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Supplementary information

Transcriptional programmes underlying cellular identity and microbial responsiveness in the intestinal epithelium

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SUPPLEMENTAL TABLE 1: SUMMARY OF RECENT KEY FINDINGS

Gene	summary of insight	host organism(s)	references
NF-κB	Characterizes the localization and expression patterns of TLRs on IECs of both small intestine and colon, and TLR5 induced gene program in Paneth cells and colonic IECs using organoids.	Mouse, mouse organoid	[1]
	Demonstrates TLR activation is needed to maintain intestinal homeostasis in DSS induced colitis.	Mouse	[2]
	IEC specific MyD88 knockout shows mice are more susceptible to DSS and have reduced ability to keep microbiota from colonizing colonic mucus. This is associated with reduced pIgR, Muc2 and AMP production.	Mouse	[3]
	Revealed dynamic patterns of NF-κB activity in vivo in response to microbiota colonization.	Zebrafish	[4]
	RelA regulates IEC homeostasis and protects against intestinal inflammation	Mouse	[5]
	Mechanisms through which NEMO prevents intestinal inflammation. Also describes phenotype of RelA, RelB and c-Rel triple intestinal specific knockout mice.	Mouse	[6]
	Showed TLR4 overexpression in mouse intestine leads to increased susceptibility to colitis.	Mouse	[7]
	TLR4 overexpression in mouse intestine shapes microbiota, which can transfer increased susceptibility to colitis to wild type mice.	Mouse	[8]
	TLR5 intestinal specific knockout leads mice to develop metabolic syndrome, increased susceptibility to colitis, and low-grade inflammation.	Mouse	[9]
	Microbial products activate ROS production in the intestine, which resulted in intestinal damage and early death.	Drosophila	[10]
	Hyperosmotic shock activates NF-κB in IECs and mediates inflammatory cytokine production.	Human IECs	[11]
	NF-κB is a mediator of intestinal ischemia/reperfusion injury induced cell death.	Rat	[12]
	Microbiota are important for IL-18 production in IECs, which then activates NF-κB and its gene program.	Mouse	[13]
	Mice deficient for NLRP6 develop colitogenic microbiota.	Mouse	[14]
	NLRP12 serves as a checkpoint for the non-canonical NF-κB pathway, and suppresses colonic	Mouse	[15]

	inflammation.		
IFN/IRF	p53 and p21 are ISGs which can be induced by IFN signaling, and promote apoptosis and senescence of IECs.	Mouse	[16]
	SNPs in IFN receptor genes are associated with IBD.	Human	[17]
	Describes signaling pathways leading to IRF3 activation.	Human proteins in cell-free assays, human embryonic kidney 293T cells, mouse embryonic fibroblasts, Human bone osteosarcoma (U-2 OS) cells.	[18]
	IRF3-mediated transcription of Tslp, an important gene for intestinal homeostasis.	Mouse	[19]
STATs	STAT6 functions independently of IL-4 as a regulator of chromatin compaction.	Mouse	[20]
	Constitutive activation of STAT6 in IECs effectively combats helminth infections.	Mouse	[21]
	Long-term activation of STAT3 during chronic inflammation promotes colon tumor formation.	Mouse	[22]
	STAT3 serves a protective role in IECs against injury and inflammation, promoting mucosal healing.	Mouse	[23]
	STAT3 activates gene networks that restrict microbial translocation through the intestinal epithelium.	Mouse	[24]
	Segmented filamentous bacteria (SFB) induce Th17 cell production of IL-22 which signals to IECs.	Mouse	[25]
	In the lung and gastric epithelia, STAT3 binds the promoter of RegIIIg and drives transcription of the gene.	Mouse	[26,27]
ISCs	Modelling asymmetric division of mouse ISCs.	Mouse, in silico	[28]
	Modelling symmetric ISC growth and lineage tracing.	Mice	[29]
	Optimizing the conditions for mouse, human epithelial organoids and examining their proliferative potential.	Human and mouse organoids	[30]
	Chromatin accessibility and histone marks in LRG5+ stem cells.	Mouse	[31]
Sox2	Sox2 expression is required for proper patterning along the anterior gut.		[32]
	Sox2 can direct anteriorization of the gut, suggests	Mouse	[33]

