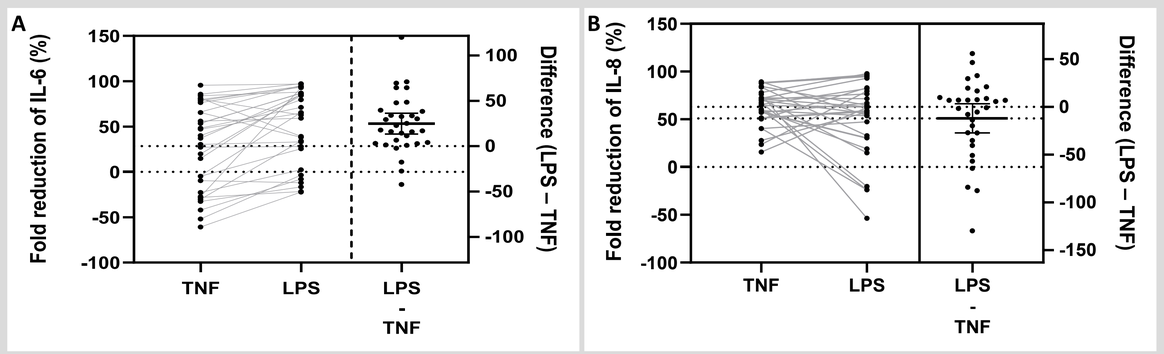

Figure 2. Pre-incubation of HaCaT cells with LAB strains for 6 h attenuated TNF- or LPS-induced IL-6 and IL-8 secretion during the subsequent 18-h stimulation period, with bacteria remaining in the culture

Comparison of the effects of TNF and LPS stimulation on induced IL-6 (A) and IL-8 (B) secretion by HaCaT cells pre-incubated with LAB strains. Graphs are representative of the results obtained for the 1st group of LAB strains. Each point represents an individual LAB strain, and the lines connect the corresponding values for TNF and LPS (paired analysis). The panel on the right shows the distribution of the difference (LPS – TNF) (paired t-test; p = 0.1169).

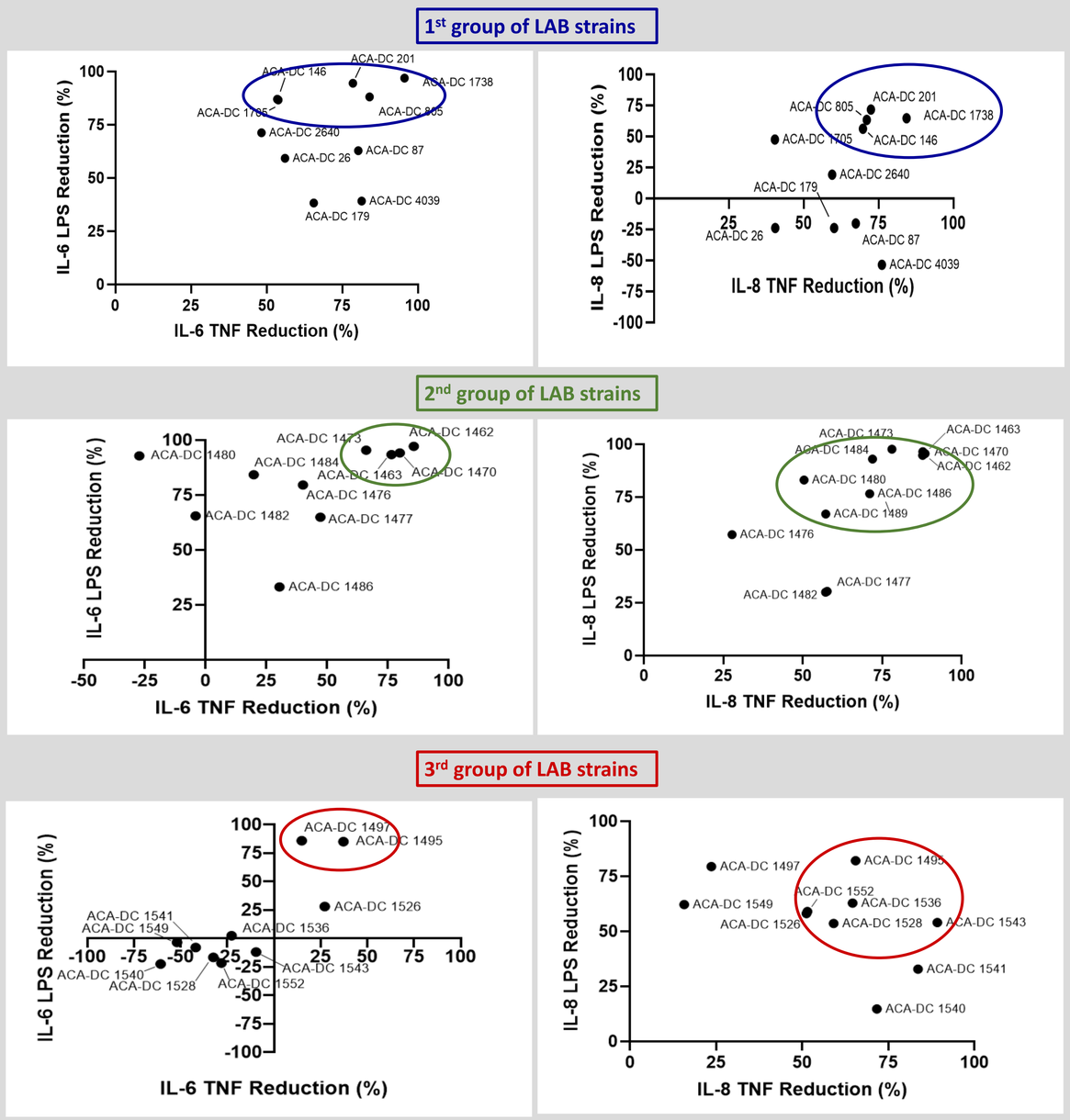

Figure 3. 9 out of the 32 LAB strains reduced IL-6 and IL-8 secretion by more than 50% relative to the control when HaCaT cells were pre-incubated with the strains for 6 h prior to an 18-h stimulation period with either TNF or LPS

Comparison of LAB strain-mediated reduction of IL-6 and IL-8 secretion in HaCaT cells pre-incubated with LAB strains and subsequently stimulated with TNF or LPS. Results are presented according to LAB strains' group. Each point represents an individual LAB strain and indicates the percentage reduction (%) of the respective cytokine following TNF stimulation (x-axis) and LPS stimulation (y-axis) compared to the control (stimulated cells with TNF or LPS without the presence of bacteria).