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Original Article

Histomorphology of intestinal inflammation in inflammatory bowel diseases (IBD) mouse models and its relevance for IBD in men

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Abstract: The intestine is a central part of the immune system and nearly all immune-related disease models in mice show intestinal phenotypes and are hence suitable to investigate aspects of human inflammatory bowel diseases (IBD). The histopathological features of 95 reported IBD mouse models are reviewed and their relation to histomorphological features of intestinal tissues derived from patients with ulcerative colitis (UC) or Crohn's disease (CD) are discussed. Predominant small-intestinal histopathology resembling CD was reported only for 17% of the mouse models. An involvement of the small intestine occurred in 35% of all models. Pathologic changes restricted to the colon were reported in 65% of the mouse models; overall, the colon was involved in 83% of all models. Histomorphological hallmarks of intestinal inflammation illustrated from hematoxylin/eosin-stained sections of tissue samples from various IBD mouse models and from patients suffering from IBD highlighted similarities and differences between mouse and men. Also addressing differences in mouse and human immunology and anatomy, an initial histomorphological screening could not only test validity of a model and the experimental performance but clearly helps to choose the most relevant mouse model to approach a specific component of human IBD.

Keywords: Inflammatory bowel disease, ulcerative colitis, Crohn's disease, mouse models, histopathology

Introduction

Europeans have the highest risk to develop inflammatory bowel diseases (IBD), a chronic recurring inflammation of the gut with ulcerative colitis (UC) and Crohn's disease (CD) as the two most common forms [1]. IBD diagnosis relies on the medical history, endoscopic examination including tissue biopsies, and the exclusion of infections. Intestinal segments, not readily accessible via endoscopy, require additional imaging including magnetic resonance imaging, computer tomography as well as ultrasound. Highlighting the importance of histomorphology, the final diagnosis of CD or UC is often established by the characteristic findings in intestinal tissue biopsies [2-4].

The pathogenesis of IBD is still incompletely understood, though it is widely accepted that three not mutually exclusive factors are involved: the genetic susceptibility [5-7], the immune system [8-10], and the environment including the intestinal microbiota [11-13]. Aiding our understanding of the pathogenesis but also enabling the study of therapeutic interventions in IBD, numerous animal models of IBD were developed during the past six decades. Most IBD models are rodent models with mice constituting the major part [14] and comprise genetically engineered, chemically induced, antigen-specific, adoptive cell transfer and spontaneous (congenic) models [15]. Over the years, IBD models have been reviewed abundantly in general [16-18], mostly addressing molecular and cellular mechanisms [19], the role of the models in translational medicine [20], or the host's response to the microbiota [21]. Taken together, IBD seems to occur in

genetically predisposed individuals due to an exuberant immune response to commensal microbiota possibly triggered by urbanization.

Focussing on the histomorphological characteristics of mouse models of IBD fills a gap as histopathology is a relevant tool in diagnosing human disease. Additionally, histopathology provides especially robust information about processes taking place in the gut, and may confirm other experimental data sets. Furthermore, knowledge of the histopathological characteristics of a mouse model that closely resemble central aspects of human IBD facilitates choosing the most appropriate IBD model for each experimental approach.

Thus and despite the large numbers of IBD models, the majority of individual models inevitably only reflects parts of the complex and multifactorial human disease [14]. Our systematic study on the histopathology of intestinal inflammation in mouse models of IBD that especially addresses histomorphological similarities and differences to human CD or UC aims to assist identifying the most relevant model for an experimental approach and its potential to translate into the clinic.

Materials and methods

Animals

C57BL/6 wild-type mice were obtained from the Bundesinstitut für Risikobewertung (Berlin, Germany). B6.129S7-Rag1$^{tm1Mom/J}$ (Rag1 ko) mice were obtained from The Jackson Laboratory (Maine, USA). Mice deficient for interleukin (IL)-10 on the 129/SvJ background (IL10 ko) were generously provided by R. Balfour Sartor (Chapel Hill, USA); mice deficient for IL-2 on the B6.129P2 background (IL2 ko) by Ivan Horak (Berlin, Germany). Mice were bred, housed and treated under specific pathogenic free conditions at the Forschungseinrichtungen für Experimentelle Medizin of the Charité-Universitätsmedizin Berlin. The authorities approved the protocols for the animal experiments.

Patient samples

Archived formalin-fixed and in paraffin-embedded (FFPE) samples of intestinal tissues from patients diagnosed with UC or CD were obtained from the Central Biomaterialbank Charité (ZeBanC, Charité-Universitätsmedizin Berlin, Germany). Samples were used blinded with respect to patient's data but assigned to diagnosis. The study was performed under the approval of the local ethics committee (registration number EA1/316/13).

Colitis induction

Colitis was induced as previously described. For acute dextran sulphate sodium (DSS)-induced colitis, wild-type mice received 3% DSS (36,000-50,000 Da; ICN, Berlin, Germany) via the drinking water *ad libitum* [22]. Intraperitoneal transfer of $4x10^5$ $CD4^+CD45RB^{high}$ T cells into syngeneic Rag1 ko mice induced intestinal inflammation within 4-8 weeks [23]. Colitis in IL10 ko mice was assessed starting at 4 months of age and in IL2ko mice starting at 4 weeks of age. Wild-type mice were orally infected with 100 cysts [24] or 10 cysts [25] of *Toxoplasma gondii* (*T. gondii*) strain ME49. Samples of the terminal ileum were obtained 5-7 days after infection. Wild-type mice were orally infected with *Heligmosomoides polygyrus* (*H. polygyrus*). Formalin-fixed samples of the duodenum were obtained 6-7 days after infection and generously provided by Susanne Hartmann (Berlin, Germany) [26]. Samples of mouse intestine were fixed at room temperature in 4% formalin for at least 24 hours before embedding in paraffin.

Histopathology

Sections (1-2 µm) from FFPE samples were cut, dewaxed and histochemically stained with hematoxylin and eosin (H&E) or subjected to periodic acid-Schiff reaction (PAS). Immunohistochemical staining of CD31-positive endothelial cells was performed after heat-induced epitope retrieval using anti-CD31 (clone SZ 31; Dianova, Hamburg, Germany). For detection, the LSAB method was used employing the Dako REAL™ Detection System (Dako, Glostrup, Denmark). Nuclei were counterstained using hematoxylin and negative controls were performed by omitting the primary antibody. Stained sections were coverslipped in corbit balsam and evaluated in brightfield microscopy using an AxioImager Z1 microscope (Carl Zeiss MicroImaging, Jena, Germany).