	that interplay with Cdx2 important for proper patterning in primitive gut.		
Cdx2	Cdx2 is required for establishing intestinal identity.	Mouse	[34]
	Cdx2 is required for proper binding of HNF4A and maintains permissive chromatin state.	Mouse	[35]
	Bile acids regulate Cdx2.	Rat	[36]
	Stimulation of the intestinal Cdx2 homeobox gene by butyrate in colon cancer cells.	Human adenocarcinoma cell line	[37]
	Characterizes Cdx2 expression in the posterior gut at E8.5.	Mouse	[38]
	Cdx2 is expressed in small intestine and colon of adult mice.	Mouse	[39]
	Cdx2 regulates chromatin remodeling through Brg1-SWI/SNF complex recruitment.	Mouse, human colon cancer (C2bbe1) cells and human embryonic kidney 293 cell lines	[40]
	Cdx2's role in body segmentation, patterning, and development of intestinal polyps.	Fly	[41]
	Intestine-specific KO of Cdx2 leads to a loss of intestinal identity.	Mouse	[42]
	Cdx2 expression in parietal cells of the gastric mucosa develop into intestinal metaplasia.	Mouse	[43]
	Cdx2 expression driven by Foxa3 in the gastric mucosa led to intestinal neoplasia.	Mouse	[44]
	Expression of Cdx2 at transitional basal cells leads to Barrett's esophagus-like phenotypes.	Mouse	[45]
	Transgenic overexpression of Cdx1b using Krt5p promoter induces intestinal metaplasia in the squamous epithelium of the zebrafish esophagus.	Zebrafish	[46]
	Repressive interaction between Cdx2 and Sox2 at stomach-intestine border.	Mouse	[47]
	Cdx2 has key, differentiation-specific occupancy of the genome, co-occupies some loci with GATA6 and HNF4A.	Mouse	[48]
	Cdx2 is vital for specification of intestinal cell types from gut stem cells during development.	Mouse, mouse organoids	[49]
	Cdx2, in combination with GATA4 and HNF4A, control IEC homeostasis.	Mouse	[50]
	Cdx2 homologs are important in early intestinal epithelial specification in vertebrates.	Zebrafish	[51]

Tcf-4	Tcf4 is required for establishment of ISC niche in crypt.	Mouse	[52]
Sentinal Goblet Cells	Sentinel goblet cells guard the colonic crypt by triggering Nlrp6-dependent Muc2 secretion.	Mouse	[53]
Secretory Cells	Atoh1/Math1 is required for terminal differentiation of secretory cell.	Mouse	[54]
	Intestinal Atoh1/Math1 is involved in IEC homeostasis.	Mouse	[55]
H3K27ac	Differentiating active vs poised enhancers and effects on developmental programs.	Mouse	[56]
	H3K27ac, a marker for active enhancers, is regulated by microbiota colonization.	Mouse	[57]
Mediator, Enhancers	Mediator and cohesin connect enhancers and core promoters via DNA looping contributing to maintenance of embryonic stem cell state.	Mouse embryonic stem cells	[58]
	Defines the enhancer and promoter landscape in IBD.	Human	[59]
	Sub-classification of human IBDs based on transcriptional profiles.	Human	[60]
Polycomb, CRRs	Describes the duality of CRRs as enhancers and repressors in general.	Drosophila	[61]
Polycomb	PRC2 target genes and bivalent domains in the adult somatic intestinal cells.	Mouse	[62]
	PRC2 contributes to stemness in disease states via Wnt signaling.	Mouse organoids	[63]
	PRC2 prevents hypomethylated developmental enhancers from becoming reactivated.	Mouse	[64]
TF Binding	ChIP-seq mapping of binding sites of TFs known to play roles in ES cell development.	Mouse ES cells	[65]
angptl4, CRRs	Identifies cis-regulatory region for angptl4 expression, under microbial control.	Zebrafish	[66]
Chromatin accessibility	Microbially associated transcriptional changes are not accompanied by changes in established chromatin landscape along the intestine.	Mouse	[67, 57]
	Gut microbiome changes gene expression of colonocytes in vitro and for some genes, also the accessible chromatin surrounding TSS.	Human colonocyte cell line	[68]
	Role of chromatin accessibility during secretory to ISC dedifferentiation.	Mouse	[69]
Transcripts/Epigenetics/Metabolome	Diurnal oscillations of gut microbiota impact gene expression, histone modifications, and serum metabolites.	Mouse	[70]
Regionality	Regional gene expression in adult zebrafish gut.	Zebrafish	[71]

