the photogenerated electrons transferred extremely quickly to Pt or TiO_2. Instead, rather persistent, strong Franz-Keldysh–related features arising from the dipole electric field created by the carrier separation were seen. From these features, the static electric field, as well as the dynamics of the electric field near the junctions, can be deduced. The Franz-Keldysh features persisted an order of magnitude longer in the $GaInP_2/TiO_2$ sample (it hardly decayed in the time frame of the experiments) when compared to the $GaInP_2$/Pt sample because of improved separation of the charge carriers.

Measurements of $GaInP_2/TiO_2$ samples with TiO_2 thicknesses from 0.5 to 35 nm also showed that the decay time for the Franz-Keldysh features increased with thicker layers, which improved charge separation by impeding recombination. Yang *et al*. measured the structures in the "dry" state without electrolyte, but in the relevant wavelength range, the electrolyte is highly transparent. Thus, measurements might be performed in operando (for example., at varying bias light intensity) under mild conditions, where gas bubble formation is negligible. Such measurements are important because for some protection layers, the charge transport mechanism is not even entirely clear—for example, TiO_2 protection of photoanodes (*5*, *6*).

The detailed insight into the charge separation at the absorber-protection layer interface offered by the method of Yang *et al*. promises to speed up the development of well-behaved protected photoelectrodes, which then have to be coupled to good catalysts. The H_2 evolution catalyst could be the effective, earth-abundant MoS_2 catalyst (*7*), or even Pt, which was recently shown to be scalable to the terawatt power production level (*8*). Known O_2 evolution catalysts, however, are much less effective, and despite substantial efforts, very little progress has been made (*9*) because of scaling relations that limit all known inorganic catalysts (*10*). Nevertheless, some of the best metal-oxide catalyst materials for O_2 evolution (*9*), such as iron-treated NiO, are both efficient catalysts and protection layers (*11*). ■

REFERENCES

1. A. Fujishima, K. Honda, *Nature* **238**, 37 (1972).
2. O. Khaselev, J. A. Turner, *Science* **280**, 425 (1998).
3. Y. Yang *et al*., *Science* **350**, 1061 (2015).
4. B. Seger *et al*., *Energy Environ. Sci.* **7**, 2397 (2014).
5. S. Hu *et al*., *Science* **344**, 1005 (2014).
6. B. Mei *et al*., *J. Phys. Chem. C* **119**, 15019 (2015).
7. T. F. Jaramillo *et al*., *Science* **317**, 100 (2007).
8. E. Kemppainen *et al*., *Energy Environ. Sci.* **8**, 2991 (2015).
9. C. C. L. McCrory *et al*., *J. Am. Chem. Soc.* **135**, 16977 (2013).
10. A. Vojvodic, J. K. Nørskov, *Natl. Sci. Rev.* **2**, 140 (2015).
11. B. Mei *et al*., *J. Phys. Chem. Lett.* **5**, 3456 (2014).

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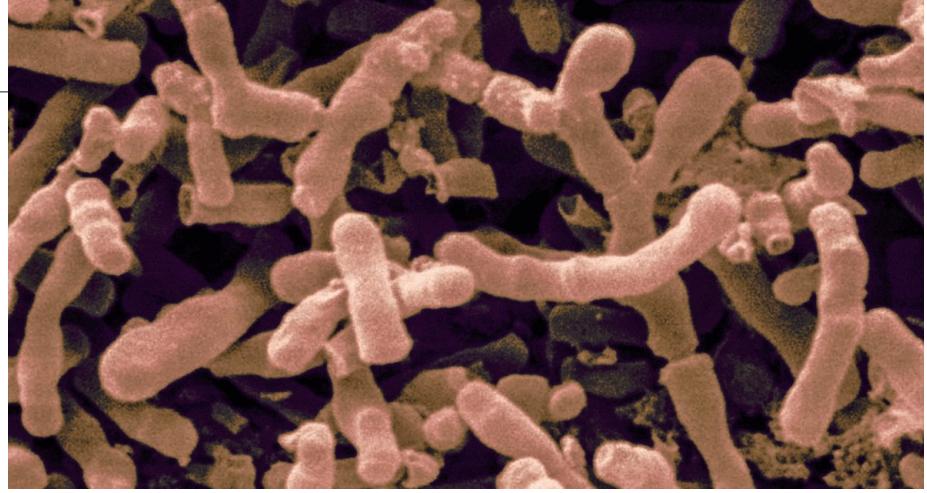

Gut microbe. *Bifidobacterium* is found in the intestines of most mammals, including humans.

IMMUNOTHERAPY

Could microbial therapy boost cancer immunotherapy?

Intestinal microbes affect immunotherapy responses in mouse models of cancer

By **Alexandra Snyder,[1] Eric Pamer,[2] Jedd Wolchok[3]**

Immunotherapies known as checkpoint blockades are rapidly changing standard treatment and outcomes for patients with advanced malignancies, as they lead to long-term disease control in a subset of patients (*1*). On pages 1084 and 1079 of this issue, Sivan *et al*. (*2*) and Vétizou *et al*. (*3*), respectively, illustrate an important role for the gut microbiome in modulating the efficacy of this treatment.

