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| **Table S2 Preclinical models with a cause-effect relationship between commensals and anticancer effects.** | | | | | | | | | | | | | | | | | | | | |
| **Cancer models** | | | **ATB/FMT** | | | | **Drugs** | | | **Commensals** | | **Commensal Regimen** | | | | **Effect** | | **Mode of action** | | **Reference** |
| **NATURAL IMMUNOSURVEILLANCE** | | | | | | | | | | | | | | | | | | | | |
| Pre-leukaemic myeloproliferation (PMP)  in *Tet2*-/-mice | | | ATB and GF and IL-6R wt versus KO bone marrow | | | | None | | | Differences assigned to *Lactobacilli reuteri, L. johnsonii, L. intestinalis* | | None | | | | Accelerated and increased incidence of PMP development, Tet2 deficiency-induced gut permeability and translocation of Lactobacilli in secondary lymphoid organs | | TLR2L and IL-6- induced myeloproliferation, expansion of IL-6Ra expressing GMP | | (Meisel et al. 2018) | |
| Ovarian and breast tumors in *Tlr5-/-*mice | | | Tlr5 wt versus Tlr5 KO mice  Tlr5−/− γδ-deficient mice  Co-housing experiments | | | | None | | | Differences assigned to genera of Allobaculum, Bacteroides, and Lactobacillus | | None | | | | Deleterious role of flagellin-harboring gut commensals on (IL-6 or IL-17 driven) peripheral inflammation | | Crosstalk between MDSC and γδ-T cells related to gut commensals. Role of IL-6 and IL-17 in tumor-induced inflammation and propagation. | | (Rutkowski et al. 2015) |
| KP autochthonous lung cancer model | | | SPF | | | | None | | | *Veillonella parvula*  Increased total bacterial burden and reduced diversity *(*enrichment with *Herbaspirillum* and *Sphingomonadaceae,* and reduced *Aggregatibacter* and *Lactobacillus)* | | Interalveolar spreading in lower airway tract | | | | Enhancing tumor engraftment and local dissemination | | Induction of PD-L1 on tumor cells and IL-17 local inflammation and turning on the MAPK/mTOR pathway. γ6δ1 T cells producing IL-17 triggered by neutrophils | | (Tsay et al. 2020)  (Jin et al. 2019) |
| \*BRPKp110 HR+ mouse mammary cancer  \*PyMT mammary tumors  \*LKRasG12Dp53flx/flxL-Stop-L-Myristoylated p110a\_GFP. mice | | | ATB (bacitracin, neomycin)  and FMT | | | | Dysbiosis prior to tumor inoculation | | | ATB-induced drop in bacterial richness | | Oral administration of dysbiotic caecal content | | | | Increased fibrosis and collagen deposition in mammary gland and TME | | Dysbiosis+tumor inoculation increased Cxcl2 and CCL2 and Cxcl10 in the mammary gland and IL-23, Arg1, IL-6 producing myeloid MDSC recruitment in tumor beds leading to increased stromal inflammation | | (Buchta Rosean et al. 2019) |
| \*CT26 and MC38 colon cancers  \*4T1 mammary cancer | | | SPF mice | | | | None (eubiosis) | | | Nanoparticles from Gram negative bacteria and E. coli ΔmsbB OMV | | Intravenous injection of outer membrane vesicles from E. coli (OMV) every 3 days for 20 days | | | | Cxcl10 and IFNγ systemic secretion  T and NK cell stimulation | | T and NK cell dependent tumor growth retardation with OMV | | (Kim et al. 2017) |
| **IMMUNOTHERAPY** | | | | | | | | | | | | | | | | | | | | |
| ***Immune Checkpoint inhibitors (ICI) +/- chemotherapy*** | | | | | | | | | | | | | | | | | | | | |
| \*Melanoma B16.SIY  \*Bladder cancer MB49 | SPF  Taconic (TAC) vs Jackson (JAK) lab  no ATB | | | | | anti-PD-1 mAbs | | | | *Bifidobacterium* spp cocktail (*B. breve, B. longum*) | | | Oral gavage with anti-PD1 mAbs | | | Restoring efficacy of ICI  in mice coming TAC vendor | Enhanced DC functions and CD8+ T cell priming and CTL recruitment in the TME | | | (Sivan et al. 2015) |
