

Table S0: Microbial regulation of systemic immunity

Bacteria	Immune-effect in the gut	Mechanism of interaction in the gut	Additional information on mechanism	Disease phenotype in the gut	Systemic immune effect	Mechanism of systemic immune effect	Systemic disease phenotype	Mechanism linking gut to systemic effects
Segmented Filamentous Bacteria	Induction of Th17 cells (Ivanov et al., 2009)	Intestinal DC MHC-II dependent presentation of SFB antigens in the LP (Goto et al., 2014); Serum amyloid A production by IECs, potentially impacting DC cytokine production (Ivanov et al., 2009)	SAA induces DC-dependent Th17 differentiation in vitro, induces IL-6 and IL-23 cytokine production in DCs isolated from LP in vitro (Ivanov et al., 2009)	Increased mucosal protection to infection with <i>C. rodentium</i> (Ivanov et al., 2009)	Mono-association with SFB resulted in a considerable increase in pro-inflammatory IL-17A and IFN- γ production in the spinal cords of EAE-challenged mice (Lee et al., 2011)	Unknown	Induces EAE (Lee et al., 2011)	Unknown; hypotheses include direct sampling of luminal antigens by DCs (Goto et al., 2014) (Rescigno et al., 2001) and subsequent trafficking of primed T cells from the intestine into peripheral lymphoid organs (Sigmundsdottir and Butcher, 2008)
					SFB induced increased numbers of Th17 cells in the spleen of K/BxN mice, as well as elevation of GPI autoAb titers (Wu et al., 2010)		Induces Rheumatoid Arthritis (Wu et al., 2010)	
Commensals	Expansion of CNS-auto-reactive Th17 cells in GALT (Berer et al., 2011)	Unknown			Development of activated germinal centers in cervical lymph nodes and generation of autoantibody producing B cells (Berer et al., 2011)	Unknown	Induce development of EAE (Berer et al., 2011)	

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<i>Bacteroides fragilis</i>	Induction of IL-10 production in colon; expansion of inducible T _{regs} in mesenteric lymph nodes (Round and Mazmanian, 2010a)	PSA mediated differentiation of Tregs and IL-10 production in a TLR2-dependent manner (Round and Mazmanian, 2010a)	Outer membrane vesicles containing PSA can be recognized by TLR2 on DCs which subsequently drive T _{reg} differentiation and production of IL-10 in vitro (Shen et al., 2012)	Protection from experimental colitis (Shen et al., 2012) (Round and Mazmanian, 2010a)	Intestinal colonization with <i>B. fragilis</i> /administration of PSA is associated with a significant accumulation of CD103 ⁺ DCs and T _{regs} in the cervical LNs of EAE-challenged mice, dependent on IL-10 (Ochoa-Reparaz et al., 2010a; Ochoa-Reparaz et al., 2010b)	Unknown	Protects from EAE (Ochoa-Reparaz et al., 2010a; Ochoa-Reparaz et al., 2010b)	Unknown; hypotheses include: Trafficking and migration of a population of gut-derived CD103 ⁺ DCs to CNS-associated lymphoid tissue (Ochoa-Reparaz et al., 2010b); The gut is the site of tolerogenic DC induction followed by cell migration to the CNS; alternatively PSA may somehow activate DCs outside the intestine (Shen et al., 2012).

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					Corrects systemic Th1/Th2 imbalance, assessed in splenic CD4 ⁺ T cells of germ-free animals (Mazmanian et al., 2005)	DC uptake of PSA and presentation to CD4 ⁺ T cells; requirement for IL-12, STAT4 and MHCII in vitro (Mazmanian et al., 2005)		Unknown; hypotheses: T cell migration from mLNs to spleen may mediate the cellular signal transduction mechanisms required for PSA- mediated immune development at extraintestinal sites (Mazmanian et al., 2005)
Clostridia	Induction of T _{regs} in the colon (Atarashi et al., 2011)	Clostridia activate IECs to produce TGF- β and other T _{reg} -inducing molecules within the colon (Atarashi et al., 2011)		Alleviated DSS-mediated colitis (Atarashi et al., 2011)	Induced substantial increases in the number of IL10 ⁺ CD4 ⁺ cells in the liver, lung, and spleen (Atarashi et al., 2011)		Attenuated IgE serum responses in vivo, increased splenic IL-10 production ex-vivo (Atarashi et al., 2011) (Stefka et al., 2014); Increased asthma severity upon neonatal depletion of Clostridia via vancomycin (Russell et al., 2012)	Unknown