Table 1. Histomorphological characteristics of human UC and CD

Ulcerative colitis	Crohn's disease
Diffuse (sub) mucosal infiltration of inflammatory cells, basal plasmacytosis, cryptitis, crypt abscesses	Discontinuous and transmural infiltration of inflammatory cells, crypt abscesses
Denuded mucosa, erosions, ulcerations	Aphthous/fissuring ulcers, fistulas
Mucin depletion/goblet cell loss	Preserved or increased mucin secretion/increase in goblet cells
Distorted crypts, crypt loss	
Irregular or villiform surface	Villous blunting
Thickening of muscularis mucosae	Edematous, fibrotic submucosa
	Inflamed vessels and lymphatics, neuronal hyperplasia
	Lymphoid aggregates, granulomas (non-caseating)

Table 2. Specific intestinal histopathological features and extraintestinal manifestations of established mouse models for IBD. Referenced models were grouped according to the "first hit" initiating the inflammation and its first reported local appearance downstream from the stomach [14, 83]. The main organ inflamed is listed in the first column; tissue areas also involved are mentioned in brackets

Organ	Model	Histopathological features and extraintestinal manifestation	Refs
A "First hit" from the outside			
A.1 Induced by erosive chemicals			
Colon	Acetic acid	Infiltration: mucosal/submucosal; leukocytes Hyperplasia Erosion/ulceration Crypt abscesses Goblet cell loss Edema Necrosis Granulation tissue	[84, 85]
Colon	Butyric acid	Infiltration: leukocytes Crypt abscess Goblet cell loss Edema Erythema	[86]
Colon	Carageenan	Infiltration: mucosal; leukocytes Hyperplasia, crypt distortion Ulceration	[87]
Colon	Oxazolone	Infiltration: mucosal; leukocytes (mainly lymphocytes, few granulocytes) Ulceration Edema	[88]

Colon	TNBS (acute)	Infiltration: mucosal/submucosal/transmural; lymphocytes, macrophages and granulocytes Crypt distortion Ulceration Crypt abscesses/crypt loss Goblet cell loss Edema Necrosis/fibrosis Lymphoid aggregates Exsudate Expansion of stroma	[84, 89-91]
Colon	TNBS (chronic)	Infiltration: mucosal/submucosal/transmural; leukocytes Ulceration Edema Necrosis	[92]
Colon (distinct on left side)	DSS (acute)	Infiltration: mucosal/submucosal; leukocytes (predominantly neutrophils) Hyperplasia Erosion/ulceration Crypt abscesses/crypt loss Goblet cell loss Edema Fibrosis Exsudate	[93, 94]
Colon (distinct on left side)	DSS (chronic)	Infiltration: mucosal/submucosal; lymphocytes, plasma cells and macrophages Dysplasia Erosion/ulceration Crypt loss Goblet cell loss Lymphoid aggregates Wall thickening	[95, 96]
A.2 Mediated by luminal antigen			
Small intestine	*Heligmosomoides polygyrus bakeri*-infection	Infiltration: mucosal/submucosal/transmural; leukocytes Hyperplasia Ulceration Crypt abscesses Goblet cell hyperplasia Villous blunting/villous atrophy Wall thickening	[97]
Small intestine	*Strongyloides ratti*-infection	Infiltration: mucosal; leukocytes Hyperplasia Villous blunting	[98]
Ileum	*Toxoplasma gondii*-infection	(100 cysts of ME49 strain peroral) Inflammation: discontinuous, around tachyzoites Severe necrosis Villous destruction *Extraintestinal* liver, lung	[99]

Ileum	*Toxoplasma gondii*-infection	(10 cysts of ME49 strain peroral) Infiltration: mucosal/submucosal/transmural; leukocytes Erosion/ulceration Necrosis/fibrosis Villous distortion *Extraintestinal* liver	[100]
Small intestine (0.1% cecum and proximal colon), colon	Hsp60-specific	*Small intestine* Infiltrate: lymphocytes Hyperplasia Erosion Hemorrhages Villous shortening *Colon* Infiltration: mucosal/submucosal; leukocytes Erosion/ulceration Crypt abscesses/crypt loss Goblet cell hypertrophy Edema *Extraintestinal* liver	[101, 102]
Cecum, colon	*Eimeria falciformis*-infection	Infiltration: mucosal/submucosal/transmural; leukocytes Hyperplasia Ulceration Crypt abscesses/crypt loss Goblet cell loss	[103]
Cecum, colon	OVA	Infiltration: discontinuous; lymphocytes, macrophages or predominantly polymorphonuclear cells Hyperplasia Cryptitis/crypt abscesses Goblet cell loss Small granulomas	[104, 105]
Cecum, colon	Typhlocolitis	Infiltration: mucosal/submucosal/transmural; lymphocytes, plasma cells, macrophages, neutrophils Hyperplasia Erosion/ulceration Lymphoid aggregates Perivasculitis *Extraintestinal* liver	[106]
Colon	OVA	Infiltration: mucosal/submucosal/transmural; leukocytes Hyperplasia Ulceration Crypt abscesses/crypt loss Goblet cell loss	[107]

B "First hit" from inside			
B.1 Mediated by disturbed immune cell homeostasis			
Intestine	Cb1-b ko	Infiltration: activated T/B cells *Extraintestinal* salivary glands, liver, pancreas, lung, kidney, heart, skeletal muscle, bladder, connective tissue	[108]
Small intestine	Atg7/Xbp1$^{\Delta IEC}$	Infiltration: mucosal/submucosal/transmural, discontinuous; leukocytes Fissuring ulceration/fistulous tracts	[109]
Small intestine	BACH2 ko	Infiltration: mucosal; lymphocytes, macrophages Hyperplasia	[110]
Small intestine	N-Cadherin DN	Infiltration: focal mucosal/submucosal/transmural; lymphocytes, macrophages, plasma cells Ulceration Cryptitis/crypt abscesses Goblet cell loss Lymphoid aggregates Villous shortening Hyperplasia of Paneth cells, increase in intraepithelial lymphocytes	[111]
Small intestine	Roquin ko	Infiltration: leukocytes Hyperplasia Ulceration Crypt abscesses Villous shortening Increase in intraepithelial lymphocytes *Extraintestinal* liver, spleen	[112]
Small intestine, cecum, colon	Common γ chain ko	*Small intestine* Decreased lamina propria lymphocytes; missing intraepithelial lymphocytes; absent gut associated lymphoid tissue (GALT) *Cecum* Infiltration: mucosal; leukocytes Hyperplasia Absent GALT *Colon* Infiltration: mucosal; lymphocytes, macrophages Hyperplasia Goblet cell loss Crypt abscesses/crypt distortion Absent GALT	[113, 114] [113, 115]

