MICROBIOME AND IMMUNITY

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Overview

- Bacterial metabolites, anti-microbial peptides and bacteria can prime dendritic cells (DCs) which migrate to the lymph nodes to stimulate T and B cells.
- Pathogen associated molecular patterns (PAMPs) from the gut may also interact directly with immune cells, inducing activation and maturation of antigen-presenting cells (APCs) including DCs.
- These mature APCs may then translocate into mesenteric lymph nodes and mediate priming of lymphocytes, and disseminate systemically and induce the differentiation of naïve T cells into CD4+ T cells which function at distant sites.

Short chain fatty acids

- Short chain fatty acids (SCFAs) and polyamines are the most abundant microbial metabolites in the gut.
- SCFAs include acetate, propionate and butyrate.
- Produced by bacterial fermentation in the gut from dietary fibers that remain undigested or partially digested.
- Serve as the major energy sources of intestinal epithelial cells and maintain gut barrier integrity.
- SCFA may bind to G-coupled protein receptors (GPR43 and GPR41) of intestinal epithelial cells, altering host gene expression and inducing autophagy and stimulating production of anti-inflammatory cytokines.

Short chain fatty acids

- SCFAs deactivate NF-κB and abrogate the expression of the pro-inflammatory cytokine TNF in mononuclear cells and neutrophils
- Also mediate immune cell phenotype through epigenetic mechanism, by inhibiting histone deacetylases (HDACs)
- This mechanism can promote CD8+ memory cell differentiation.
- SCFAs also influence antigen-specific adaptive immunity by stimulating the synthesis of IgA by B cells

Short chain fatty acids

- The acetate producing bacterium Bifidobacterium longum prevents the translocation of toxins from enteropathogenic Escherichia coli O157:H7 into the systemic compartment.
- Segmented filamentous bacteria (SFB) can induce secretion of IL-22 from ILC3 cells.
- Drive TH17 polarization in lamina propria DCs via production of serum amyloid A

Other metabolites

- Compounds such as tryptophan, indole, and bile acids may interact with aryl hydrocarbon receptor (AhR) and pregnane X receptor (PXR).
- Upregulate the expression of tight junctions
- Induce cytokine production by AhR expressing lymphoid cells.
- In contrast, AhR expression on Tregs affects their homing and suppressive activity

Other metabolites

- Lactobacillus spp., produce metabolites by metabolizing dietary tryptophan. These metabolites bind to the aryl hydrocarbon receptor (AHR) on a variety of cells, regulating colonic inflammation.
- IL-22 producing IL C3 cells activated.
- The oral ingestion of Bifidobacterium infantis leads to increased levels of the serotonin precursor, tryptophan, and may ameliorate depressive symptoms.

Other metabolites

- Propionate exacerbates autism spectrum disorder symptomatology as well as Parkinson's Disease symptomatology.
- Butyrate decreases depressive-like behavior with parallel changes in histone deacetylation and BDNF expression.
- SCFAs also regulate the gut immune system and this may have consequences on the central nervous system. The maturation and activation of microglia is also regulated by the gut microbiota.

Other metabolites

- Prenatal exposure to the mood stabilizer valproate is a major risk-factor for autism
- Lactobacillus reuteri strain not only augments levels of oxytocin but also ameliorates synaptic dysfunction in offspring of mothers on a high fat diet

Other metabolites

- Inosine significantly promotes the differentiation of Th1 cells in the presence of exogenous IFN-γ by acting on the A2A receptor on T cells.
- IFN-γ inhibits the function of M2 macrophages induced by IL-4/IL-13.