	Conserved regional signature genes and cis-regulatory regions.	Zebrafish, Mouse	[72]
scRNA-seq	scRNA-seq of IECs.	Mouse	[73]
	scRNA-seq of enterocytes along crypt-villus axis.	Mouse	[74]
Gastric identity	Loss of stomach accompanied by loss of pepsinogen and proton pump genes.	Fish	[75]
	Barx1, a stomach marker, is still expressed in the stomach-less zebrafish.	Zebrafish	[76]
Intestinal development / Morphogen gradients	Zebrafish intestinal development.	Zebrafish	[77]
	Intestinal stem cell crypt develops via morphogenic field.	Chicken, Mouse	[78]
SCFAs	SCFA along the length of the intestine	Pig, Human	[79]
	Microbially produced SCFA important to regulate inflammation in the intestine.	Mouse	[80]
	HDACs and SCFAs are drivers of histone crotonylation.	Mouse	[81]
	Supplementation of SCFAs in germ-free mice can recapitulate histone modification patterns associated with microbial colonization in the proximal colon and liver.	Mouse	[82]
SCFAs, HDACs	Microbiota inhibits histone de-acetylation via SCFAs.	Human colorectal adenocarcinoma cell line (HT-29)	[83]
	Butyrate inhibition of HDACs can change depending on metabolic state (e.g., Warburg effect).	Mouse	[84]
	n-butyrate controls HDAC activity in intestinal macrophages.	Mouse	[85]
HDACs	HDAC1 and HDAC2 restrain the intestinal inflammatory response by regulating intestinal epithelial cell differentiation.	Mouse	[86,87]
	HDAC3 is required for Paneth cells in the presence of microbiota.	Mouse	[88]
DNA methylation	DNA methylation is a determinant of stem cell maintenance and differentiation in small intestine.	Mouse	[89]
	Differences in DNA methylation and H3K27me3 in embryonic and adult ISCs.	Mouse	[90]
	Suggests that the microbiota is capable of regulating the postnatal, DNA methylation	Mouse	[91]

	landscape of ISCs.		
	Describes the effects of microbiota on DNA methylation of IECs.	Mouse	[92]
	DNA methylation is crucial for intestinal homeostasis.	Zebrafish	[93]
	DNA methylation regulates intestinal development and establishment of crypts.	Mouse, mouse organoids	[94]
	Differential DNA methylation associated with IBD.	Human	[95]
	Dnmt1 and Suv29h1 are required for intestinal terminal differentiation.	Zebrafish	[96]
	Differential DNA methylation in intestinal fibroblasts from Crohn's disease patients' occurred mostly within introns & intergenic regions, with a few genes showing inversely correlated methylation and transcription.	Human fibroblasts	[97]
	DNA methylation differences in ISCs vs differentiated IECs.	Mouse	[98]
	DNA methylation patterns differ across anteroposterior regions of the intestine.	Human patients and organoids	[99,100]
	DNA methylation examined directly in IECs by genome-wide bisulfite-sequencing, revealed roles for DNA methylation in different aspects of IEC identity.	Human, mouse	[58,59]
Anti-TNF therapy	Infliximab infusions help manage disrupted barrier function in Crohn's disease patients.	Humans	[101]
Microbiota and cytokines	Microbiota composition and function impact cytokine expression.	Humans	[102]
ELF3	Identification of Elf3 as a TF expressed in developing and mature intestinal tract.	Mouse	[103,104]
	Elf3 is essential for life, intestinal differentiation.	Mouse	[105]
	Elf3 is the upstream regulator of TGF-betaRII receptor.	Mouse	[106]
GATA Factors	GATA4 most highly expressed in the duodenum and jejunum, regulates marker of intestinal differentiation, LPH.	Mouse	[107]
	Gut development demonstrates specific spatio-temporal patterns of TF expression.	Mouse	[108]
	Gata4 is essential for the maintenance of jejunal-ileal identities in the adult mouse small intestine.	Mouse	[109]
	GATA4 is essential for jejunal function in mice.	Mouse	[110]
	GATA4 is sufficient to establish jejunal versus ileal identity in the small intestine.	Mouse	[111]

