PANCREATIC CANCER

CD11b agonism overcomes PDAC immunotherapy resistance

A new study has shown that immunotherapeutic responses in pancreatic ductal adenocarcinoma (PDAC) can be improved by agonism of an integrin molecule expressed on the cell surface of myeloid cell subsets.

Although successful in some cancers, checkpoint inhibitors have not led to a clinical benefit in PDAC. "One factor is the extensive infiltration of PDAC by multiple lineages of immunosuppressive myeloid cells," explains co-senior author David DeNardo. "These cells, which include tumour-associated macrophages (TAMs) and myeloid-derived suppressor cells, can drive T cell exclusion and dysfunction." In the latest study, these cells were targeted to improve T cell-mediated immunity in PDAC.

Current myeloid-targeting strategies are prone to compensatory effects by untargeted cell subsets, suggesting that a nonselective approach for all tumour-infiltrating myeloid cells might be optimal. CD11b (integrin α_M) is expressed on most myeloid cells and plays an important part in myeloid cell migration and function, but to achieve CD11b blockade requires antagonist doses not tolerable in humans. "To overcome this limitation, our team developed a small molecule, allosteric agonist of CD11b," reports co-senior author Vineet Gupta. This agonist (ADH-503) results in a partially active CD11b conformation upon binding and suppresses myeloid cell infiltration by increasing adhesion to endothelium.

Using various mouse models and ex vivo assays, the team assessed the effect of treatment with ADH-503 on immune responses and the potential for immunotherapeutic synergy. "Our data demonstrate that CD11b agonism rapidly repolarizes TAMs to support antitumor immunity without the compensatory mechanisms seen from other myeloid-targeting agents," says DeNardo. "The combination of CD11b-agonists with checkpoint immunotherapy leads to tumour regression, long-term survival and immunological memory in PDAC models that are otherwise resistant to immunotherapy."

> "This work identifies CD11b agonism as an alternative approach for reprograming innate immunity in PDAC"

This work identifies CD11b agonism as an alternative approach for reprograming innate immunity in PDAC. "We think the unique activity of CD11b agonism in altering tumour immunity is very exciting and warrants further study," observes Gupta. "These studies have led to the development of ADH-503 for planned testing in human patients, although more studies are also needed to understand if the novel mechanisms of action observed in animals are similar in humans."

Iain Dickson

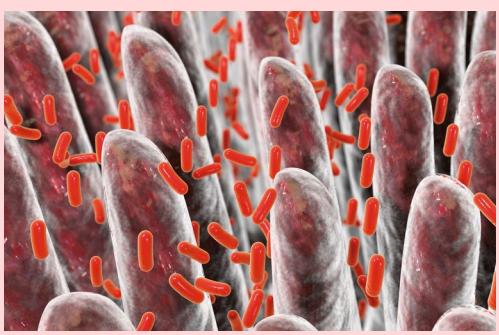
ORIGINAL ARTICLE Panni, R. Z. et al. Agonism of CD11b reprograms innate immunity to sensitize pancreatic cancer to immunotherapies. *Sci. Transl. Med.* **11**, eaau9240 (2019)

GUT MICROBIOTA

Microbiota supplements to improve metabolic health

Commensal microbiota in the gastrointestinal tract contribute to the regulation of host metabolic health. In addition, complex metabolic diseases are associated with imbalances in microbiome composition. For instance, obesity and type 2 diabetes mellitus are correlated with decreased abundance of the commensal bacterium *Akkermansia muciniphila*. A new clinical study by Patrice Cani and co-workers now explores the feasibility, safety and tolerability of administering *A. muciniphila* to humans to reduce the risk factors that characterize the metabolic syndrome.

> "complex metabolic diseases are associated with imbalances in microbiome composition"



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Prior to this study, translational research in rodents by Cani's group and others had indicated that increasing *A. muciniphila* abundance might be a promising therapeutic strategy to enhance metabolic health. "We found that the bacteria were reinforcing the gut barrier leading to the blockage of gut permeability," explains Cani. "This improved glucose tolerance and enhanced the efficiency of using fat and glucose in metabolic tissues."

The researchers have now undertaken a randomized, double-blind, placebo-controlled pilot study in 32 volunteers with obesity and insulin resistance. The study participants were administered either live or pasteurized *A. muciniphila*, or placebo, daily for 3 months.

The primary end points of the study were safety, tolerability and readouts of metabolic health. Secondary outcomes were intestinal barrier function and gut microbiota composition. The researchers found that, following the 3-month regimen, study participants who were given the bacteria had improved insulin sensitivity, reduced plasma levels of total cholesterol and decreased plasma levels of biomarkers for liver dysfunction and inflammation compared with the placebo group. In addition, body weight and fat mass were slightly reduced in the groups that received *A. muciniphila* supplementation.

The intervention was safe, well tolerated and did not affect the overall gut microbiome structure. "Furthermore, the tests in humans confirm what had already been observed in mice; the pasteurized form of *A. muciniphila* was more efficient than the live bacteria on several parameters," adds Cani. "The most important thing is to confirm the results of this small pilot study in a larger cohort."

Anna Kriebs, Associate Editor, Nature Communications

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ORIGINAL ARTICLE Depommier, C. et al. Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers: a proof-of-concept exploratory study. *Nat. Med.* **25**, 1096–1103 (2019)