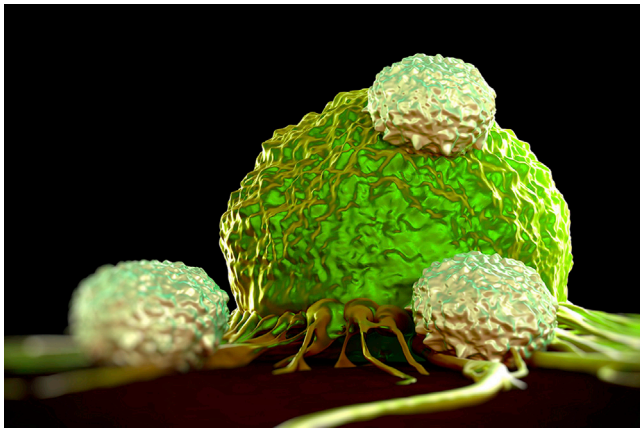
Cell

Immunotherapy Meets Microbiota

The recent success of immunotherapy in cancer treatment has brought exhilaration to the field of oncology and cancer research. Seeing patients who have exhausted conventional therapeutic options recover from immune checkpoint blockade or adoptive T cell therapy is undoubtedly a big shot in the arm for clinicians and researchers. While the promise of harnessing the immune system to fight cancer is exciting, an issue that is common to all the existing cancer therapies remains—it doesn't work on everyone. Where does this heterogeneity in response come from? If possible, how do we manipulate the cause to expand the responder population and boost the efficacy? Two recent studies exploring these questions converge to the same answer—gut microbiota (Sivan et al., 2015, Vétizou et al., 2015).

While crosstalk between microbiota and the immune system is appreciated, Thomas Gajewski and his team in Chicago set out to specifically ask whether, and if so how, gut microbiota composition affects immune responses against tumor. Their first clue of a positive correlation came from the observation that C57BL/6 mice from two facilities mounted significantly different levels of immune responses against subcutaneously implanted melanoma cells. Either cohousing or fecal transplantation between the mice was sufficient for eliminating the difference in tumor growth, indicating that gut microbiota were the underlying cause of the discrepancy. Since the differential impact on tumor growth seemed related to the level of activation and infiltration of tumor-specific CD8+ T cells, the authors tested whether manipulating microbiota composition modulated the efficacy of anti-PD-L1 therapy that is known to unleash the anti-tumor activity of CD8+ T cells. Indeed, transplantation of microbiota with higher anti-tumor activity elevated T cell response and inhibited tumor growth. By cross-referencing changes in bacterial content upon different manipulations and those associated with increased immune responses, the authors pinpointed the particular genus of bacteria responsible for the effect, *Bifidobacterium*, raising the intriguing possibility that altering the amount of *Bifidobacterium* in human gut could expand the spectrum of patients responding to anti-PD-L1 therapy and enhance its efficacy (Sivan et al., 2015).



T cells attacking a cancer cell. Image from istock.com.

Another established immunotherapy approach is CTLA-4 blockade. While effective, the monoclonal antibody against CTLA-4, ipilimumab, was shown to cause "subclinical colitis." This connection with gut homeostasis prompted Laurence Zitvogel and her team to look into the relationship between microbiota and the effect of anti-CTLA-4 treatment. Strikingly, the experiments in germ-free mice demonstrated that the therapeutic efficacy of ipilimumab, in particular the activation of CD4+ T cell upon treatment, completely depended on the presence of microbiota. Further exploration revealed that ipilimumab was able to alter microbiota composition at the genus level, favoring the dominance of distinct *Bacteroides* app., such as *B. fragilis,* in both mice and patients, and that this alteration was essential for defeating cancer cells. Indeed, transplantation of feces from patients after treatment restored the efficacy of anti-CTLA-4 therapy in germ-free mice. As it turned out, this particular genus of bacteria did not cause the adverse effect of ipilimumab on gut homeostasis, the observation that initially triggered this line of investigation, making it even more promising to use them for modulating the efficacy of anti-CTLA-4 therapy (Vétizou et al., 2015).

It is worth noting that while both studies concluded that components of gut microbiota could be beneficial in the context of immune checkpoint blockade, the specific bacteria that they identified differed. Moreover, their impacts on therapeutic efficacy vary, one mostly augmenting the activity of anti-PD-L1 treatment and the other absolutely required for anti-CTLA-4 therapy to work. Although it seems that both genera of bacteria influence the immune responses through modulating dendritic cells, which in turn regulate T cell responses, it remains to be determined how exactly such influence occurs. In addition to expanding the responder population and enhancing the therapeutic efficacy, another issue that is yet to be fully explored for immunotherapy is resistance. Whether and how would patients develop resistance to immunotherapy? Would the manipulability of microbiota make them the partner in crime of cancer cells during such development? Or would we be able to make them our ally against cancer despite the context? It is conceivable that a deeper appreciation of the complex dynamics between microbiota and anti-cancer immune responses would be of great value for solidifying and promoting our progress in cancer treatment.

REFERENCES

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