Small intestine, colon	CD4CD45RB^{hi} into RAG1 ko mice	*Small intestine* Infiltration: mucosal/submucosal; leukocytes Hyperplasia Crypt abscesses Villous atrophy Goblet cell loss/Paneth cell loss Wall thickening *Colon* Infiltration: mucosal/submucosal/transmural; leukocytes Hyperplasia Erosion Crypt abscesses Goblet cell loss *Extraintestinal* liver	[116]
Small intestine, colon	CD4/PDK1 ko	Infiltration: mucosal/submucosal/transmural; leukocytes Hyperplasia, crypt distortion Erosion/ulceration Crypt abscesses	[117]
Small intestine, colon	LIGHT tg	*Small intestine* Infiltration: mucosal/submucosal/transmural; lymphocytes Hyperplasia, crypt distortion Ulceration/fissures Goblet cell loss Villous atrophy Intramuscular lymphocyte aggregates/granuloma *Colon* Infiltration: lymphocytes (mostly T cells), plasma cells, neutrophils Erosion/ulceration/fissures Crypt abscesses Intramuscular lymphocyte aggregates/granuloma Wall thickening *Extraintestinal* spleen, lymph nodes, liver, reproductive organs	[118-120]
Small intestine, colon	Pofut1$^{\Delta IEC}$	Infiltration: mucosal/submucosal/transmural; predominantly T cells and macrophages Hyperplasia Crypt abscesses/crypt loss Cystic dilatation of crypts Goblet cell hypertrophy and hyperplasia Edema Lymphoid aggregates Dysplasia	[121]

Small intestine, colon	TAK1 ko	Infiltration: leukocytes Erosion	[122]
Duodenum, cecum, colon	Gαi2 ko	*Duodenum* Infiltration: leukocytes Villous atrophy *Cecum, colon* Infiltration: mucosal/submucosal; predominantly lymphocytes and plasma cells (some neutrophils) Ulceration Crypt abscesses Goblet cell loss Adenocarcinoma	[123]
Duodenum, colon	CD4CD45RB^{hi} into TCR ko mice	*Duodenum* Infiltration: lymphocytes, neutrophils Hyperplasia Goblet cell hyperplasia Paneth cell hyperplasia Villous blunting/villous atrophy Wall thickening *Colon* Infiltration: mucosal/submucosal/transmural; lymphocytes, neutrophils Hyperplasia, crypt distortion Crypt abscesses Goblet cell loss	[116]
Jejunum, ileum, colon	IL10$^{-/-}$CD4^{+} into RAG1 ko mice	Infiltration: mucosal/submucosal/transmural; leukocytes Hyperplasia, Erosion Crypt abscesses Goblet cell loss *Extraintestinal* liver	[116]
Ileum	Casp8$^{\Delta IEC}$	Infiltration: mucosal/submucosal; lymphocytes, granulocytes Hyperplasia Erosion Crypt loss Villous blunting/atrophy	[124]
Ileum, cecum, colon, rectum	TCRα ko	*Ileum* Infiltration: mucosal; leukocytes Hyperplasia, crypt distortion Goblet cell loss Crypt abscesses *Cecum, colon, rectum* Infiltration: mucosal/submucosal; lymphocytes, plasma cells, neutrophils Hyperplasia, crypt distortion Crypt abscesses Goblet cell loss	[125, 126]

Ileum, colon	GPX1/2 DN	Infiltration: mucosal/submucosal/rarely transmural; leukocytes Hyperplasia Ulceration Crypt abscesses Goblet cell loss	[127, 128]
Ileum, colon	CD40L/B tg	Infiltration: mucosal/submucosal/transmural; lymphocytes Hyperplasia Goblet cell loss Villous atrophy *Extraintestinal* spleen, kidneys; development of systemic lupus erythematodes	[129]
Cecum, colon	B7.2 tg	Infiltration: mucosal/submucosal; lymphocytes, myeloid cells Lymphoid aggregates *Extraintestinal* spleen, mesenteric lymph nodes	[130]
Cecum, colon	FAS villin-Cre	Infiltration: mucosal; mononuclear cells Hyperplasia Crypt loss Edema	[131]
Cecum, colon	Integrin αV ko	Infiltration: lymphocytes, plasma cells, macrophages Hyperplasia Ulceration Crypt abscesses Adenocarcinoma *Extraintestinal* peritoneum, liver, nasal cavity, respiratory tract	[132]
Cecum, colon	Keratin8 ko	Infiltration: mucosal/submucosal; leukocytes Hyperplasia *Extraintestinal* liver	[133]
Cecum, colon (ascending)	C3H/HeJBir	Infiltration: mucosal/submucosal (multifocal to diffuse); leukocytes Hyperplasia Ulceration Crypt abscesses Fibrosis	[134]
Cecum, colon (proximal)	TLR5 ko	Infiltration: mucosal/submucosal/sometimes transmural; lymphocytes Hyperplasia Erosion Crypt loss Edema Extraintestinal spleen, lymph nodes	[135]
Cecum, colon, rectum	Ahr ko with haplodeficiency for RORγt	Infiltration: mucosal/submucosal; lymphocytes, plasma cells Hyperplasia, crypt distortion Cryptitis/crypt abscesses/crypt loss Goblet cell loss Lymphoid aggregates Fibrosis	[136]

