Cell Reports Medicine

CellPress
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Preview

More fuel for the fire: Gut microbes and toxicity to immune agonist antibodies in cancer

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https://doi.org/10.1016/j.xcrm.2021.100482

SUMMARY

Microbes in the gut impact response, resistance, and toxicity to numerous cancer therapies, though mechanisms remain incompletely understood. Blake et al. provide further evidence that gut microbes promote toxicity to immune-agonistic antibodies, with opportunities to target these in cancer treatment.[1]

T cells possess a remarkable ability to recognize and reject transformed cancer cells; however, this is often attenuated by tolerogenic "off" signals within the tumor microenvironment (TME). These inhibitory signals originate from inhibitory immune cells such as regulatory T cell (T_{reg}), myeloid derived suppressor cells (MDSC), and tumor associated macrophages (TAM), and also include immunomodulatory checkpoint proteins such as PD-L1/PD-1 and CTLA-4 on tumors and immune cells that can suppress T cell-mediated tumor rejection. In this light, many of the current approved strategies to enhance anti-tumor immunity involve the use of immune checkpoint blocking (ICB) antibodies against these checkpoint molecules to reinvigorate T cell activity within the TME. Similarly, anti-tumor T cell activation may be augmented via the use of immune agonist antibodies (IAA) targeting immunostimulatory ligands, such as ICOS, OX40, CD40, and 4-1BB.[2] While both these classes of antibodies have significantly improved clinical outcomes in cancer patients, they have failed to reach their full potential due to frequent treatment-limiting clinical toxicities, including acute liver damage and strong systemic inflammation. Therefore, there is a critical need for (1) identifying novel predictive biomarkers of response and toxicity to antibody-based immunotherapies and (2) elucidating basic mechanisms responsible for these phenomena to improve the future clinical impact of antibody-based immunotherapies.

An emerging biomarker and potential therapeutic target in response and toxicity to cancer treatment, particularly with regard to immune checkpoint blockade, is the human microbiome. A large fraction of the trillions of microbes inhabiting the human body reside in the gastrointestinal tract (gut) where they contribute to normal host physiology. Critically, the gut is also host to a dense network of immune cells and fosters constant and dynamic interactions between microbes and host immune cells to induce tolerance to many of these microbes so that they can facilitate their critical normal function. Groundbreaking studies published in 2018 demonstrated that responders and non-responders to ICB regimen in cancer had different and distinct gut microbial signatures, with a higher diversity of gut microbes and specific taxa associated with response.[3,4,5] Mechanistic studies suggest that gut microbes play a key role in immune activation in the tumor microenvironment, including via c-di-AMP-mediated activation of the STING-IFN-I pathway (especially in NK cells), to promote robust anti-tumor immune responses (Figure 1).[6] However, excessive immune activation with combined immune checkpoint blockade (CICB; anti-PD-1 and anti-CTLA-4) may drive immune-related adverse events (irAE), and gut microbes may contribute to this through stimulation of cytokines such as IL-1B and IL-6, with options to therapeutically target these.[7] However, gut microbes have been less well-studied in the context of treatment with IAAs.

In this issue of *Cell Reports Medicine*, Blake et al. present compelling evidence from pre-clinical models suggesting a potential mechanism through which the gut microbiota influences systemic immunity and exacerbates toxicity in the setting of treatment with anti-CD40 and anti-CD137 IAAs.[1] Briefly, the authors demonstrate that in the context of treatment with CD40 IAAs, the presence of diverse gut flora leads to a MyD88-dependent activationof the host immune system, especially macrophages, which results in the rapid production of inflammatory cytokines such as TNFa, IL-6, and IFN-I and an acute induction of macrophage- and neutrophil-dependent liver damage. Interestingly, toxicity observed with CD137 IAAs also appears to converge at the level of host MyD88 activation by gut microbiota, which results in a CD8 T cell-dependent liver damage and IFNg-driven systemic inflammation (Figure 1). Importantly, toxicity to IAA therapy was reduced in germ-free or antibiotic-treated mice in this model without a deleterious impact on anti-tumor immunity. Thus, toxicity associated with IAA treatment may relate to activation of these usually microbe-tolerant T lymphocytes and other cellular subsets that are interacting