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Commensal metabolites	Induction of T _{regs} in the colon	Increased luminal levels of butyrate, by feeding of butyrylated high-amylose maize starches, significantly augmented colonic T _{regs} (Arpaia et al., 2013; Furusawa et al., 2013); Addition of SCFAs to drinking water of germ-free mice increased colonic T _{reg} frequency and number (Smith et al., 2013)	Treatment of naive T cells with butyrate enhanced histone H3 acetylation in the promoter region of the FOXP3 locus (Furusawa et al., 2013); SCFA-mediated effects, inc. HDAC inhibition, were dependent on T cell GPCR43 (Smith et al., 2013); GPR109a in colonic DCs and macrophages facilitated CD4 ⁺ T _{reg} expansion in the colon (Singh et al., 2014)	Ameliorated the development of colitis induced by adoptive transfer of CD4 ⁺ CD45RB ^{hi} T cells in Rag1 ^{-/-} mice (Furusawa et al., 2013) (Smith et al., 2013)	T _{reg} -cell generation in the periphery was induced by addition of butyrate, as well as propionate to drinking water of antibiotic-treated mice (Arpaia et al., 2013)	Butyrate increased Foxp3 protein acetylation and H3K27 acetylation at the Foxp3 promoter in CD4 ⁺ T cells in vitro; DCs briefly exposed to butyrate/propionate potentially induced FOXP3 expression in CD4 ⁺ T cells in vitro. Further experiments supported butyrate-mediated HDAC inhibition in DCs (Arpaia et al., 2013)		Unknown

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Early exposure to commensals	Prevention of iNKT accumulation in colon (Olszak et al., 2012)	Prevention of increased intestinal expression of the chemokine ligand CXCL16 that recruits iNKT cells (Olszak et al., 2012)	Prevention of hyper-methylation of the CXCL16 gene in colon (Olszak et al., 2012)	Prevention of increased morbidity in oxazolone-driven colitis (Olszak et al., 2012)	Prevention of iNKT accumulation in lungs (Olszak et al., 2012)	Prevention of increased pulmonary expression of the chemokine ligand CXCL16 and hyper-methylation of the CXCL16 gene in lungs (Olszak et al., 2012)	Prevention of increased morbidity in ovalbumin-driven allergic asthma (Olszak et al., 2012)	Unknown
Commensals					Type I interferon production from innate immune cells (Abt et al., 2012; Gallo et al., 2015; Ganai et al., 2012; Kawashima et al., 2013)	Binding of NfKb and IRF3 to their respective promoters was impaired in DCs purified from spleens of germ-free mice, which correlated with the absence of activating histone marks. Commensal sensing was TRIF- and MYD88-dependent (Ganai et al., 2012); Defective interferon response in peritoneal macrophages of Abx-treated mice (Abt et al., 2012)	Facilitate NK cell priming and anti-viral immunity (Ganai et al., 2012); Enhance CD8 ⁺ T cell responses and clearance of LCMV or IFV (Abt et al., 2012)	Unknown; hypotheses: Translocation of bacteria or bacterial products; modulation of intestinal epithelial or stromal cells impacts on peripheral immune cells (Abt et al., 2012)