Colon	A20 ko	Infiltration: mucosal/submucosal; leukocytes Crypt branching Crypt abscesses *Extraintestinal* liver, kidneys, joints, bone marrow, spleen, skin	[137]
Colon	Anti-CD40	Infiltration: mucosal; leukocytes Hyperplasia Erosion Goblet cell loss *Extraintestinal* spleen, lymph nodes, liver	[138]
Colon	Atg5 ko	Infiltration: mucosal/submucosal; leukocytes Hyperplasia *Extraintestinal* uterus, liver, lung, harderian glands	[139]
Colon	C1GalT1$^{\Delta IEC}$	Infiltration leukocytes Hyperplasia Ulceration Crypt abscesses Goblet cell loss	[140]
Colon	CD4/TSC1 ko	Infiltration: mucosal/submucosal/transmural; predominantly lymphocytes Hyperplasia, crypt distortion Goblet cell loss *Extraintesinal* liver, spleen, lymph nodes	[141]
Colon	CD40L/T tg	Infiltration: mucosal/submucosal/transmural; granulocytes Dysplasia Ulceration Crypt loss *Extraintestinal* lung, liver, pancreas	[142]
Colon	CD4CD45RB^{hi} into SCID mice	Infiltration: mucosal/submucosal/transmural; lymphocytes, macrophages, neutrophils, eosinophils, multinucleated giant cells Hyperplasia, crypt branching Erosion/ulceration Crypt abscesses/crypt loss Goblet cell loss Lymphoid aggregate formation; granuloma	[143, 144]
Colon	CD4CD62L into SCID mice	Infiltration: mucosal; leukocytes Erosion/ulceration Crypt distortion, Goblet cell loss	[145]
Colon	ConA-blasts into RAG1 ko mice	Infiltration: mucosal/submucosal; leukocytes Hyperplasia Crypt abscesses Goblet cell loss	[146]

Colon	Gimap5 ko	Infiltration: mucosal, submucosal Hyperplasia, crypt distortion Crypt abscesses Goblet cell loss *Extraintestinal* liver	[147]
Colon	Integrin αVβ8 ko	Infiltration: mucosal/submucosal/transmural; plasma cells, eosinophils Cyst formation *Extraintestinal* liver, spleen, lymph nodes	[148]
Colon	Muc2 x IL10 DKO	Infiltration: mucosal/submucosal; predominantly lymphocytes, Erosion/ulceration Hyperplasia Crypt abscesses Goblet cell loss	[149]
Colon	$NEMO^{IEC}$ ko	Infiltration: mucosal/submucosal; leukocytes (predominantly $CD4^+$ T cells, $CD11c^+$ cells, granuloctyes) Erosion	[150]
Colon	PC ko x PC tg	Infiltration: mucosal Hyperemia	[151]
Colon	$RBP\text{-}J^{\Delta IEC}$	Infiltration: mucosal; predominantly dendritic cells, $CD4^+$ T cells, $CD11b^+$ cells Crypt distortion Crypt loss Goblet cell hyperplasia Rectal prolapse	[152]
Colon (small intestine)	RUNX3 ko	Infiltration: mucosal/submucosal; plasma cells, macrophages, dendritic cells, eosinophils, lymphocytic cluster formation (mainly B cells, scattered T cells and dendritic cells) Hyperplasia Crypt loss Fibrosis	[153]
Colon	T/Blimp1 ko	Infiltration: mucosal/submucosal; lymphocytes, neutrophils Hyperplasia, crypt distortion Erosion Crypt abscesses	[154]
Colon	WASP ko	Infiltration: mucosal; $CD4^+/CD8^+$ T cells, neutrophils Hyperplasia Crypt abscesses	[155]
Colon, rectum	TRUC	Infiltrate: leukocytes Cryptitis/crypt abscesses/crypt loss Erosion/ulceration Goblet cell loss	[156]

B.2 Mediated by genetically altered cytokine balance			
Small intestine	SAMP/Yit	Infiltration: mucosal/submucosal; leukocytes Hyperplasia Crypt abscesses/crypt loss Villous atrophy (Enlarged lymphatics in distal jejunum, ileum and cecum) *Extraintestinal* skin, liver	[157]
Small intestine	TNFSF15 tg	Infiltration: mucosal/submucosal; lymphocytes, macrophages, neutrophils Goblet cell hyperplasia Wall thickening	[158]
Small intestine	XBP1 ko	Infiltration: mucosal (discontinuous); polymorphonuclear cells, Ulceration Crypt abscesses Goblet cell loss Villous shortening Absence of Paneth cell	[109, 159]
Jejunum, ileum (proximal)	IL15 tg	Infiltration: lymphocytes Hyperplasia Erosion Hyperemia Villous atrophy Paneth cell loss	[160]
Ileum	SAMP/YitFc	Infiltration: mucosal/submucosal/transmural (discontinuous); leukocytes (neutrophils, lymphocytes, macrophages, plasma cells Hyperplasia Cryptitis/crypt abscesses Ulceration Basal plasmocytosis Villous blunting Goblet cell hyperplasia Paneth cell hyperplasia Granuloma Muscular hypertrophy Neuronal hyperplasia Fistulae (5-10% of the mice) Stricture formation	[161-163]
Ileum	SHIP1 ko	Infiltration: mucosal/submucosal/transmural; leukocytes (multifocal infiltration with foci of predominantly mononuclear infiltrates and foci of predominantly polymorphonuclear infiltrates) Hyperplasia Crypt abscesses Ulceration Villous distortion Granulomas/fibrosis, stricture (Inflammation in mesentery, gastro-esophageal juncture) *Extraintestinal* lung, rare thrombosis, rare vasculitis	[164]