	GATA6 is required for differentiation of colonic epithelium.	Mouse	[112]
	GATA6 is required for normal morphology and enterocyte gene expression in the ileum but may function redundantly with GATA4 in the jejunum.	Mouse	[113]
HNF4 (NR2A1, NR2A2, NR2A3)	HNF4 TFs help shape chromatin landscape.	Mouse	[114]
	Mapping TSS and organ expression of HNF4 gene suggests complex transcriptional regulation.	Mouse	[115]
	Two alternative promoters for HNF4A produce products with different trans-activation properties.	Human embryonic kidney 293T cells	[116]
	HNF4A protects against DSS induced colitis.	Mouse	[117]
	In the liver, knockdown of HNF4A expression induces a proinflammatory feedback circuit that continues to repress HNF4A expression and upregulate proinflammatory genes.	Mouse	[118]
	HNF4A activity impacts Wnt signaling and cell lineage commitment in the intestine.	Human hepatocyte cell line	[119]
	Structure, mapping, expression and transcriptional activity of mouse HNF4G gene.	Mouse	[120]
	HNF4A knockouts fail to complete gastrulation and die early during embryogenesis.	Mouse	[121]
	HNF4 is required for gastrulation via expression in the visceral endoderm.	Mouse	[122]
	HNF4A regulates liver development and morphogenesis.	Mouse	[123]
	HNF4A required for hepatocyte differentiation.	Mouse	[124]
	HNF4A required for colonic crypt formation.	Mouse	[125]
	HNF4A protects against DSS-induced colitis.	Mouse	[126]
	HNF4A may interact with DNA repair machinery.	Human colorectal cancer cells	[127]
	HNF4A regulates Cldn15 expression and thereby mediates ion transport.	Mouse	[128]
	SNPs at HNF4A locus associated with UC and CD.	Human	[17,129,130]
	Differentially active enhancers in IBD are enriched for HNF4A binding sites.	Human	[131,132]
	HNF4A protects against ROS and promotes gut neoplasia.	Mouse	[133]
	HNF4A triggers morphological changes in the intestinal epithelium.	Mouse, human pancreatic	[134]

		adenocarcinoma cell line (MIA PaCa-2), and mouse embryonic fibroblast cell line (NIH-3T3)	
	Human gut microbiota can modify linoleic acid into conjugated linoleic acids.	Bacteria from human colon	[135]
	SNPs at HNF4G locus associated with UC.	Human	[136]
	Hnf4g knockout mice have lowered energy expenditure and physical activity during nighttime, and increased weight.	Mouse	[137]
	HNF4A and HNF4G can heterodimerize.	HepG2 cells	[138]
	HNF4G has an intestinal expression border at the pyloric boundary.	Mouse	[139]
	HNF4A has 12 different isoforms with differing N- and C-termini, 11 of which are expressed in the small intestine.	Human	[140]
	HNF4G is upregulated in intestinal-metaplasia of the stomach.	Human	[141]
	HNF4G drives enterocyte differentiation.	Mouse organoids	[142]
	Hnf4g is required for proper balance of cell lineages in the intestinal epithelium, with mutants displaying increased numbers of GLP-1 expressing enteroendocrine cells.	Mouse	[143]
	Feed-forward loop between HNF4 and SMAD factors contribute to maintenance and stability of enterocyte identity.	Mouse	[144]
	HNF4 family members bind to long chain fatty acids such as palmitic acid, palmitoyl-CoA, and linoleic acid	Rat, Human, Mouse, Drosophila	[145-149]
	HNF4A is important for small intestinal absorption of dietary lipids.	Mouse	[150]
RXR (NR2B1, NR2B2, NR2B3)	Identified vitamin A metabolite, 9-cis retinoic acid as the ligand for RXR	Human	[151]
	The RXR family of nuclear receptors arose shortly after HNF4-like nuclear receptors evolved.	N/A	[152]
PPAR (NR1C1, NR1C2, NR1C3)	PPARB/D is highly expressed in enterocytes and regulates expression of fatty acid binding protein in enterocyte cultures.	Mouse	[153]
	Induction of PPARG activity by chemical ligands,	Mouse	[154,155]