The checkpoint blockade immune therapies currently approved by the U.S. Food and Drug Administration for treating advanced melanoma and lung cancers target suppressive receptors on the surface of T cells. Anergic and/or exhausted T cells are released from inhibition by agents that target cytotoxic T lymphocyte–associated protein 4 (CTLA-4) or programmed cell death 1 (PD-1) so that T cells may then recognize and attack tumor cells. However, checkpoint blockade agents show variable efficacy within and across disease types. Concurrent with the development of these agents, tumor-intrinsic (*4*), tumor microenvironmental (*5, 6*), and circulating (*7*) factors have been associated with benefit or resistance to therapy; considered alone, each is an imperfect predictor.

Gut microbiota play a role in immune system development (*8*) and can affect the occurrence of autoimmunity (*9, 10*). In cancer, a diverse gut microbiome independently predicts for better outcomes after allogeneic stem cell transplant (*11*). The antibody against CTLA-4 (anti–CTLA-4) agent ipilimumab is thought to alter gastrointestinal immunity (*12*).

Sivan *et al*. and Vétizou *et al*. provide strong evidence for the role of stool microbiota (i.e., intestinal microbes) in response and resistance to immunotherapy. Sivan *et al*. illustrate the importance of *Bifidobacterium* to antitumor immunity and anti–PD-L1 antibody against (PD-1 ligand) efficacy in a mouse model of melanoma. The authors demonstrate that mice raised in two different facilities [Jackson Laboratory (JAX) and Taconic Farms (TAC)] that are known to harbor distinct microbiota exhibit differential tumor growth that disappears upon cohousing of the animals. Furthermore, when fecal material from JAX mice, whose tumors grow more slowly, was transferred into the intestine of TAC mice, the latter exhibited delayed tumor growth and enhanced $CD8^+$ T cell infiltration of the tumor. Anti–PD-L1 therapy was more effective in JAX mice, and the combination of JAX fecal transfer to TAC mice undergoing anti–PD-L1 therapy was more effective than either intervention alone. Si-

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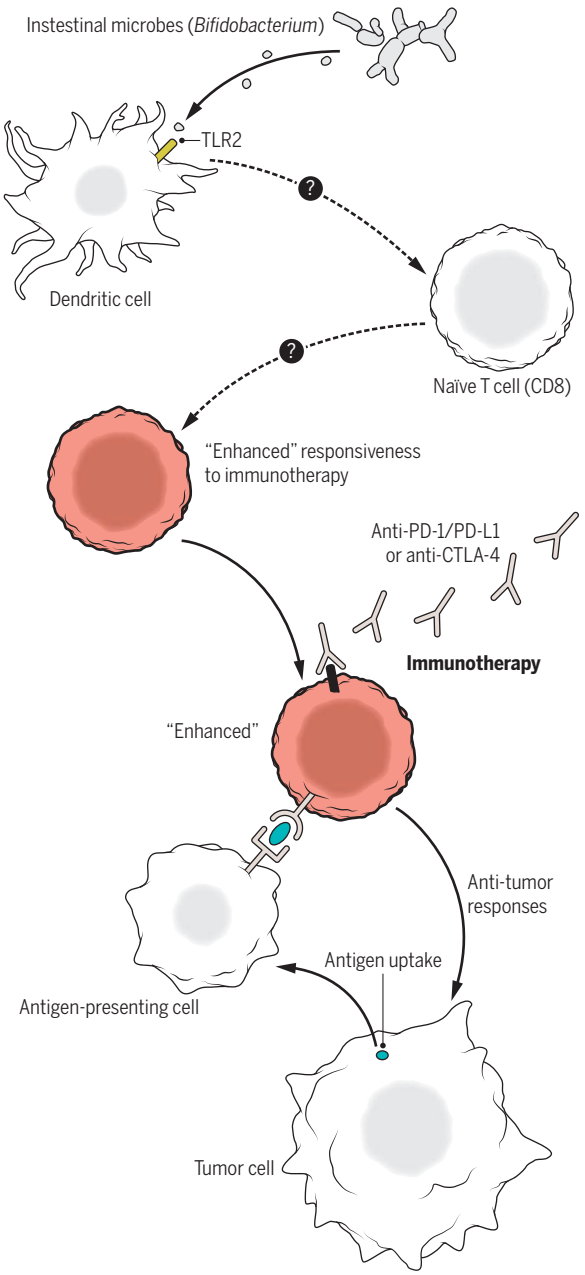

Gut bacteria affect immunotherapy effectiveness. Intestinal microbes, such as *Bifidobacterium*, may cause dendritic cells to enhance T cell responsiveness to checkpoint blockade therapies, although the mechanism of this effect remains to be elucidated.

van *et al.* also show that *Bifidobacterium* confers nearly the same effect as JAX stool transfer and that bacteria must be alive for the treatment to be effective. Investigation of the underlying mechanisms of this effect reveals that *Bifidobacterium* alters dendritic cell activity, which in turn leads to improved tumor-specific $CD8^+$ T cell function.