Ileum (proximal colon)	TNFΔ^{ARE}	Infiltration: mucosal/submucosal/transmural; leukocytes Lymphoid aggregates/granuloma Villous atrophy *Extraintestinal* skin, joints	[165, 166]
Ileum, colon	STAT4 tg	Infiltration: mucosal/submucosal/transmural; lymphocytes, granulocytes, macrophages Ulceration Crypt distortion Edema	[167]
Cecum, colon, rectum	AP-1B ko	Infiltration: mucosal/submucosal; neutrophils, $CD4^+$ T cells, dendritic cells Hyperplasia, crypt distortion Goblet cell loss Edema	[168]
Cecum, colon, rectum	SHP2$^{\Delta IEC}$	Infiltration: mucosal/submucosal/transmural Hyperplasia Crypt abscesses	[169]
Cecum, rectum	gp130$^{\Delta STAT}$	Ulceration (Inflammation of gastric pylorus) *Extraintestinal* nasolacrimal glands, conjunctivae, joints	[170]
Cecum, rectum	NFATc2xRAG DKO	Infiltration: leukocytes (mostly myeloid cells), Crypt abscesses	[171]
Colon	CD4/PP4 ko	Infiltration: mucosal/submucosal; predominantly mononuclear cells Hyperplasia Goblet cell loss Rectal prolapse *Extraintestinal* spleen, lymph nodes	[172]
Colon	CD4/TGFβ1 ko	Infiltration: mucosal/submucosal; leukocytes Hyperplasia, crypt distortion Crypt abscesses *Extraintestinal* lung, liver	[173]
Colon	dnTGFβ RII tg	Infiltration: mucosal/submucosal/sometimes transmural; neutrophils, macrophages, lymphocytes, plasma cells Hyperplasia Goblet cell loss Crypt abscesses *Extraintestinal* multiple organs i.e. liver, lung, kidneys, stomach	[174, 175]
Colon (duodenum)	IL10 ko	Infiltration: mucosal/submucosal/transmural; neutrophils, eosinophils, macrophages, lymphocytes, plasma cells Hyperplasia Ulceration Crypt abscesses Adenocarcinoma	[176]

Colon	IL2 ko	Infiltration: mucosal; lymphocytes, plasma cells, some granulocytes Hyperplasia, crypt distortion Ulceration Crypt abscesses Goblet cell loss *Extraintestinal* liver, kidney, spleen	[177]
Colon	IL2Rα ko	Infiltration: mucosal; lymphocytes, granulocytes Hyperplasia, crypt branching Ulceration Crypt abscesses Goblet cell loss	[178]
Colon	IL7 tg	Infiltration: lymphocytes, eosinophils, (neutrophils restricted to rectum) Erosion Crypt abscesses Goblet cell loss	[179, 180]
Colon	IREα$^{\Delta IEC}$	Infiltration: mucosal; lymphocytes Crypt distortion Goblet cell loss	[181]
Colon	JAK3 ko	Infiltration: mucosal; lymphocytes, macrophages Hyperplasia, crypt distortion Goblet cell loss Crypt abscesses	[115]
Colon	SOCS1 tg	Infiltration: leukocytes Hyperplasia Crypt abscesses Goblet cell loss Adenocarcinoma	[182]
Colon	SOCS1xTCRα DKO	Infiltration: leukocytes Hyperplasia Crypt abscesses Goblet cell loss	[183]
Colon	STAT3 ko (LysMCre/Stat3^{flox})	Infiltration: mucosal/submucosal/transmural (30%); leukocytes (predominantly CD3^{+} T cells and macrophages) Erosion/ulceration Crypt abscesses Goblet cell loss	[184, 185]
Colon	STAT3 ko (MCre/Stat3^{flox})	Infiltration: mucosal/submucosal; lymphocytes, neutrophils Crypt distortion Ulceration Crypt abscesses/crypt loss Goblet cell loss	[186]
Colon	TGFβ ko	Infiltration: mucosal; lymphocytes, plasma cells, macrophages Necrosis *Extraintestinal* heart, stomach, liver, lung, pancreas, salivary glands, striated muscles	[187, 188]

Colon, rectum	IL1RAxRAG2 DKO	Infiltration: mucosal/submucosal Hyperplasia, crypt distortion Rectal prolapse	[189]
Colon, rectum	TNFxIL10 DKO	Infiltration: mucosal (continuous); large numbers of neutrophils Hyperplasia Crypt Abscesses Ulcerations	[190]
B.3 mediated by genetically altered epithelial and mucus integrity			
Small intestine, colon	Mdr1a ko	*Small intestine* Infiltration: mucosal; leukocytes Villous blunting, atrophy *Colon* Infiltration: mucosal/submucosal; lymphocytes, macrophage, granulocytes Hyperplasia (severity increases from proximal to distal) Erosion/ulceration (severity increases from proximal to distal) Goblet cell loss Interstitial edema *Extraintestinal* spleen, lymph nodes	[191-193]
Jejunum, ileum	Enteric glia ko	Infiltration: discontinuous; leukocytes Hyperplasia Ulceration Goblet cell loss Villous blunting, atrophy Necroses (hemorrhagic) Loss of brush border Intravascular microthrombi Edema (subepithelial)	[194, 195]
Ileum, colon	AGR2 ko	Infiltration: mucosal/submucosal; predominantly neutrophils Hyperplasia Lymphoid follicles and hyperplasia of the Peyer's patches (granulomatous inflammation)	[196]
Cecum, rectum	PI3Kp110d ki	Infiltration: leukocytes Hyperplasia Crypt abscesses Erosion	[197]
Colon	Muc2 ko	Infiltration: mucosal/submucosal; predominantly lymphocytes Hyperplasia Erosion/ulceration Crypt abscesses Goblet cell loss	[198]
Colon	Winnie	Infiltration: mucosal; large numbers of neutrophils Hyperplasia Erosion Goblet cell loss Crypt abscesses Rectal prolapse	[199, 200]

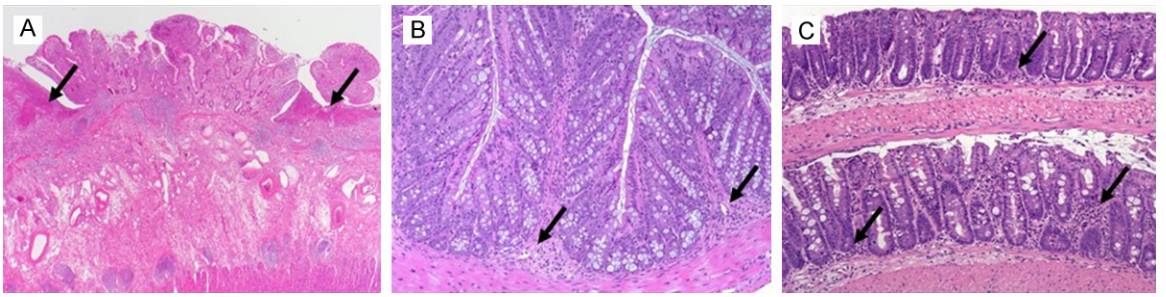

Figure 1. Focal infiltrations of immune cells. Representative images of H&E stained tissue sections of a (A) Crohn's disease patient exhibiting skip lesions (arrows) in the small intestine; original magnification x20. (B, C) Show multifocal infiltrations (arrows) in mouse models; colons of a mouse with (B) DSS-induced colitis and (C) transfer colitis; original magnification ×100.