Polyamines

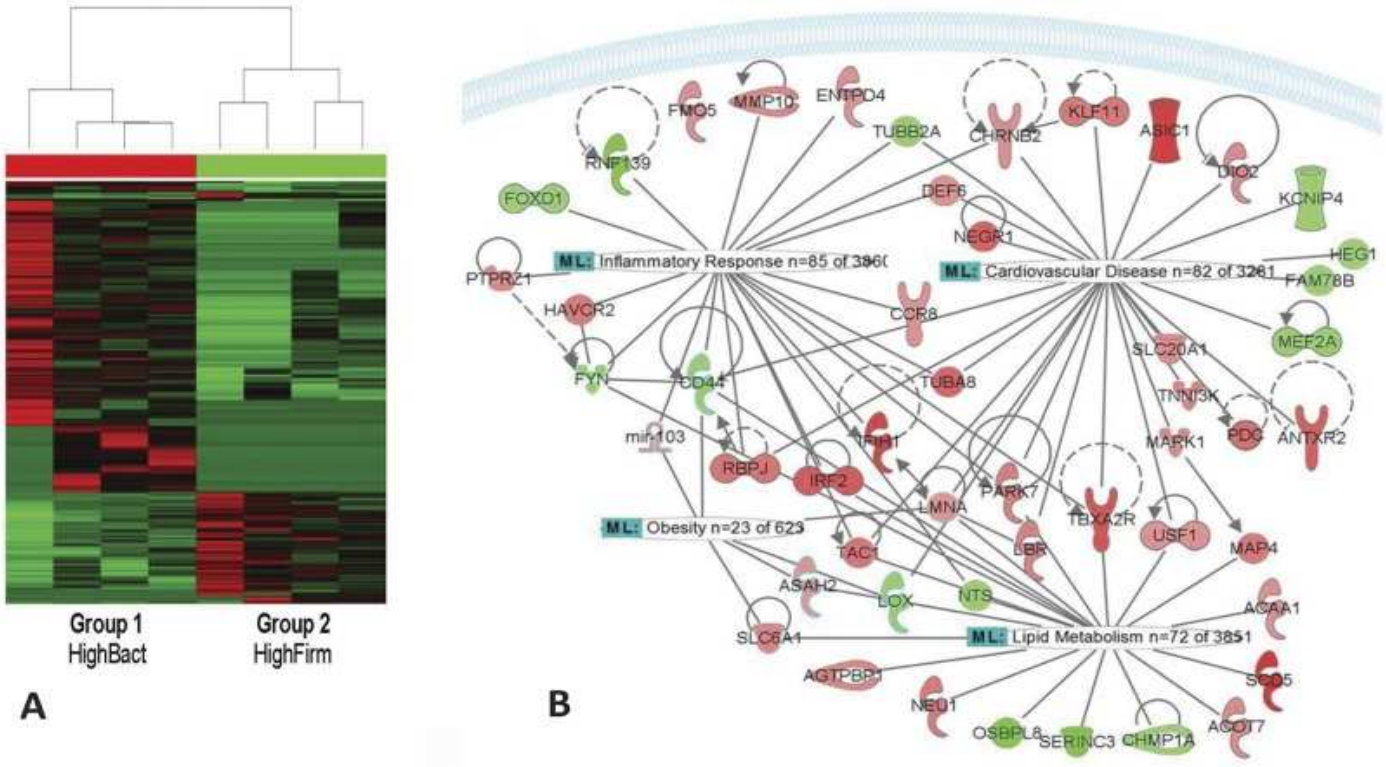
- Polyamines such as putrescine, spermidine and spermine induce the secretion of IgA in the gut as well as maintain barrier integrity.
- Elevated levels of polyamine in breastmilk promote the maturation of gut CD8+ and CD4+ T cells.
- The polyamine-producing bacterial strain Bifidobacterium animalis subsp. lactis LKM512 along with arginine diminishes levels of intestinal inflammatory cells.

Gut microbiota

- Gut microbes can stimulate the body to produce CD47 antibodies by activating STING signaling
- Bifidobacteria may affect activating DC cells, thereby improving the activity of antigen-specific $CD8^+$ T cells.
- Translation of gram-positive bacteria into secondary lymphoid tissues stimulate Th17 and Th1 immune response.
- IL-12 dependent.
- Bacteroides fragilis inhibits CTLA-4, restoring Th1 immune responses

Gut microbiota

- The gut microbial composition affects the DNA methylation status of genes primarily linked to cardiac diseases, with associations to lipid metabolism, inflammatory response, and obesity.
- Supplementation with inulin and fructo-oligosaccharide may select for such beneficial bacteria as Lactobacillus and Bifidobacterium



