

Supplementary Table 1: Intratumoral microbiota and their impact on cancer immunotherapy efficacy

| Function to anti-tumor immune response | Microbiota type | Tumor type | Target cell | Main pathway or molecule | Mechanism | Reference |
|---|------------------------|---------------|-----------------------------|-----------------------------|--|-----------|
| Enhance | <i>Bifidobacterium</i> | Breast cancer | Monocyte, Dendritic cell | STING pathway | Activating dendritic cells <i>via</i> the STING signaling pathway | [1] |
| | <i>A.muciniphila</i> | Melanoma | NK cell, Dendritic cell | STING pathway | Promoting antigen presentation | [2] |
| | <i>Clostridiales</i> | Breast cancer | CD8 ⁺ T-cell | PERK pathway | Related metabolite trimethylamine N-oxide induced pyroptosis in tumor cells by activating the endoplasmic reticulum stress | [3] |

| | | | | | |
|----------|--|-------------------|-------------|---|--|
| | | | | kinase PERK and thus enhanced CD8 ⁺ T cell- mediated anti-tumor immunity in TNBC <i>in vivo</i> | |
| | <i>S. caprae,</i> <i>A. odontolyticus</i> | Melanoma | T cell | HLA-bound peptides | Deriving immunogenic HLA-I and HLA-II bacterial peptides and activating cellular immunity after being presented to T cells [4] |
| | <i>H. hepaticus</i> | Colorectal cancer | Tfh cell | TLS | Increasing the number of Tfh cells in the colon and promoting the maturation of the TLS adjacent to the tumor [5] |
| Decrease | <i>F. nucleatum</i> | Colorectal cancer | Cancer cell | TLR4 and MYD88 pathway | Targeting TLR4 and MYD88 innate immune signaling and specific microRNAs to [6] |

| | | | | | |
|-------------------------|-----------------------------------|---------------------------------|----------------------|---|------|
| | | | | activate the autophagy pathway | |
| <i>B. fragilis</i> | Colorectal cancer | Macrophage | NLRP3 pathway | Inhibiting macrophage activation and reducing the release of proinflammatory cytokines such as IL-18 and IL-1 β | [7] |
| <i>Malassezia</i> | Pancreatic ductal adenocarcinoma; | TH2 and innate lymphoid cells 2 | KRAS pathway | Facilitating IL-33 secretion | [8] |
| <i>Alternaria</i> | | | | | |
| <i>Fusobacterium</i> | Pancreatic ductal adenocarcinoma; | Myeloid cell | ROS | Increasing production of ROS and inflammatory cytokines | [9] |
| <i>Methylobacterium</i> | Gastric cancer | CD8 $^+$ T cell | TGF- β pathway | Inhibiting immune infiltration of CD8 $^+$ T cells | [10] |
| <i>N. ramosa</i> | Prostate cancer | | immunosuppression | Inducing inflammation, promoting immunosuppression | [11] |

A.muciniphila: *Akkermansia muciniphila*; *S. caprae*: *Staphylococcus caprae*; *A. odontolyticus*: *Actinomyces odontolyticus*; *H. hepaticus*: *Helicobacter*

hepticus; *F. nucleatum*: *Fusobacterium nucleatum*; *B. fragilis*: *Bacteroides fragilis*; *N. ramosa*: *Nevskia ramosae*; Tfh: T follicular helper; TLS: tertiary lymphoid structures; ROS: reactive oxygen species; IL: interleukin; TGF- β : transforming growth factor- β .

REFERENCES

1. Shi Y, Zheng W, Yang K, Harris KG, Ni K, Xue L, *et al.* Intratumoral accumulation of gut microbiota facilitates CD47-based immunotherapy *via* STING signaling. *J Exp Med* 2020;217(5):e20192282.
2. Lam KC, Araya RE, Huang A, Chen Q, Di Modica M, Rodrigues RR, *et al.* Microbiota triggers STING-type I IFN-dependent monocyte reprogramming of the tumor microenvironment. *Cell* 2021;184(21):5338–5356.e21.
3. Wang H, Rong X, Zhao G, Zhou Y, Xiao Y, Ma D, *et al.* The microbial metabolite trimethylamine N-oxide promotes antitumor immunity in triple-negative breast cancer. *Cell Metab* 2022;34(4):581–594.e8.
4. Kalaora S, Nagler A, Nejman D, Alon M, Barbolin C, Barnea E, *et al.* Identification of bacteria-derived HLA-bound peptides in melanoma. *Nature* 2021;592(7852):138–143.
5. Overacre-Delgoffe AE, Bumgarner HJ, Cillo AR, Burr AHP, Tometich JT, Bhattacharjee A, *et al.* Microbiota-specific T follicular helper cells drive tertiary lymphoid structures and anti-tumor immunity against colorectal cancer. *Immunity* 2021;54(12):2812–2824.e4.
6. Liang P, Chen Q, Chen X, Zhang X, Xiao Y, Liang G, *et al.* Microbiota modulate immune repertoires in lung adenocarcinoma *via* microbiota-immunity interactive network. *Transl Lung Cancer Res* 2024;13(10):2683–2697.
7. Shao X, Sun S, Zhou Y, Wang H, Yu Y, Hu T, *et al.* *Bacteroides fragilis* restricts colitis-associated cancer *via* negative regulation of the NLRP3 axis. *Cancer Lett* 2021;523:170–181.
8. Alam A, Levanduski E, Denz P, Villavicencio HS, Bhatta M, Alhorebi L, *et al.* Fungal mycobiome drives IL-33 secretion and type 2 immunity in

pancreatic cancer. *Cancer Cell* 2022;40(2):153–167.e11.

9. Wei MY, Shi S, Liang C, Meng QC, Hua J, Zhang YY, *et al.* The microbiota and microbiome in pancreatic cancer: more influential than expected. *Mol Cancer* 2019;18(1):97.

10. Peng R, Liu S, You W, Huang Y, Hu C, Gao Y, *et al.* Gastric microbiome alterations are associated with decreased CD8⁺ tissue-resident memory T cells in the tumor microenvironment of gastric cancer. *Cancer Immunol Res* 2022;10(10):1224–1240.

11. Ma J, Gnanasekar A, Lee A, Li WT, Haas M, Wang-Rodriguez J, *et al.* Influence of intratumor microbiome on clinical outcome and immune processes in prostate cancer. *Cancers* 2020;12(9):2524.