Results

Histomorphological characteristics of inflammatory bowel diseases

The clinical symptoms in UC and CD present with a broad spectrum from bloody diarrhea and weight loss on the one hand and fever, nausea and abdominal pain on the other hand. In 30-40% of the CD patients, the small bowel is affected with about 90% involvement of the terminal ileum [27]. Forty to 55% of the patients show small and large intestinal inflammation [27]. An affection of solely the large bowel occurs in only 15-25% of the CD patients [27]. In UC patients, the inflammation is restricted to the colon and only rarely spreads to the terminal ileum causing a phenotype named "backwash ileitis" [28]. Both entities of IBD clearly differ in their main histomorphological characteristics and distribution (**Table 1**) [29].

Since the intestine comprises the largest part of the immune system, intestinal phenotypes are common in most of the mouse models interfering with immune-related mechanisms but not all qualify as IBD models. Focussing on the main pathologies in the small and large intestine, alterations in other organs are referred to as extraintestinal. The main histomorphological features of intestinal inflammation reported for 95 IBD mouse models are summarized in detail (**Table 2**). More than half of the models showed exclusive inflammation in the colon (65%). In contrast, 17% were restricted to the small intestine and an additional 18% affected most or all parts of the large and the small intestines.

The following paragraphs will discuss histomorphological features in human UC and CD and directly compare them to corresponding mouse models of IBD.

Mouse models histomorphologically resembling human Crohn's disease

The inflammation in human CD is discontinuous (skip lesions) and transmural. Discontinuous inflammation is defined as areas of inflammatory cells surrounded by otherwise normal mucosa (**Figure 1A**) and can be found in the small intestine of SAMP/YitFc mice [161, 162], of mice with dominant negative (DN) N-cadherin [111] and models of ovalbumin (OVA) colitis [104, 105]. Enteric glia ko mice also exhibit skip lesions in jejunum and ileum [194]. In early DSS-induced colitis (**Figure 1B**) or early transfer colitis, i.e. colitis upon transfer of $CD4^{+}CD45RB^{high}$ T cells into syngeneic Rag1 ko mice, the inflammatory infiltrate is discontinuous (**Figure 1C**). As in the colon of CD patients (**Figure 2A**) the inflammation becomes more diffuse and severe resulting in transmural inflammation during the course of transfer colitis (**Figure 2B**). Transmural inflammation is described in about one third of the IBD mouse models with occasional or rare occurrence in the colon of oxidative stress-related GPX1/2 DN [127], Toll-like receptor (TLR)5 ko [135], transforming growth factor β-receptor II transgenic (dnTGFβRII tg) [174] and STAT3 ko ($LysMCre/Stat3^{flox}$) mice [183]. Models with inflammation of the small intestine or ileum were more prone to the transmural type: knockout in the transcription factor XBP1 (XBP1 ko) [109], N-cadherin DN [111], CD4/PDK1 ko [117], LIGHT tg [119], intestinal epithelial cell (IEC)-specific deletion of a protein

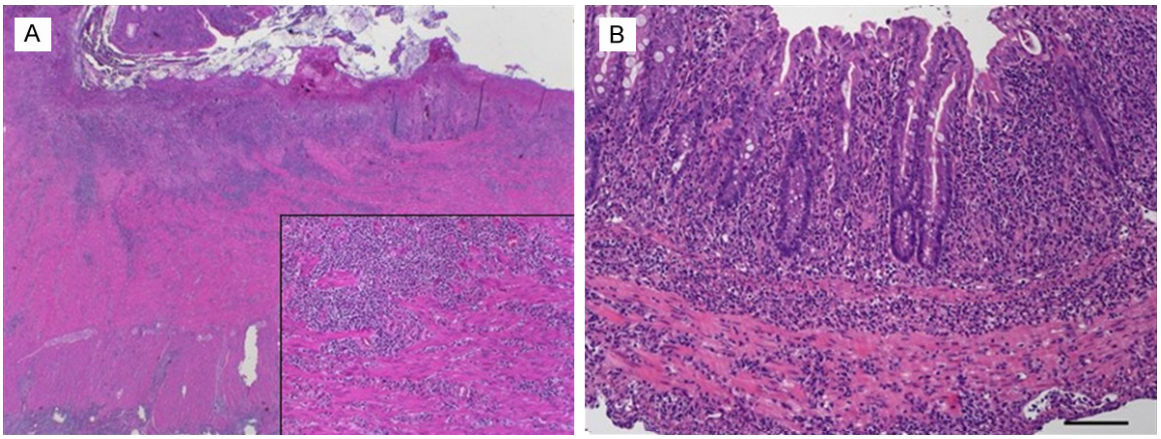

Figure 2. Transmural inflammation. Representative images of H&E stained tissue sections showing transmural inflammation in (A) the colon of a patient with Crohn's disease (original magnification ×20, insert ×100), (B) the colon of a mouse with transfer colitis (original magnification ×100, scale bar represents 100 μm).