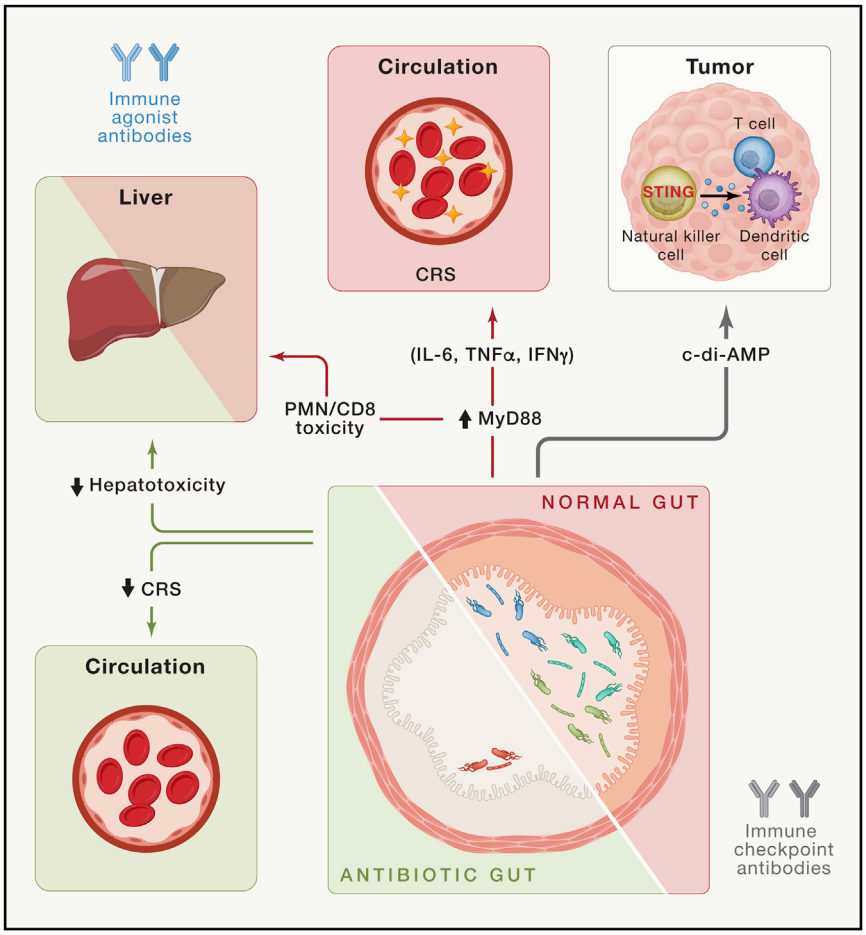

Figure 1. Friends or foes: gut microbes in cancer immunotherapy

Commensal gut microbes actively shape systemic and anti-tumor immune responses. Elegant mechanistic studies have now identified host targets through which gut microbes mediate anti-tumor immune responses to ICB via STING-mediated interferon signaling (gray arrow).[6] Additionally, Blake et al. show that gut microbes drive hepatotoxicity and cytokine release syndrome (CRS) to immune agonist antibodies (IAA) via MyD88 and other mechanisms in pre-clinical models (red arrow), with therapeutic targeting of gut microbes (via antibiotic treatment in this case) associated with reduced toxicity to therapy

with microbes in the gut and in other tissues. However, extensive characterization of the gut microbiota for potentially causative taxa or specific mechanisms involved was not performed in these studies, leaving room for further studies interrogating the role of specific taxa (or functional aspects of gut microbes) associated with toxicity on treatment with IAAs.

While it might be tempting to combine antibiotics with IAA ± ICB in light of this data, it is important to note that other hallmark studies have shown that microbiome depletion using broad-spectrum antibiotics prior to immunotherapy significantly worsens clinical outcomes.[8,9] This dichotomy suggests that the manipulation of patient gut microbiota (using antibiotics or probiotics) to enhance response to ICB is a complex approach and one that needs to be determined on a per-patient basis by skilled oncologists.[10] Importantly, specific, druggable proteins identified by deep mechanistic studies such as the ones discussed above can circumvent some of the complexities associated with the antibiotic-based combination regimen. Finally, gut microbes may ultimately exert their influence on response, resistance, and toxicity by functioning as a consortium rather than as independent species as is also shown by Blake et al.[1] Therefore, future studies using multi-omics approaches to identify consortium-derived metabolites, secretory proteins, and cytokines/chemokines may be critical in parlaying these interesting clinical findings into next-gen microbe-based translational therapies. Nonetheless, the future is bright and there is a great deal to be learned about the influence of gut and other microbes on immunity and overall health.

DECLARATION OF INTERESTS

J.A.W. is an inventor on a US patent application (PCT/US17/53.717) relevant to the current work; reports compensation for speaker's bureau and honoraria from Imedex, Dava Oncology, Omniprex, Illumina, Gilead, PeerView, MedImmune, and Bristol-Myers Squibb (BMS); and serves as a consultant/advisory board member for Roche/Genentech, Novartis, AstraZeneca, GlaxoSmithKline (GSK), BMS, Merck, Biothera Pharmaceuticals, and Micronoma.

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