HighBact Bacteroidetes and Proteobacteria
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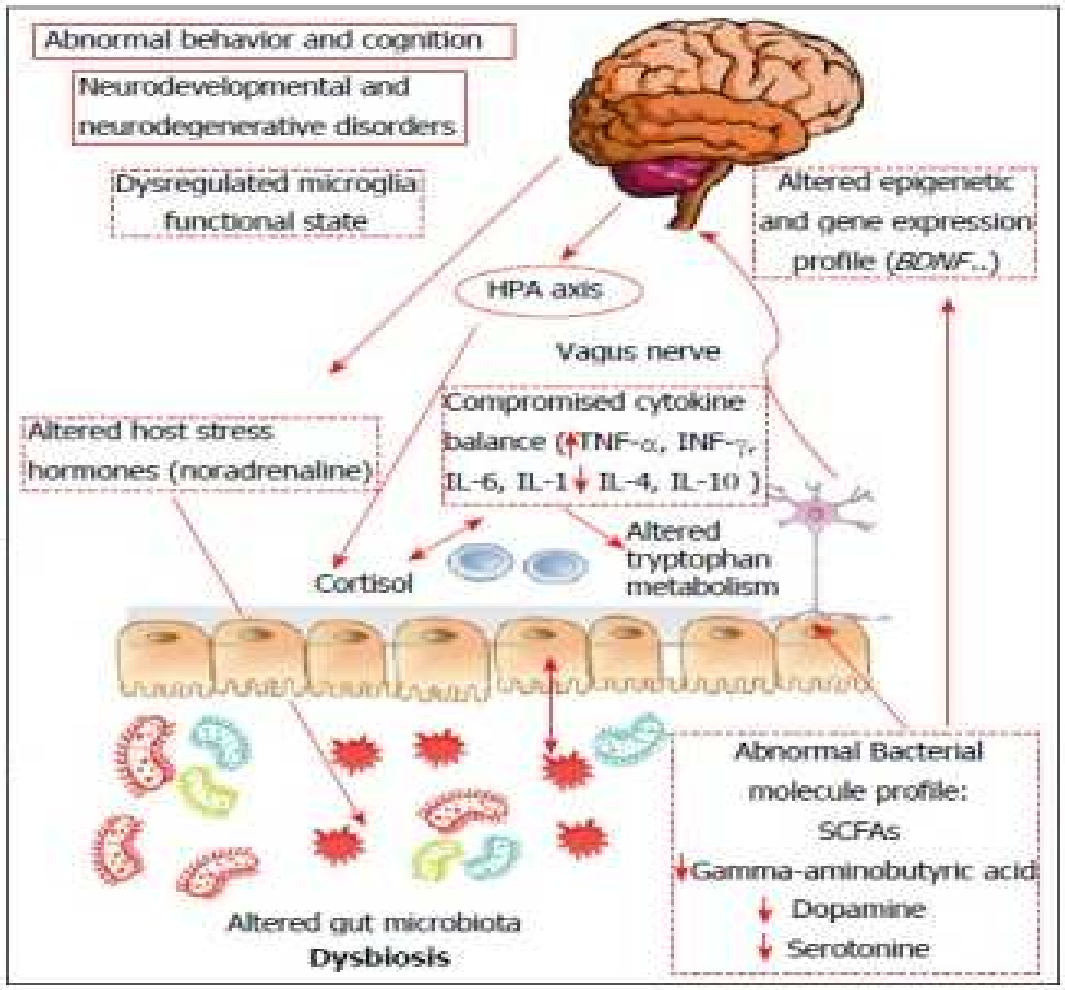

10.3748/wjg.v23.i30.5486

Gut microbiota and tumor response

Tumor microenvironment

- The main cells of the tumor microenvironment (TME) in cancer immunity are NK cells, DC cells, CD8 + T cells, Treg cells, fibroblasts, tumor associated macrophages (TAMs), and myeloid derived suppressor cells (MDSCs).
- NK cells induce the death of tumor cells by the ways of releasing perforin and granzyme, secreting tumor necrosis factor-a, and mediating cytotoxicity by TRAIL and FAS1 receptors.

Tumor microenvironment

- Myeloid cDC1 cells are able to promote the differentiation and maturation of $CD8^+$ T cells, and cDC1 cells can recruit CCL5 and XCL1, which induce the accumulation of cDC1 cells in the TME, thereby improving the immune control of tumors.
- IL-2 contributes to enhancing the antitumor activity of NK cells.
- When CD4 + T cells migrate to lymph nodes, cDC2 can activate $CD4^+$ T cell responses. cDC2 resistant CD4 $^+$ T cells can be inhibited by Treg cells.