	rosiglitazone and troglitazone, suppresses colonic inflammation associated with DSS administration in mice.		
	PPARs heterodimerize with RXR and induce the expression of target genes by binding peroxisome proliferator responsive elements (PPREs) throughout the genome.	Human	156
	The SCFA butyrate and PPARG agonists stimulate PPARG dependent expression of Angptl4.	Human colon adenocarcinoma cell line	157,158
	Butyrate-PPARG signaling is important in limiting the availability of luminal nitrate.	Mouse	159
	PPARG regulates beta-defensin in the colonic epithelium, and Pparg deficiency resulted in impaired microbicidal capacity of the colonic mucosa.	Mouse	160
	Genetic variants at human PPARG are associated with increased risk for both UC and CD.	Human	161-163
	UC is associated with decreased PPARG expression.	Human	164,165
	Microbial-TLR4 signaling induces PPARG expression in IECs.	Human Caco2 cell line, primary mouse colonocytes	164
	Mice lacking TLR4, specifically in the intestinal epithelium showed a significant downregulation of PPARG target genes	Mouse	166
	PPARG suppresses TLR signaling by exporting a NF-κB subunit, RELA, out of the nucleus and inhibiting transcription of proinflammatory genes	Human Caco2 cell line	167
	PPARA is expressed in the intestine.	Mouse	168
	Ppara transcript is reduced by microbiota colonization.	Mouse	169
	Ppara regulates IL-22 production by innate immune cells in response to intestinal microbiota, suppressing pro-inflammatory signaling and promoting expression of antimicrobial peptides and IL10.	Mouse	170
	Pparg activity is dysregulated in the small intestine of mice fed a high-fat diet, and treatment with the PPARG agonist rosiglitazone improved many of the changes in gene expression associated with high-fat diet feeding.	Mouse	171
FXR (NR1H4)	Bile acids serve as an activating ligand for the nuclear receptor FXR.	Mouse, human	172

	Intestinal microbiota modify primary bile acids through bile salt hydrolases (BSH) and other enzymes.	Human iPSC, Mouse	173,174
	Microbial modification of bile acids regulates systemic metabolic processes like fat storage.	Mouse	174-178
	Treatment with caffeic acid phenethyl ester (CAPE), an inhibitor of bacterial BSH, selectively suppressed intestinal FXR signaling by increasing levels of the bile acid, tauro-B-muricholic acid, ultimately leading to decreased gluconeogenesis in the liver.	Mouse	179
	Increasing BSH-retaining species in the microbiota (i.e., Lactobacilli and Bifidobacteria) impacted bile acid metabolism in the intestine and liver.	Mouse	177
	FXR knockouts demonstrating intestinal FXR is required for HFD induced obesity	Mouse	178,180
	Treatment with an FXR antagonist demonstrating intestinal FXR is required for HFD induced obesity.	Mouse	180
	FXR modulates proinflammatory responses by forming a repressor complex with NCOR on the NF-κB response element on the IL-1B promoter.	Mouse	181
	Loss of FXR function in mice increases their susceptibility to DSS and TNBS induced colitis.	Mouse	182
LXR (NR1H3, NR1H2)	LXR ligands are sterols such as cholesterol and oxysterols.	Human	183
	PPARA is a target of LXR, and they work together in the small intestine to regulate cholesterol homeostasis.	Mouse	184
	Suppresses inflammation in macrophages by inhibiting NF-κB; microbial ligands repress expression of LXR target genes in immune cells.	Mouse macrophage (RAW 264.7) cell line, mouse peritoneal macrophages	185,186
	LXR deficient mice were more susceptible to DSS-induced colitis.	Mouse	187
	LXR homologs were significantly reduced in the inflamed regions of biopsies from CD and UC patients.	Human	187
Glucocorticoid receptor (GR, NR3C1)	Glucocorticoids suppress NF-κB and AP-1 activity and increased GR expression is associated with decreased NF-κB activity.	Rat, human PBMC	188,189
	Glucocorticoids reduce microbially induced TNF inflammation.	Mouse	190
	Genetic variants at human GR, NR3C1 are associated with risk for CD.	Human	191