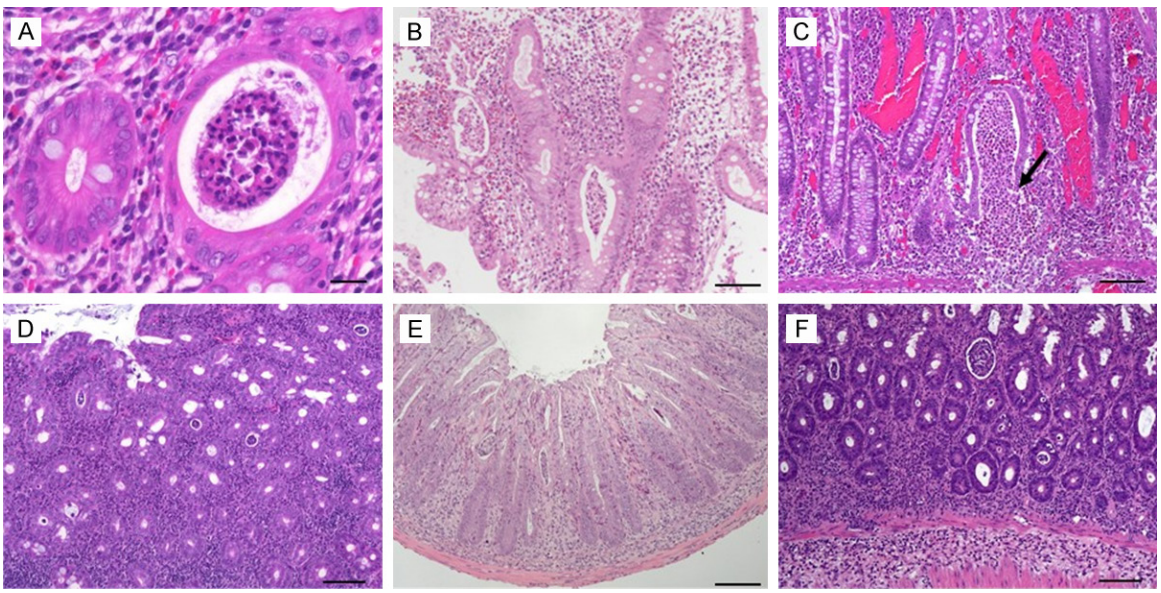

Figure 3. Crypt abscesses. Representative images of H&E stained colon sections from (A) a patient with Crohn's disease showing a crypt abscess with flattened epithelium and neutrophils in the lumen (right) alongside with a normal crypt (original magnification x400, scale bar represents 20 μm), (B) a patient with ulcerative colitis (original magnification x100, scale bar represents 100 μm), (C) a patient with Crohn's disease showing crypt herniation (arrow); original magnification ×100, scale bar represents 100 μm and (D-F) mouse models of IBD (original magnification ×100, scale bars represent 100 μm). Multiple crypt abscesses in the moderately inflamed colons of (D) an IL10ko mouse, (E) an IL2ko mouse and (F) a mouse with transfer colitis.

O-fucosyltransferase (Pofut$^{\Delta IEC}$) [121], GPX1/2 DN [127], CD40L/B tg [129], SHIP1 ko [164], STAT4 tg mice [167], SAMP/YitFc [161, 162] and TNF$^{\Delta ARE}$ [30]. Transfer of IL10$^{-/-}$CD4^{+} T cells into RAG1 ko mice [116] also resulted in transmural inflammation of ileum and jejunum in the recipients as well as the infection with either *H. polygyrus* [97] or with 10 cysts of *T. gondii* (not shown).

Crypt abscesses are a common feature in most models though they are not as common in CD as in UC. Crypt abscess is defined as the presence of neutrophils in the crypt lumen (**Figure 3A**). When the crypt abscess ruptures, it spills its luminal content into the surrounding tissue (crypt herniation, **Figure 3C**). However, crypt herniation was not observed or reported in any mouse model of IBD. While crypt abscesses

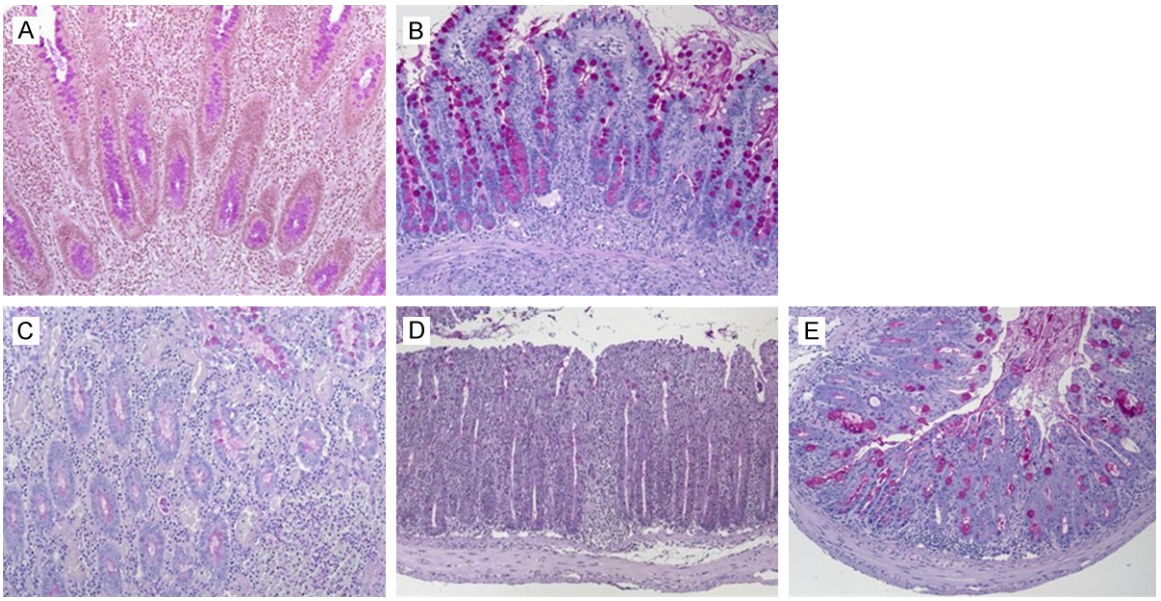

Figure 4. Mucin producing goblet cells. Representative images of PAS stained tissue sections showing goblet cell hyperplasia in the small intestine of (A) a patient with Crohn's disease with an abundance of purple stained goblet cells and (B) a mouse after *H. polygyrus* infection. (C-E) show goblet cell loss in the colon of (C) a patient with ulcerative colitis with only few purple stained goblet cells, (D) a mouse with transfer colitis and (E) a mouse with chronic DSS-induced colitis. Original magnification ×100.

occur in every chemically induced colitis except for oxazolone colitis [88] or the chronic models [92, 95, 96]. About 60% of the genetic models show crypt abscesses independent of the mechanism to alter immune responses and 75% of the transfer colitis models and all congenic models (**Figure 3D-F**). They are not described after transfer of $CD4^+CD62L^+$ T cells into severe combined immunodeficiency (SCID) mice [145]. In the small intestine, crypt abscesses are only seen in XBP1 ko [159], N-cadherin DN [111], $Pofut^{\Delta IEC}$ [121], zinc-finger protein Roquin ko [112], $CD4^+$ T cell-specific knockout of the phosphoinositide-dependent-protein-kinase 1 (CD4/PDK1 ko) [117], T-cell receptor (TCR)α ko [125, 126], GPX1/2 DN [127, 128], SAMP/YitFc [161] and SHIP1 ko mice [164] In models mediated by luminal antigen, crypt abscesses are only described in infections with either *H. polygyrus* [97] or *Eimeria* (*E.*) *falciformis* [103], OVA-induced colitis [104, 105], as well as in the colon but not in the small intestine of heat-shock protein (HSP) 60-specific colitis [102].