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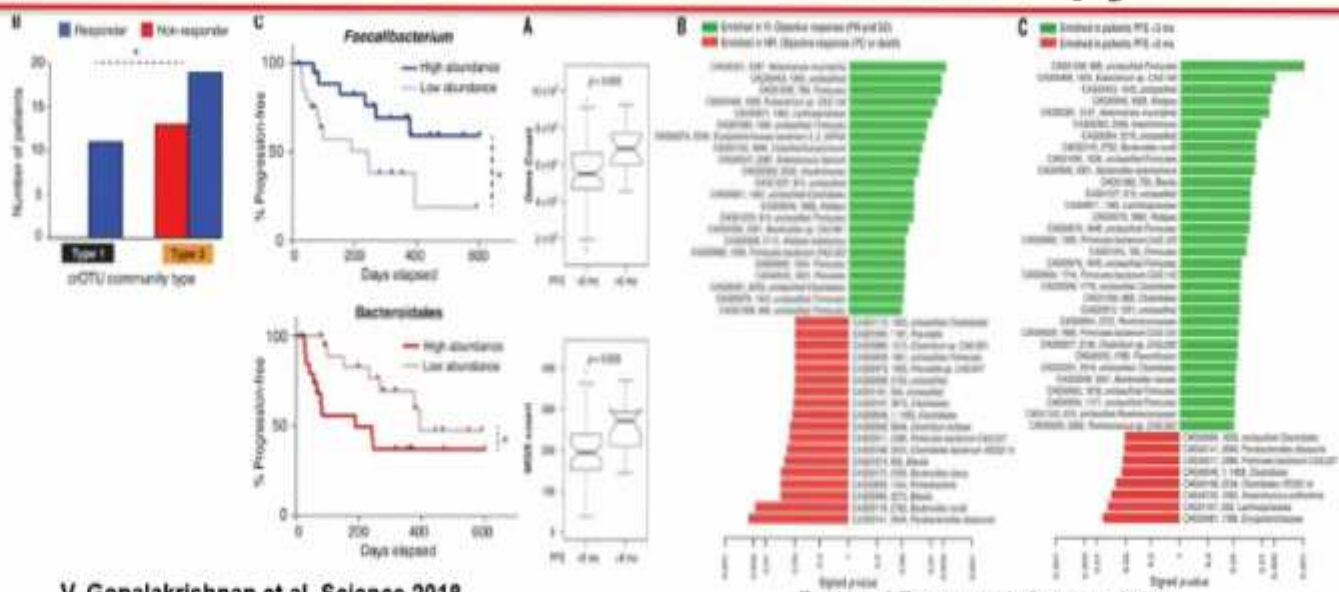
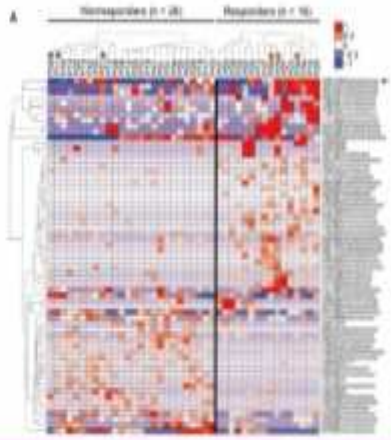
Gut microbiota predicts response to cancer immunotherapy



