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EDITORIAL

Prevention and treatment of cancers by tumor antigen-expressing *Staphylococcus epidermidis*

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ABSTRACT
In a recent paper in *Science,* Chen *et al*. reported the genetic engineering of *S. epidermidis* expressing tumor cross-reactive antigens that trigger T cell responses and exhibit anticancer effects after topical administration. Here we discuss direct local effects and indirect systemic effects of exposure to engineered *S. epidermidis* strains.

KEYWORDS
Immunotherapy; Microbiome; Immunity

Main text

Oncogenesis and tumor progression are influenced by multiple extratumoral factors including the gut microbiota[1]. Bacteria may improve immunosurveillance by two major effects. First, bacteria can contribute to the conditioning of a general (body-wide) or local (intestinal or tumoral) environment that non-specifically favors the activity of anticancer immune effectors (or reduces the activity of immunosuppressive cells), hence exerting an adjuvant effect that improves the immune tonus[2]. Second, bacterial proteins can induce specific T cell immune responses against antigenic peptides that are cross-reactive with tumor-associated antigens[3]. It appears plausible that both effects can concur to reduce tumorigenesis or to ameliorate anticancer immune responses in conjunction with chemotherapy or immunotherapy[1].

Although much emphasis has been placed on the central role of the intestinal microflora, which is the most diverse and quantitatively abundant microbiota, other microbial communities including those of the bladder and the skin may play an important role in determining anticancer immune responses as well[4,5]. In a fascinating paper that was recently published in *Science*, Chen et al. demonstrate that, in mice, *Staphylococcus epidermidis* can be genetically manipulated to express tumor antigens and then used to prevent or treat cancers expressing such antigens[6]. *S. epidermidis* is part of the normal human skin microbiota and is usually not pathogenic, meaning that only patients bearing intravenous catheters or compromised immune systems develop clinically relevant infections by this Gram-positive bacterium. Nonetheless, even in the absence of clinical signs of skin inflammation and barrier breaches, *S. epidermidis* can elicit antigen-specific $CD4^+$ and $CD8^+$ T cell responses[7].

In their paper, Chen et al. set out to develop a method for the genetic manipulation of *S. epidermis*[6]. Using this method, the authors engineered *S. epidermidis* strains that expressed different variants of ovalbumin (OVA)-derived MHC class I-(OT1) or MHC class II-restricted (OT2) peptides, showing that the combination of soluble OT1 peptide and cell wall-attached OT2 was particularly efficient in inducing immune responses that restrained the growth of OVA-expressing B16F10 melanomas implanted under the skin of C57Bl/6 mice. The absence of either OT1 or OT2 from *S. epidermis*, the absence of OVA from B16F10 melanomas or the depletion of $CD8^+$ T lymphocytes precluded the anticancer effects observed in this system, supporting the therapeutic relevance of a cellular response against bacterium-cancer cross-reactive antigens. Of note, OVA-expressing *S. epidermidis* (that express both the OT1 and the OT2 peptides) could elicit immune responses that reduced the metastatic dissemination of intravenously injected OVA-expressing B16F10 melanomas into the lung. Even more convincingly, *S. epidermidis* engineered to express two neoantigen-containing peptides naturally present in B16F10 melanomas reduced lung metastases of native B16F10 cells (lacking OVA). Moreover, *S. epidermidis* manipulated to express SPAS-1 MHC class I epitope and the entire SPAS1 protein that is present in TRAMP-C2 prostate carcinoma swabbed on the skin of mice, could promote a significant reduction of tumor growth of subcutaneously injected TRAMP-C2 cancers, as compared to *S. epidermidis* expressing irrelevant control antigens[6]. Hence, the antitumor immunity elicited by *S. epidermidis* was observed in several models of transplantable cancers involving several distinct tumor antigens, supporting the generalizability of the findings.