| \*MCA-205 sarcoma  \*RET melanoma  \*MC38 colon carcinoma | GF or ATB and FMT from melanoma patients | | | | | anti-CTLA-4 mAbs | | | | Bacteroidales or Burkholderialesorder(*B. fragilis, B.thetaiotaiomicron) B. cepacia)* | | | Oral gavage with anti-CTLA-4 mAbs | | | Restoring therapeutic response to anti-CTLA-4 mAb in FMT- or ATB treated mice | Maturation of tumor DC and induction of IL-12-dependent systemic TH1-immune responses | | | (Vétizou et al. 2015) |
| \*MCA-205 sarcoma  \*MC38 MSI colon carcinoma  \*CT26 MSS colon cancer | GF recipient  or ATB  SPF or FMT from colon cancer patients | | | | | Sequential oxaliplatin chemotherapy  and anti-PD-1 mAbs | | | | Erysipelatotrichaceae  Bacteroidaceae Fusobacteriaceae  Prevotellaceae  family members. (*B. fragilis, E.ramosum,*  *P. clara, F. nucleatum*) | | | Combinations of ileal commensals+oxaliplatinum-anti-PD1 mAbs in MSS colon cancers | | | Synergistic effects of OXA+anti-PD1 in the presence of immunogenic ileal commensals | Ileal apoptosis+ ileal immunogenic bacteria induce IL-1β and IL-12 DC release and elicitation of B cells, IgG2b serum levels and TFH immunity associated with tumor regression. | | | (Roberti et al. 2020; Picard et al. 2020) |
| \*BP melanoma | FMT from R and NR melanoma patients | | | | | anti-PD1 mAbs | | | | Oral gavages of hosts with FMT from melanoma patients | | | *None* | | | Increased responsiveness to anti-PD1 mAbs | Immune changes in gut, spleen and TME: increased of TH1 and decrease of TH17 TILs in TME, ascribed to enrichment in *Faecalibacterium* spp. | | | (Gopalakrishnan et al. 2018; Rutkowski et al. 2015) |
| \*MCA-205 sarcoma  \*RET melanoma \*Orthotopic LLC lung carcinoma | GF or ATB in SPF or prior to FMT from NSCLC NR patients | | | | | anti-PD-1 mAbs  +/- anti-CTLA4 Abs | | | | *Akkermansia muciniphila (Akk)* (+/-*Enterococcus hirae*) | | | FMT from NR-NSCLC patients in avatar mice supplemented with oral gavages of Akk during anti- PD-1 mAb+/- anti CTLA4 Ab-based therapy | | | Compensation of dysbiosis and restoration of response to anti-PD-1 mAbs | \*Recruitment of CCR9+CXCR3+CD4+ T cells in the TME via IL-12 \*Increased CD4/Foxp3 ratio in TILs | | | (Routy et al. 2018) |
| \*Orthotopic RENCA kidney carcinoma | ATB or FMT from R vs NR RCC cancer patients | | | | | antiPD-1 mAbs + antiCTLA 4 mAbs | | | | *Akkermansia muciniphila* or *B. salyersae* | | | FMT from NR-RCC patients in avatar mice supplemented with oral gavages of Akk during anti- PD-1 mAb+/- anti CTLA4 mAbs | | | Restoring responses to combination of ICI | Not done | | | (Derosa et al. 2020) |
| \*MC38 colon carcinoma  \*Braf V600E Pten-/- melanoma | GF or SPF conditions without antibiotics | | | | | anti-PD-1 or anti-CTLA 4 mAbs | | | | Mixture of a 11 bacteria consortium | | | Repetitive oral supplementation early after tumor inoculation | | | Enhancing the efficacy of ICI | Induction of colonic and intratumor IFN𝛄 producing CD8+ T lymphocytes, activation of systemic DC  Metabolomic changes with the bacteria consortium | | | (Tanoue et al. 2019) |
| \* CT26 and MC38 colon cancer  \**Msh2LoxP/LoxPVillin-Cre autochthonous colon cancer* model | ATB | | | | | anti-CTLA4, CpG and chemotherapy | | | | *Bifidobacterium pseudo longum and Akkermansia* (gut or possibly intratumoral bacteria) | | | Oral *B. pseudolongum, L. johnsonii, Olsenella spp.+ICI* | | | DC exposed to *B. pseudolongum* or A.muc produce IL-12 which, through IL-12Rβ cosignaling with A2AR on T cells induce TH1 differentiation | Anticancer metabolite inosine translocates from gut to tumor beds.  Inosine (ip, iv or per os) synergized with anti-CTLA4 mAbs in an IL-12 and A2AR-dependent manner | | | (Mager et al. 2020) |