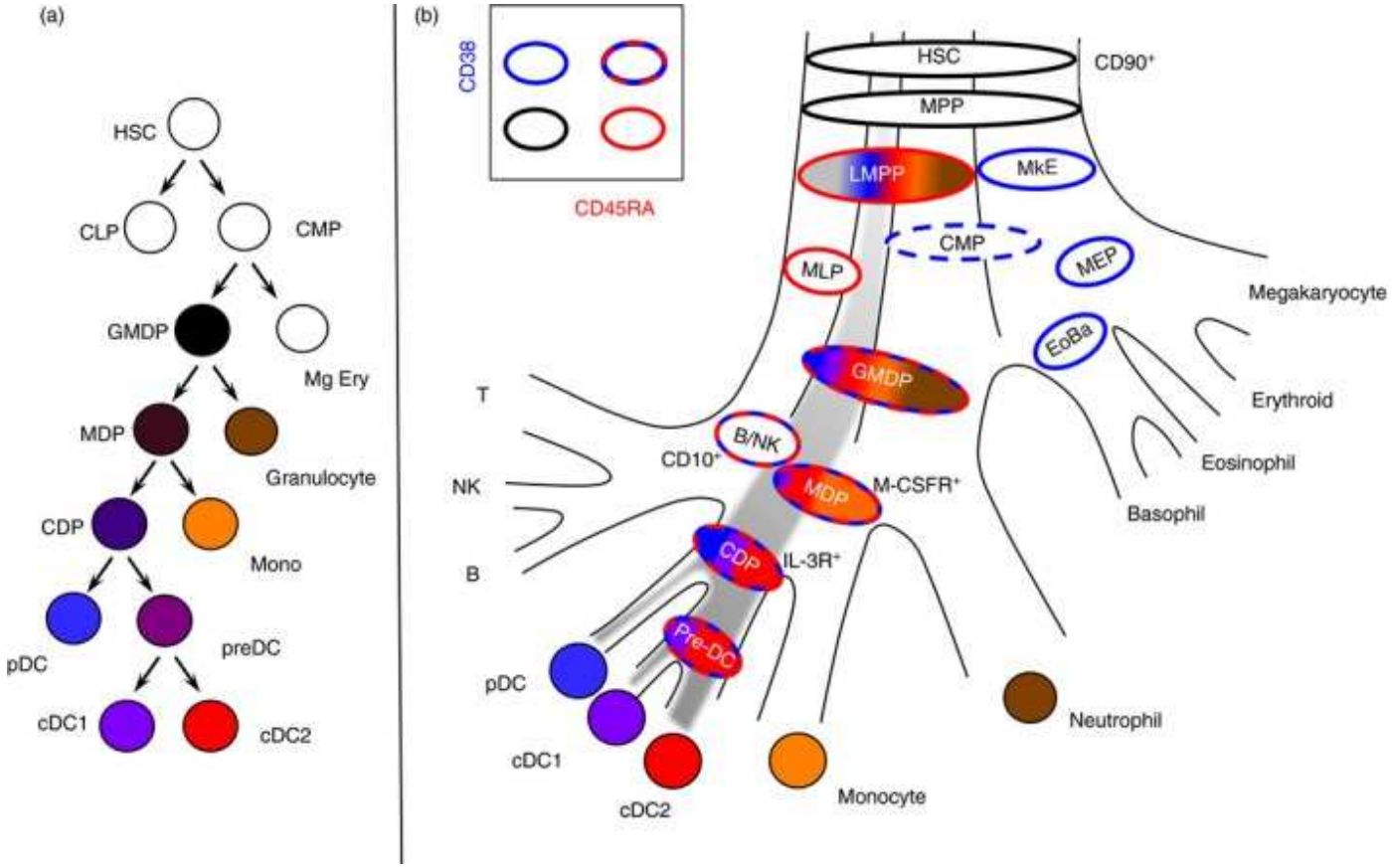
V. Gopalakrishnan et al. Science 2018

Bertrand Routy et al. Science 2018



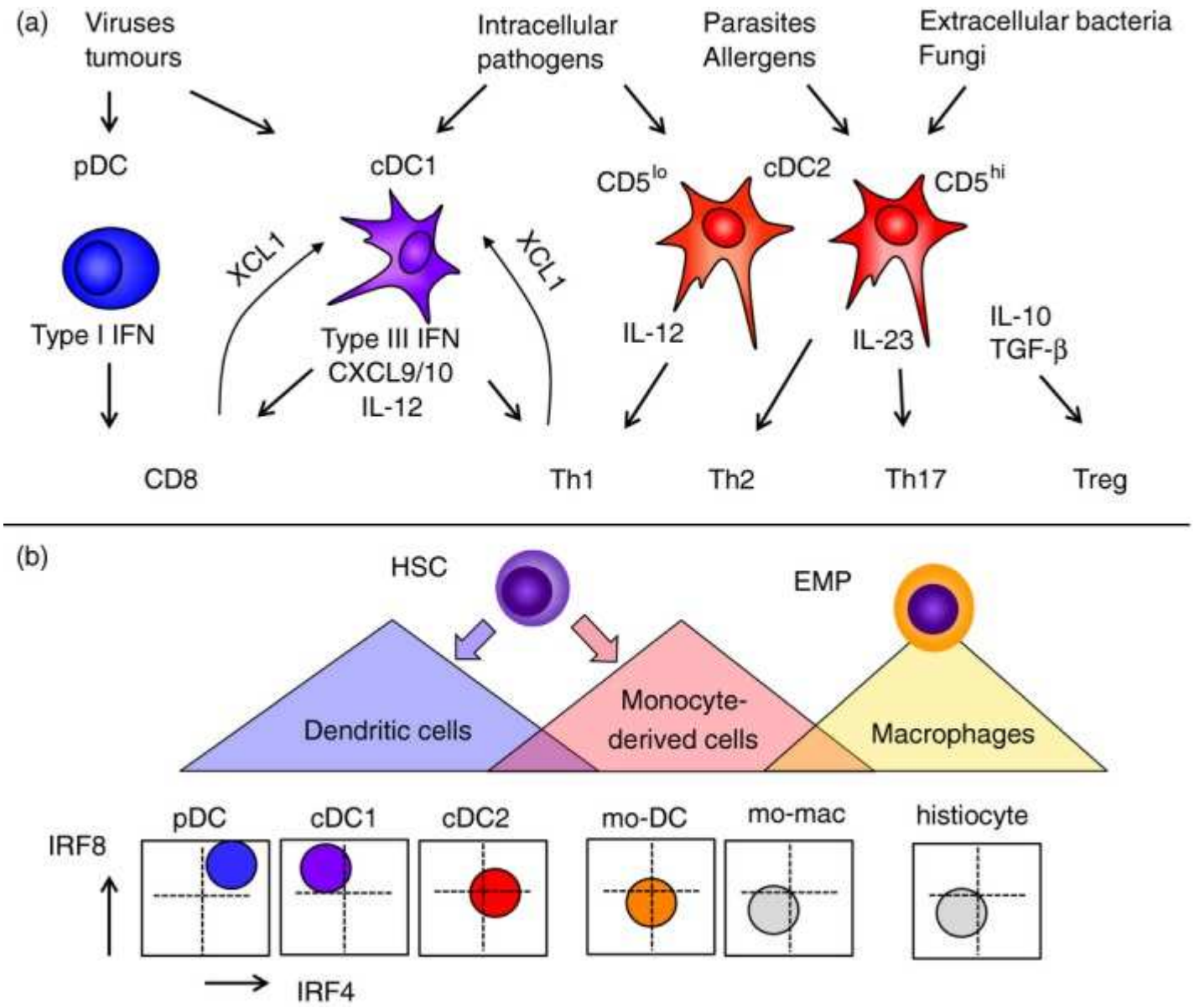
Vyara Matson et al. Science 2018

Classic and revised models of hematopoiesis



Common myeloid progenitors are mixtures of mega-erythroid and myeloid precursors and the most significant early partitioning of cell fate occurs when megakaryocyte and erythroid potentials separate from lympho-myeloid potentials.