	Some genetic variants at NR3C1 are associated with hormone resistant therapies in UC and CD.	Human	192,193
Mineralocorticoid receptor (MR, NR3C2)	MR is expressed in the duodenum and colon.	Mouse	194
	MR in the colon is important for sodium balance and blood pressure.	Mouse	195
Vitamin D Receptor (VDR, NR1I1)	VDR knockout mice spontaneously develop colitis.	Mouse	196
	VDR knockout mice have modified microbial communities, greater susceptibility to DSS-induced colitis, and defective barrier and Paneth cell function.	Mouse	197-199
	VDR overexpression improves several genetic models of colitis in mice.	Mouse	200,201
	Low levels of vitamin D are associated with IBD.	Human	202
Constitutive androstane receptor (CAR, NR1I3)	Differences in CAR expression between GF and CV mice.	Mouse	203,204
	CAR mutant mice were more susceptible to DSS-induced colitis.	Mouse	205
	CAR knockout mice spontaneously develop insulin sensitivity, CAR agonist prevented obesity.	Mouse	206
	Mutations in CAR alter intestinal microbiota community and function through bile acid metabolism.	Mouse	207
	CAR was decreased in biopsies from CD and UC patients.	Human	205
Pregnane X Receptor (PXR, NR1I2)	PXR alters intestinal microbiota community and function through bile acid metabolism	Mouse	207
	Indole metabolites induced expression of PXR target genes in jejunal enterocytes.	Mouse	208
	PXR mutants have impaired small intestinal barrier function.	Mouse	208
	PXR agonist attenuated barrier defects observed in DSS-treated animals.	Mouse	209,210
	Decreased PXR expression observed in biopsies from actively inflamed CD tissue.	Human	211
	Other environmental chemicals such as drugs and spices impact PXR activity.	Mouse, human colon cell line	212-214

		(LS180), human primary hepatocytes, human hepatic stem cell line (HepaRG)	
HIF	Consumption of SCFA by the colonic epithelia decreases oxygen concentrations colonocytes, activating HIF.	Mouse	[215]
	HIF activity results in transcriptional activation of Defensin beta, an antimicrobial peptide, MUC3 and ITF, thereby maintaining epithelial barrier function	Mouse	[216-218]
	HIF induces transcription of the antimicrobial peptide LL77 and protects against *Candida albicans* infection	Mouse	[219]
Notch	Microbial repression of RBPJ, an effector transcription factor of Notch signaling is dependent on MyD88.	Zebrafish	[220]
	Mice lacking RBPJ in their IECs develop a microbiota-dependent and Th17 cell-mediated chronic colitis.	Mouse	[221]
	Hes1 deficiency in IECs causes an intestinal inflammatory phenotype and dysbiosis.	Mouse	[222]
	Microbiota colonization results in transient repression of transcripts involved in Notch signaling and a rapid expansion of goblet cells.	Mouse	[223,224]
	Microbiota colonization results in reduced EEC populations	Mouse	[225]
	Microbiota colonization induces an expansion of mature goblet cell populations.	Rat	[226]
	Microbiota colonization promotes goblet cell differentiation.	Zebrafish	[227]
	NFAT5 suppresses the metabolic regulator mTORC1 and suppresses Notch signaling, which results in an expansion of goblet cells and MUC2 expression.	Human embryonic kidney 293 cells	[228,229]
WNT	Both GF and antibiotic treated mice have slowed IEC proliferation rates compared to SPF mice, though this was not associated with transcriptional alterations in Wnt pathway target genes that promote proliferation, but rather phosphorylation of ERK and STAT3 activation.	Mouse	[230]
	GF zebrafish have reduced IEC cytoplasmic beta catenin compared to CV or monoassociated fish,	Zebrafish	[231]