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Lactic Acid Bacteria, dsRNA				LAB administration ameliorated DSS-induced colitis in an IFN- β dependent manner (Kawashima et al., 2013)		Oral administration of LAB induced IFN- β production in GALT-resident and splenic DCs, in a TLR3-dependent manner (Kawashima et al., 2013)	Oral administration of LAB increased splenic NK cell activity and suppressed IFV proliferation in the lungs and bronchoalveolar lavage fluids (Kawashima et al., 2011)	
Bacterial Amyloid-DNA complexes						Amyloid protein curli+DNA complexes induced type I interferon expression in splenic DCs from wild-type and young prediseased NZBxW/F1 lupus-prone mice (Gallo et al., 2015)	Mice infected with commensal curli-producing bacteria rapidly produced anti-dsDNA and anti-chromatin autoantibodies, a hall- mark of lupus autoimmunity (Gallo et al., 2015)	

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Commensals					Induced plasma cell differentiation in peripheral lymph nodes in response to trivalent inactivated influenza vaccine (Oh et al., 2014); Induced CD4 T-, CD8 T-, and B-cell immunity following intranasal infection with influenza virus (Ichinohe et al., 2011)	Induced pLN macrophage production of plasma cell growth factors, dependent on TLR5-mediating sensing of commensal bacteria (Oh et al., 2014); Induction of pro-IL-1 β , pro-IL-18, and NLRP3 in broncho-alveolar lavage and DC migration from the lung to the draining lymph nodes (Ichinohe et al., 2011)	Increased Ab titers induced by flu vaccination (Oh et al., 2014); Improved clearance of IFV (Ichinohe et al., 2011)	Unknown; Hypotheses: Products of commensal bacteria stimulate leukocytes either locally in the gut or systemically leading to inflammasome activation (Ichinohe et al., 2011)
<i>Bifido-bacterium longum</i>					Oral administration enhanced NK cell activity in spleen and lung of IFV-infected mice (Kawahara et al., 2015)	Oral administration stimulates production of IFN- γ , IL-2, IL-12 α and IL-18 in the lungs of IFV-infected mice (Kawahara et al., 2015)	Oral administration suppressed IFV replication in the lungs (Kawahara et al., 2015)	Unknown; hypotheses: Trafficking of cells from GALT to spleen and lungs (Kawahara et al., 2015)

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Commensals					Enhanced killing function of bone marrow-derived neutrophils (Clarke et al., 2010)	NOD1-mediated recognition of bacterial peptidoglycans (Clarke et al., 2010)	Increased protective immunity to <i>Streptococcus pneumoniae</i> and <i>Staphylococcus aureus</i> (Clarke et al., 2010)	Translocation of bacterial peptidoglycan from the gut to the serum and bone marrow (Clarke et al., 2010)
<i>Helicobacter hepaticus</i>	NfKb-associated innate and adaptive immunity inductive in lower bowel (Fox et al., 2010)				NfKb-associated innate and adaptive immunity induction in liver (Fox et al., 2010)		Promotes liver cancer progression (Fox et al., 2010)	Unknown; no bacterial translocation was observed (Fox et al., 2010)
<i>Fusobacterium nucleatum</i>	Recruits tumor-infiltrating suppressive myeloid cells (Kostic et al., 2013)			Intestinal tumor progression (Kostic et al., 2013)			TIGIT ⁺ Melanoma-infiltrating lymphocyte function was inhibited by <i>F. nucleatum</i> via Fap2 (Gur et al., 2015)	
Commensals					Increase systemic IL-6, leading to mobilization of MDSCs and suppressive $\gamma\delta$ T cells (Rutkowski et al., 2015)	TLR5-mediated sensing of gut commensals (Rutkowski et al., 2015)	Suppression of distant anti-tumor response in a p53/kras tumor model (Rutkowski et al., 2015)	

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Commensals					Prime tumor-associated innate myeloid cells for inflammatory cytokine production in response to anti-IL-10R/CpG-ODN and high-level ROS production in response to oxaliplatin (Iida et al., 2013)	<i>Ruminococcus spp.</i> and the Rikenellaceae species <i>Alistipes shahii</i> were associated with myeloid cell TNF production	Facilitate response to chemotherapy (Iida et al., 2013; Viaud et al., 2013)	
					Induce “pathogenic” T helper 17 expansion in response to cyclophosphamide (Viaud et al., 2013)			Translocation of gram ⁺ bacteria into secondary lymphoid organs (Viaud et al., 2013)