Doi: 10.1111/imm.12888



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Tumor microenvironment

- VEGFA activates cancer associated fibroblasts, which secrete FSP1.
- TAMs can promote the growth and metastasis of tumor cells through multiple pathways. They are one of the dominant cells in the tumor microenvironment.
- Lactate produced by cancer and acidification of the microenvironment increase ARG1 expression in TAMs.
- TAMs play an M2 role to produce high levels of reactive oxygen free radicals, promote DNA damage and genomic instability, tumor infiltration and metastasis, as well as participate in the digestion and reconstruction of extracellular matrix (ECM), inhibit

Tumor microenvironment

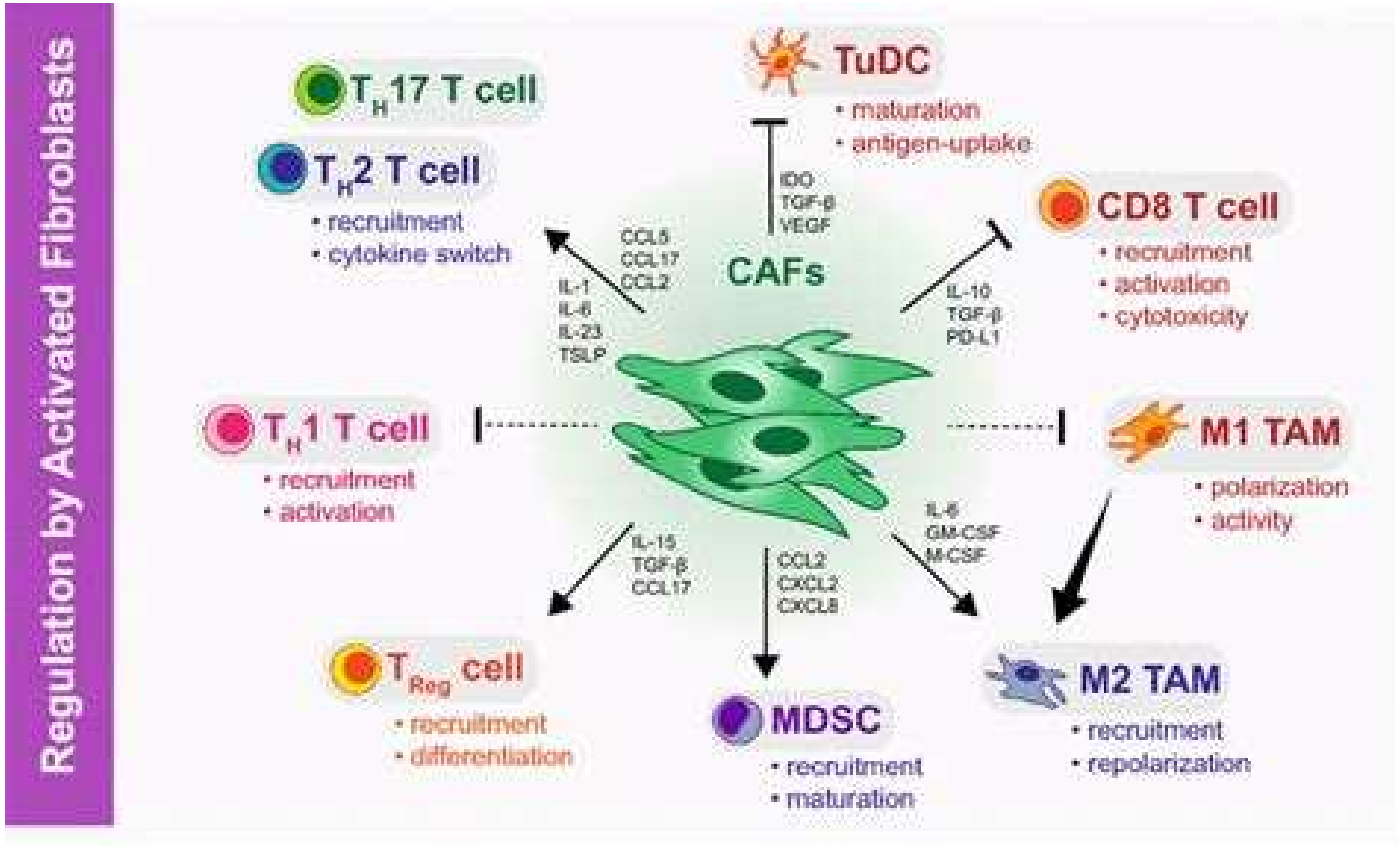
- MDSCs induce the nitration of the T-cell receptor/CD8 complex through the excessive production of reactive oxygen species and peroxynitrite in the process of cell-cell direct contact
- Leads to the inability of $CD8^+$ T cells to bind to peptide-MHC (pMHC) and affect the ability to respond to non-specific stimulation
- This $CD8^{\pm}$ T cell tolerance is one of the major mechanisms of tumor escape.
- MDSCs also increase the metabolism of L-arginine by producing arginase I, which inhibits T cell-lymphocyte reaction and blocks T-cell activation by consuming cysteine