Vétizou *et al.* show that anti–CTLA-4 therapy is efficacious in mice housed in specific pathogen-free but not completely germ-free facilities. Several experiments underscore the importance of gut microbiota to response to therapy. Treatment with broad-spectrum antibiotics (ampicillin, colistin, and streptomycin) or imipenem dampened anti–CTLA-4 efficacy. When antibiotic-treated or germ-free–housed mice were fed *Bacteroides* isolates, the anticancer effect of anti–CTLA-4 was restored. Furthermore, adoptive transfer of *Bacteroides fragilis*–specific T helper 1 cells or injection of dendritic cells loaded with *B. fragilis*–purified polysaccharide into ACS-treated mice increased (although did not entirely restore) anti–CTLA-4 efficacy. Treatment with the antibiotic vancomycin also caused an increase of *Bacteroidales* and was associated with enhanced CTLA-4 efficacy. Transfer of feces from melanoma patients who harbored *Bacteroidales* species into the intestine of mice enhanced CTLA-4 efficacy in mice, which showed that boosting checkpoint blockade therapy can be mediated by bacteria colonizing the human gut.

In addition to illustrating the importance of microbiota to drug efficacy, Vétizou *et al.* also argue that, conversely, treatment with anti–CTLA-4 therapy alters the microbiome, specifically causing a decrease in *Bacteroidales* and *Burkholderiales* and an increase in *Clostridiales*. By demonstrating that Bacteroides also colonizes the small intestine, Vétizou *et al.* begin to address but leave unanswered many interesting questions regarding the localization of different bacterial taxa along the length of the gut and their relative impact on checkpoint blockade–driven immune responses.

Although they investigate different checkpoint blockade agents, Sivan *et al.* and Vétizou *et al.* come to a conceptually important conclusion: The composition of intestinal microbiota affects checkpoint blockade efficacy and can be manipulated to improve responses. Although both studies use the same mouse model of melanoma, the difference in specific bacteria that they identify (*Bacteroidales* or *Bifidobacterium*), may be due to the checkpoint blockade agents and specific experimental conditions used. However, this difference hints at the challenges that may arise in applying the findings to human patients. Human patients live in distinct environments with contrasting dietary habits and who consequently will exhibit substantial interpatient variability in microbiota relative to mouse models. Furthermore, the frequent exposure of cancer patients to antibiotics and antibiotic-resistant bacteria also shapes their intestinal microbiome (*13*). The dose, frequency, timing relative to immunotherapy, and content of administered bacteria or microbiome-altering antibiotics remain to be determined. These data will need to be integrated into the already-complex multidimensional model of tumor, tumor microenvironment, and host factors involved in therapeutic efficacy. Consequently, studying this question in humans will be challenging.

However, there is reason for optimism: The efficacy of fecal transplant for treating *Clostridium difficile* infection in humans has been conclusively shown (*14*), so it is now possible that this treatment strategy could be applied to immunotherapy-treated patients. Administration of specific bacterial species or combinations of bacteria that would enhance responses to therapy would be preferable but will require extensive development and testing. For now, additional studies on patient populations are warranted. Stool samples can be collected and the microbiota analyzed, and thus prospective collection from all members of phase 2 or 3 clinical study is feasible. The findings of Sivan *et al.* and Vétizou *et al.* show that collection of fecal samples should be considered going forward in immunotherapy studies to characterize and ultimately manipulate this factor to favor response in immunotherapy-treated cancer patients. ■

REFERENCES

1. M. A. Postow *et al.*, *N. Engl. J. Med.* **372**, 2006 (2015).
2. A. Sivan *et al.*, *Science* **350**, 1094 (2015).
3. M. Vétizou *et al.*, *Science* **350**, 1079 (2015).
4. A. Snyder *et al.*, *N. Engl. J. Med.* **371**, 2189 (2014).
5. S. Spranger *et al.*, *Sci. Transl. Med.* **5**, 200ra116 (2013).
6. P. C. Tumeh *Nature* **515**, 568 (2014).
7. G. Y. Ku, J. Yuan *et al.*, *Cancer* **116**, 1767 (2010).
8. S. K. Mazmanian, C. H. Liu, A. O. Tzianabos, D. L. Kasper, *Cell* **122**, 107 (2005).
9. H. J. Wu *et al.*, *Immunity* **32**, 815 (2010).
10. R. Horai *et al.*, *Immunity* **43**, 343 (2015).
11. Y. Taur *et al.*, *Blood* **124**, 1174 (2014).
12. D. Berman *et al.*, *Cancer Immunity.* **10**, 11 (2010).
13. Y. Taur, E. G. Pamer, *Curr. Opin. Infect. Dis.* **26**, 332 (2013).
14. E. van Nood, *N. Engl. J. Med.* **368**, 407 (2013).

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