	correlating with increased proliferation of IECs in CV or monoassociated fish.		
	Describes how Wnt in the intestine can drive both stem and Paneth cell gene programs.	Mouse, human	232
BMP	Genetic profiling of mesenchymal and epithelial compartments of the perinatal mouse intestine.	Mouse	233
	Mutations in BMP signaling pathway members in familial juvenile polyposis.	Humans	234,235
	Mutations in BMP signaling pathway is implicated in colorectal cancer.	Humans	236
	Bmpr1a impacts the proliferation and differentiation of secretory lineage cells.	Mouse	237
	BMP levels regulate enteroendocrine cell EEC hormone expression .	Mouse	238
	SMAD4/HNF4A feedforward loop promotes enterocyte fate.	Mouse	144
	TGF-B1 signaling inhibits of NF-κB activity and IL-6 expression in response to the commensal *B. vulgatis.*	Rat	239
	TGF-B1/SMAD signaling protects against the colitogenic properties of *Enterococcus faecalis.*	Mouse	240
AHR	Dioxins lead to AHR activation.	Mammals	241
	Microbial tryptophan metabolites can activate AHR.	Human and Mouse	242-247
	ARNT can form heterodimers with HIF.	Mouse	248
	HIFs roles in intestinal sensitivity to microbes.	Mouse	249
	HIFs roles in synthesis of antimicrobial peptides.	T84 intestinal epithelial cells, Human, Mouse	216-218
	Role of AHR in innate immunity and intestinal barrier integrity.	Review	250
	AHR protects against DSS-induced colitis.	Mouse	251,252
	AHR regulates proliferation and stem cell maintenance and is expressed in Paneth cells.	Mouse	253,254
	AHR loss in colonic stem cells leads to malignancies.	Mouse	255
	Tryptophan metabolites activate IL-10 expression in the colon.	Mouse	256
	AHR is a therapeutic target for IBD.	Human	257-259
NFIL3	Nfil3 is a transcription factor involved in the response of the intestinal epithelium to circadian rhythms and the microbiota.	Mouse	260

ASCL2	Important marker of ISCs; target of Wnt signaling in the intestinal crypt; deletion leads to loss of stem cells; overexpression leads to crypt hyperplasia; part of a direct autoactivation loop that translates the level of Wnt signaling into a “ON/OFF” output and determines stem cell state.	Mouse, mouse organoid	261,262
Reviews			
Stomach loss in fishes			263
ISCs	ISCs and their niche		264
	Regulation of stem cells in intestinal homeostasis and cancer		265
	ISC renewal		266
	Stem cells and intestinal injury		267
Paneth cells			268
Tuft cells			269
Mucins			270
Metagenomics			271
Epigenetics			272
Pioneer transcription factors			273
ETS factors			274
Transcriptional enhancers			275
Transcriptional regulation			276
Histone modifications and modifying enzymes			277-279
Histone acylation			280
Histone tail acetyl- and acylations			281
DNA methylation			282
DNA methylation, miRs in IBD			283

TNF and IBD			284
Anti-TNF therapy in IBD			285,286
Microbial metabolites (SCFAs, etc.)			287
Dietary regulation of host defense peptides			288
Xenobiotics and IECs			289
Inflammasome and pro-inflammatory cytokines			290
Cell death and anoikis			291
NF-κB family			292
TLRs			293
MyD88			294
ROS production			295
NLRs			296
NLRs in IBD			297
IFN			298
IRFs			299
JAK/STAT			300
PPAR family			301,302
FXR and bile acids			303
RXR			304
VDR			305
AHR			306

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