Tumor microenvironment

- The stimulating factor 1 receptor (CSF1R) is significantly expressed in MDSCs and TAMs, which cause functionally reprogram the response of macrophage and enhance antigen presentation and anti-tumor T cell response.
- T cell checkpoint molecules, including PDL1 and CTLA4, are upregulated by CSF1R

Tumor microenvironment

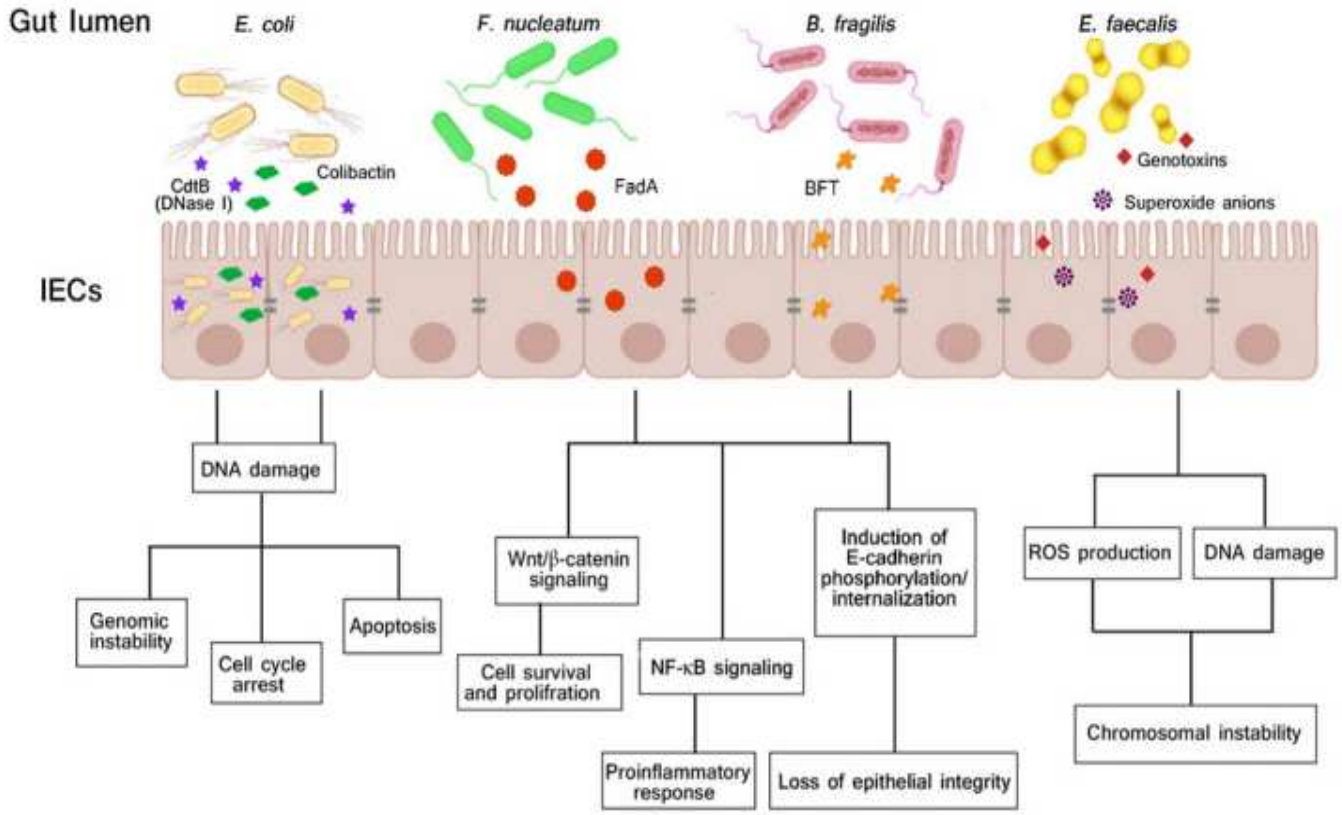
- Cancer associated fibroblasts (CAFs) inhibit the activity of cytotoxic T lymphocytes and recruit lymphocytes that produce inflammatory signals to promote cancer progression
- CAFs can direct or coordinate the infiltration of immune cells directly or through secreted cytokines and surface proteins, or indirectly and coordinate the infiltration of immune cells by depositing various ECM substrates and remodeling matrices, thereby promote cancer.