| \*MC38 colon cancer | ATB  GF  Tac versus Jax mice and  Ifnarf/fCd11cCre mice | | | | | anti-CD47 mAbs | | | | Oral inoculation of *Bifidobacteria* | | | Oral administration of Bifidobacterium and i.t. injection of anti-CD47 mAbs | | | Stimulation of the STING signaling pathway | Induction of IFNβ in tumor DC. Intratumoral (i.t) elimination of Bifidobacterium by an antibiotic cocktail reduced the cross-priming ability of tumor DCs | | | (Y. Shi et al. 2020) |
| \* Preinvasive and invasive pancreatic ductal adenocarcinoma (PDA)  \*orthotopic KPC | ATB | | | | | anti-PD1 mAbs | | | | TRAF6 inhibitors decreased while  TLR2 and TLR5 ligands  increased PDA aggressiveness | | | Oral administration of protumorigenic *B. pseudolongum* | | | MDSC and TLR signaling.  *Proteobacteria and B. pseudolongum* more abundant in gut and tumor and accelerated oncogenesis in a TLR-dependent manner | Reprogramming of M2 into M1, and TH1+ cytotoxic CTL in PDA. Combination of ATB and PD-1 blockade reduce PDA growth | | | (Pushalkar et al. 2018) |
| \*RET melanoma  \*TC1 iv metastases  \*RENCA kidney cancer  \* Humans in carb free diet interventions | Ketogenic diet (KD)  or 3OH butyrate (3HB) in SPF mice | | | | | anti-PD1 mAbs+/-anti-CTLA-4 mAbs | | | | Nutritional interventions (Ketogenic diet  or 3OH butyrate (3HB° ip, iv, or per os) | | | Diet-induced changes of microbiota composition (richness in *Eisenberghiella massiliensis*) | | | 3HB-induced TH1 differentiation  without upregulation of PDL-1 on tumor cells nor CD86 on spleen macrophages | Increased efficacy of ICI by prophylactic diet interventions  T cell dependent activity of KD or 3HB | | | (Ferrere et al. 2021) |
| ***Adoptive Cellular Therapy (ACT)*** | | | | | | | | | | | | | | | | | | | | |
| \*Large B16F10 melanoma | ATB or polymyxin or TLR4 or CD14 wt versus TLR4 or CD14 KO mice  Rag2–/–γc–/– mice | | | | | 5 Gy TBI and ACT (p-mel-1 specific CTL) | | | | Ultrapure LPS | | | Effects of host conditioning with TBI prior to ACT | | | Enhanced efficacy of ACT in the setting of TBI  due to translocation of Enterobacter cloacae, E. coli, Lactobacillus, and Bifidobacterium bacteria into mLN after TBI | Bacterial and LPS dependent increase of host spleen CD11c+CD86high DCs and serum levels of IL-12 | | | (Paulos et al. 2007) |
| \*MPKAS tumors | Tlr5 wt versus Tlr5 KO mice  Tlr5−/− γδ-deficient mice  Co-housing experiments | | | | | Spontaneous tumor growth | | | | Differences assigned to genera of Allobaculum, Bacteroides, and Lactobacillus | | | Extra-intestinal tumor growth kinetics between TLR5 wt and gene deficient littermates | | | Deleterious role of flagellin-harboring gut commensals on (IL-6 or IL-17 driven) peripheral inflammation | Cross-talk between MDSC and γδ-T cells related to gut commensals. Role of IL-6 and IL-17 in tumor-induced inflammation and propagation. | | | (Rutkowski et al. 2015) |
| \*sc B16.SIY melanoma | SPF C57BL/6 | | | | | SVY (*B. breve* epitope)-expanded T cells targeting the SIY -expressing tumor cells | | | | *Bifidobacterium breve* | | | ACT injection at day 8 post tumor inoculation, followed by 2 injections of IL-2 | | | Delay tumor growth | TILs stimulation via cross-reactivity between SVY commensal epitope and SIY melanoma neoantigen | | | (Bessell et al. s. d.) |