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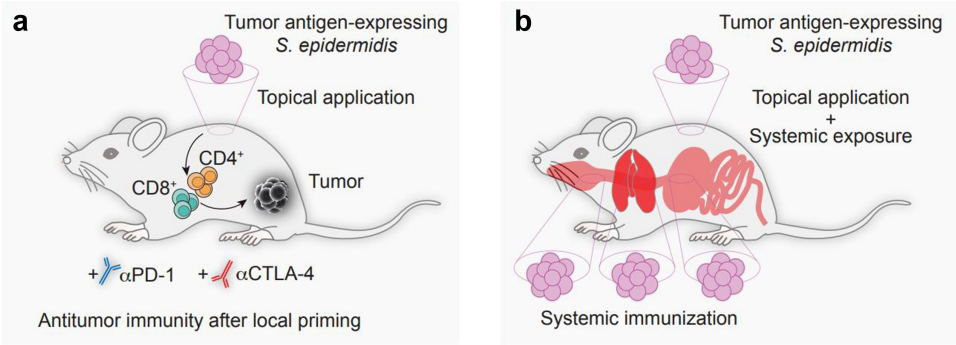

Figure 1. Direct or indirect anticancer effects of S. epidermidis expressing tumor cross-reactive antigens after the administration of the bacterium onto the skin. a. Direct effects. b. Indirect effects after contamination of the upper and lower parts of the respiratory or gastrointestinal tracts. Note that such indirect effects are purely hypothetical and require a thorough experimental exploration.

In a further twist, Chen et al. investigated the possibility to use tumor antigen-expressing *S. epidermidis* in a therapeutic setting, by first *i.v.* injecting OVA-expressing B16F10 cells and then (from 3 days later) painting the skin with OVA-expressing *S. epidermis*, again observing a reduction in metastatic tumor burden[6]. Similarly, when OVA-expressing B16F10 cells were inoculated subcutaneously, subsequent painting of the skin (from 14 days later) with OVA-expressing *S. epidermidis* together with dual immune checkpoint inhibition (with antibodies specific for CTLA-4 and PD-1) yielded efficient tumor control in most mice.[6]

The results reported by Chen et al. point to the intriguing possibility to elicit anticancer immunity by placing nonpathogenic bacteria on the skin[6]. The authors convincingly report the total absence of local inflammation in the skin from mice gently swabbed with different *S. epidermidis* strains. That said, there are multiple reports suggesting that *S. epidermidis* can be found in the gut microbiota[8,9]. Hence, in a hypothetical, yet plausible scenario, the presence of antigen-expressing *S. epidermidis* strains in the skin could lead to the contamination of other, non-skin microbiotas (such as the oral and nasal cavities and other downstream segments of the intestinal or respiratory tracts, respectively) by such strains, then causing local pro-inflammatory perturbations that are not detectable at the surface of the body, yet elicit systemic antimicrobial immune responses that participate to immunosurveillance (Figure 1). Future experimentation should exclude or confirm this possibility. Indeed, it will be of the utmost importance to develop optimal strategies for the use of bacteria in preventive or curative anticancer vaccination campaigns. Should such bacteria administered on the skin, orally or nasally be capable of eliciting desirable immune responses?

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Conflict of interest

OK is a cofounder of Samsara Therapeutics. LZ has held research contracts with Glaxo Smyth Kline, Incyte, Lytix, Kaleido, Innovate Pharma, Daiichi Sankyo, Pilege, Merus, Transgene, 9 m, Tusk and Roche, was on the on the Board of Directors of Transgene, is a cofounder of everImmune, and holds patents covering the treatment of cancer and the therapeutic manipulation of the microbiota. GK has been holding research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, Tollys, and Vascage. GK is on the Board of Directors of the Bristol Myers Squibb Foundation France. GK is a scientific co-founder of everImmune, Osasuna Therapeutics, Samsara Therapeutics and Therafast Bio. GK is in the scientific advisory boards of Hevolution, Institut Servier and Longevity Vision Funds. GK is the inventor of patents covering therapeutic targeting of aging, cancer, cystic fibrosis and metabolic disorders. GK's brother, Romano Kroemer, was an employee of Sanofi and now consults for Boehringer-Ingelheim. The funders had no role in the writing of the manuscript, or in the decision to publish.

Data availability statement

All data that led to the conclusions in this manuscript have been referenced and all sources have been described.

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