DOI:10.1007/s00262-017-2003-1

Tumor microenvironment

- TME promotes the occurrence of hepatocellular carcinoma (HCC), for example.
- NK cells and DCs participate in immune escape mechanisms
- 25% of NK cells are PD-1 positive
- Macrophages are involved in promotion of angiogenesis and tissue remodeling, and the production of cytokines and chemokines leading to persistent inflammation-related damage
- TLR4 signaling in tumor cells is able to recruit neutrophils, while TNF released by neutrophils is able to induce metastasis of tumor cells.



https://dx.doi.org/10.1002%2Fcam4.3694

Microbiota	Main effects on immunity	Potential effect on immunotherapy
Beneficial microbiota	Enhanced the antitumor efficacy of PD-L1 blockade, enhancement of DC maturation, improving activity of the tumor-specific $CD8^+$ T cells, increased IFN-γ production	Effective
Bifidobacterium		
Bacteroides fragilis, *Bacteroides thetaiotaomicron*, *Burkholderia cepacia*	Increased the efficacy of anti-CTLA-4 therapy by inducing Th1 response and promoting DC maturation, an increase in $CD8^+$ T cells and a decrease in Tregs in the tumor environment	Effective
Akkermansia muciniphila	Enhanced the infiltration of immune cells in tumor site, as $CCR9^+CXCR3^+CD4^+$ T cells were recruited to the tumor microenvironment and the ratio of $CD4^+$ T cells to $CD4^+FoxP3^+$ T cells (Tregs) was enhanced	Effective
Enterococcus hirae	Enhanced IL-12 secretion by DCs	Effective
Harmful microbiota	Increased host PD-1 and PD-L1 expression, higher level of pro-inflammatory cytokines (TNF-α), suppressed the proliferation of CD4+ T cells, the inhibitory effect can be blocked using antibodies PD-L1	Ineffective
Helicobacter pylori		
HBV, HCV, HPV, EBV	Established chronic infections in humans and increased host PD-1 or PD-L1 expression	Ineffective

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7897953/

Modification of immune response

- Elimination of gut microbiota enhances effect of TP53 mutations
- Accumulation of Bifidobacteria in the TME can significantly improve the antitumor efficacy of anti-CD47 immunotherapy
- Vancomycin enhances the blocking effect of CTLA-4 by increasing the proportion of Gram-negative Burkholderia and Bacteroides in the intestines

Modification of immune response

- The cross-priming of antigen-specific T cells of tumor-resident DCs can be enhanced by anti-CD47 therapy.
- In addition, type I IFN plays an important role in enhancing the adaptive immune response to anti-CD47 antibody therapy in tumor-resident DCs
- Patients with more Faecalibacterium have a significantly prolonged progression-free survival with a higher level of effector T cells and a stabilized cytokine response to PD-1 blockade.
- Simultaneously, systemic and anti-tumor immunity are also enhanced

Modification of immune response

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Modification of immune response

- After taking probiotics, the abundance of butyrate-producing bacteria helps maintain the intact intestinal barrier to avoid the activation of inflammation-related factors in TME, in colon cancer, for example
- Lactobacillus casei, Rhamnose and Bifidobacterium have been shown to reduce radiotherapy-associated diarrhea by inhibiting the expression of TNF, IL1b, and IL6mRNA
- Fermented Lactobacillus is considered as weakening the response to immunotherapy

Modification of immune response

- The inhibition of the production of lactic acid in cancer cells (Warburg effect) helps to recover active oxygen homeostasis of physiological mitochondrial and restore normal function of cells
- Cyclophosphamide (CTX) induces immunogenic cancer cell death and immunomodulatory effects.
- Oral administration with Enterococcus hirae restores CTX anti-tumor efficacy by inducing differentiation of TH17 and pathogenic TH17 cells, promoting tumor-specific Th1 and CTL activity.

Modification of immune response

- Abiraterone acetate is both an inhibitor of androgen biosynthesis and a highly effective drug of prostate cancer
- Reduces harmful microorganisms through altering gut microbiota
- Lenalidomide can enhance the cytotoxicity mediated by NK cell and ADCC
- IFN-γ and celecoxib inhibit M2 differentiation