| \*sc TC1 cells, HPV E6/E7 gene transduced cervix /lung cancer cells | ATB regimen  (vancomycine, versus neomycine,  versus metronidazole) | | | | | HPV-E6/E7-specific ACT | | | | Vancomycine (killing unknown specific Gram+bacteria from the Bacteroides genus) | | | Oral vancomycine (but not metronidazole or neomycine) for 10 days before ACT | | | Vancomycin increased the efficacy of ACT | Increased systemic CD8 ⍺ DC numbers resulting in enhanced efficacy of ACT in an IL-12 dependent manner | | | (Uribe-Herranz et al. 2018, 12) |
| ***Cytokine or TLR agonists*** | | | | | | | | | | | | | | | | | | | | |
| \*sc MC38 colon carcinoma, \*B16.F10 melanoma | ATB pre-exposed mice | | | | | CpG-ODN combined to anti-IL10R | | | | *Alistipes shahii and Ruminococcus genus* were pro-inflammatorywhileL. murinum, L. intestinalis, and L. fermentum  were anti-inflammatory mediators*.* | | | Oral administration of 5 or 8 doses, after one week of antibiotic cessation | | | TNFα-induced tumor necrosis  following CpG+anti-IL-10R mAbs | Increased TNF production by tumor associated myeloid cells in response to anti-IL10R/CpG-ODN | | | (Iida et al. 2013) |
| \*B16F10 melanoma  \*CT26 sc colon cancer  \*Human colon cancer tissues | SPF mice on ex vivo organotypic cultures | | | | | rIL-2 | | | | *A. muciniphila (Akk)* or TLR2 *Akk* agonist | | | Oral gavages with *Akk* every three days for 20-25 days with ip administration of rIL-2 | | | *Akk* induced tumor cell apoptosis, increased CD8/Treg ratio, activation of intratumor DCs | Increased Tc1 CTLs in tumor beds  Reduction of Treg  Increased ratios between TNFα/TGFβ in tumor beds | | | (L. Shi et al. 2020) |
| **CHEMOTHERAPY or TARGETED THERAPIES** | | | | | | | | | | | | | | | | | | | | |
| \*sc EL4 thymoma | | | | ATB or GF  and TLR4 wt versus KO mice | Oxaliplatinum (OXA) | | | Not done | | | | | Oxaliplatinum in GF or ATB treated mice | Deficient production of reactive oxygen species and cytotoxicity after chemotherapy in ATB or TLR4 KO mice | | | ABX attenuated induction of Nox1 and Cybb encoding ROS-generating NADPH oxidase 2 (NOX2) and of the ROS-responsive Nos2, Sod1, and Sod2 after OXA | | | (Iida et al. 2013) |
| \*MCA-205 sarcoma  \*B16.F10 melanoma | | | | C57BL/6J mice  Germ free or ATB treated mice in SPF conditions | Cyclophosphamide (CTX) | | | *Enterococcus hirae* and *Lactobacillus johnsonii* | | | | | Oral gavages the day after CTX administration | Elicitation of pTH17 cells compensating the loss of CTX activity in ATB-treated mice. | | | CTX-induced Gram-positive translocation from gut to splenocytes and subsequent systemic priming of pTH17 and memory TH 1 immune correlating with therapeutic efficacy of CTX. | | | (Viaud et al. 2013) |
| \*MCA-205 sarcoma  \*MC38 colon cancer  \*HPV16 TC1 lung cancer | | | | ATB or SPF | CTX | | | *Enterococcus hirae* or *Barnesiella intestinihominis* | | | | | Oral gavage the day after CTX administration or vaccination | *B. intestinihominis* restores efficacy of a cancer vaccine  *E. hirae* restores efficacy of CTX in ATB treated mice | | | *\*E. hirae* increased intratumoral CD8/Treg ratio.  \*B. intestinihominis stimulated IFN**𝛄** producing 𝛄𝝳 Tcells in the TME.  \*Both commensals mounted effector and memory CD4+TH1, CD8+ Tc1 lymphocytes | | | (Daillère et al. 2016) |
| \*MCA205 sarcoma  \*TC1 lung cancer | | | | ATB | CTX or anti-PD-1 Abs | | | Various strains of *E. hirae* containing or not a Siphoviridae phage sequence | | | | | *E. hirae* spp. harboring various genetic sequences and CTX or anti-PD-1 mAbs | H-2Kb-restricted CTL responses in spleen and tumor beds | | | Molecular mimicry between *E. hirae* TMP1 antigen and PSMB4 oncogenic driver | | | (Fluckiger et al. 2020) |
| \*YUMM1.5 melanoma  \*NRASQ61Kmouse melanoma cells | | | | Prebiotics in SPF mice | Mucine or Inulin | | | None | | | | | Oral gavage of prebiotics in conjunction with MEK or BRAF inhibitors  (mucin (3% in drinking water) or inulin (15% w/w in chow) starting 2 weeks before sc inoculation of melanoma tumor cells | Changes of the microbiota composition with prebiotics (mucin and Akk, inulin and Biifidobacteria) | | | Systemic Il-1a and Cxcl13 with mucin. TH1 cells and DC maturation with both prebiotics.  Inulin attenuated resistance of melanoma to MEK inhibitors | | | (Li et al. 2020) |
| **RADIATION THERAPY** | | | | | | | | | | | | | | | | | | | | |
| \*B16-OVA melanoma,  \*TC1 cervix/lung carcinoma | | | | SPF and vancomycine treated mice | External beam radiotherapy (RT) on tumor beds | | | Gram positive bacteria  and SCFA | | | | | Oral vancomycine before tumor inoculation | Enhanced local and abscopal anti -tumor effects of RT | | | Increases local cross- presentation of tumor antigen-specific T cells  Inhibitory effects of distinct Gram+ bacteria and butyrate | | | (Uribe-Herranz et al. 2020) |
| \*Elite mice subjected to sublethal irradiation  \*B16F10  \*EL4  \*21 leukaemia patients at strat of TBI for pre-HSCT | | | | FMT and dirty cage sharing | Partial or total body irradiation | | | Lachnospiraceae and Enterococcaceae | | | | | Oral gavages with Lachnospiraceae family members | Gut metabolic changes such as increased Propionate and H-Indole 3- carboxaldehyde Kynurenic acid that protect mice against DNA damage and ROS release | | | Increased hematopoiesis and intestinal barrier recovery post-sublethal irradiation | | | (Gao et al. 2018) |
| **STEM CELL TRANSPLANT (SCT)** | | | | | | | | | | | | | | | | | | | | |
| Major-histocompatibility-complex (MHC)-matched minor-antigen-mismatched allo-HCT model (C57BL/6→129S1/Sv) | | | | Broad spectrum ATB  compared with T cell repleted grafts | Allogeneic bone marrow transplantation (BMT) | | | *Enterococcus faecalis* | | | | | Dietary lactose depletion or elimination of Enterococci growth post-all BMT | Graft-versus-host disease (GVHD) modulated with enterococci relative overgrowth in colon LP | | | Disaccharide lactose-induced Enterococci overgrowth, creating elevated IFN**𝛄** serum levels, TH17 colonic accumulation and recirculation of CD4+ T cells | | | (Stein-Thoeringer et al. 2019; Iida et al. 2013) |
| Mice irradiated (TBI) and transplanted with B10.BR BM and T cells  7 days ampicillin, before BMT | | | | C57BL/6J mice | Allogeneic bone marrow transplantation (BMT) | | | *Lactobacillus johnsonii* | | | | | Oral reintroduction every other day for 14 days before BMT | Protection against Graft-versus-host disease (GVHD) | | | Unknown | | | (Jenq et al. 2012) |
| Mice irradiated (TBI) and transplanted with BM  7 days ampicillin, before BMT | | | | C57BL/6J mice | Allogeneic bone marrow transplantation (BMT) | | | *Lactobacillus rhamnosus GG* | | | | | Oral administration 7 days prior to BMT  or in post transplantation period proceeded by 7 days of ciprofloxacin | Reduced mortality post BMT and protect against GVHD | | | Unknown | | | (Gerbitz et al. 2004) |