Fissuring ulcers and fistulas characteristic for CD are very rare in IBD mouse models. Fissures are knife-like ulcers, which occur in a right angle to the long axis of the bowel (also depicted in **Figure 8A**). They contain acute inflammatory cells and a lining of granulation tissue. CD-associated fistulae reveal a central fissure that penetrates deep into the bowel wall and is lined by granulation tissue [31]. CD-associated fistulae originate from an epithelial defect that occurs during chronic inflammation [31] and the cellular infiltrate is distinct from the infiltrate in non-CD fistulae [32]. Fissures are reported in the colon and the small intestine of LIGHT tg mice [119] and fistulae occur in 5-10% of SAMP/YitFc mice [161]; fissures and fistulae in the small intestine of mice with IEC-specific deletion of the autophagy-related Atg7/XBP1 complex ($Atg7/Xbp1^{\Delta IEC}$) [109].

In CD, goblet cell differentiation is enhanced [33]. Therefore, a preserved or increased mucin secretion or even an increase in goblet cell numbers is a histopathological characteristic of CD (**Figure 4A**). Increased goblet cell numbers or goblet cell hyperplasia occurs in the ileum of SAMP/YitFc mice [162, 163], the duodenum of mice infected with *H. polygyrus* (**Figure 4B**) and of mice with IEC-specific deletion of the recombination signal binding protein RBP-J ($RBP\text{-}J^{\Delta IEC}$) [152] and TCR ko mice after transfer of $CD4CD45RB^{high}$ T cells [116]. A hypertrophy of goblet cells was observed in HSP60 antigen-treated B10A mice [102].

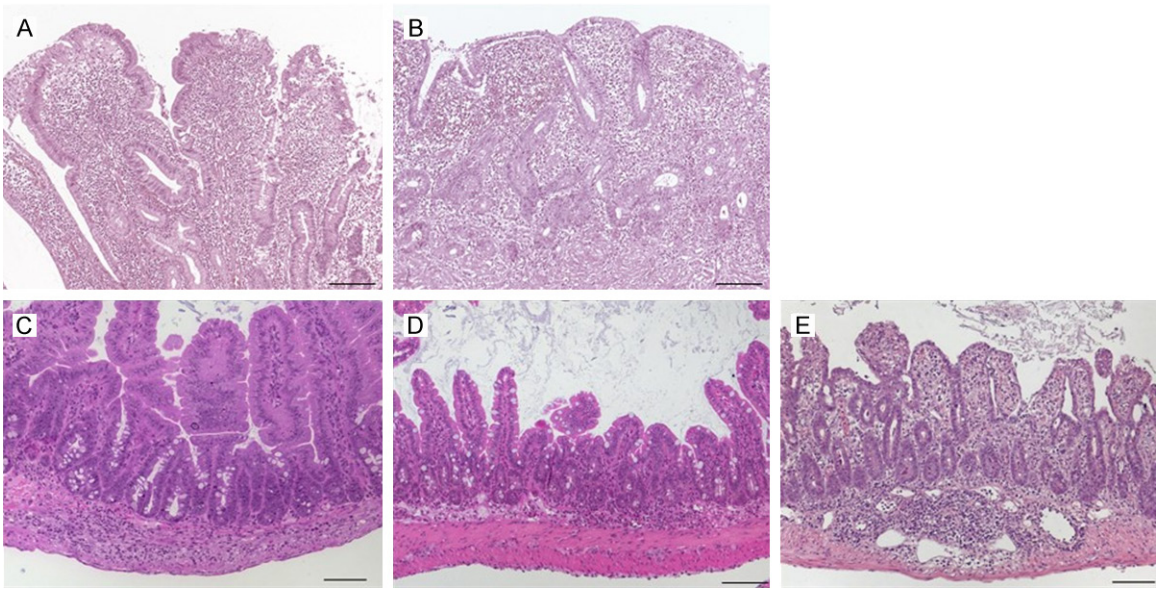

Figure 5. Altered villous morphology. Representative images of H&E stained tissue sections of the ileum of a Crohn's disease patient exhibiting (A) villous blunting and (B) atrophy; villous blunting in (C) the duodenum of a mouse infected with *H. polygyrus* and in (D) the ileum of a mouse after infection with 10 cysts of *T. gondii*. Necrotic villi in (E) a mouse after infection with 100 cysts of *T. gondii*. Original magnification ×100, scale bar represents 100 µm.

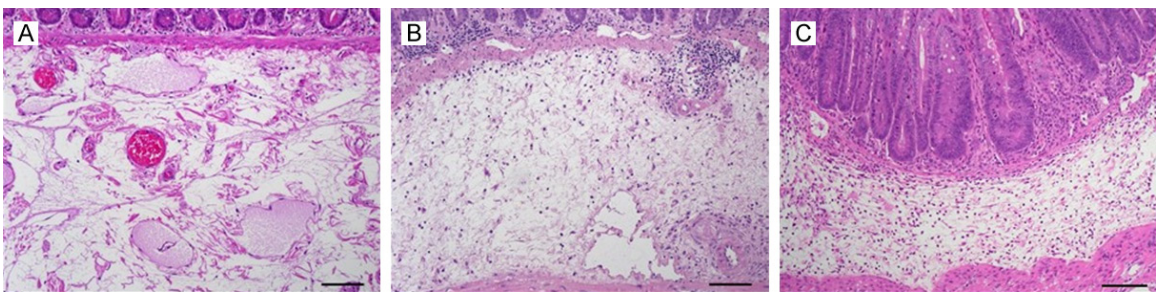

Figure 6. Edema in the submucosa. Representative images of edematous submucosa in the colon of (A) a patient with Crohn's disease, (B) a mouse with DSS-induced colitis and (C) an IL2ko mouse; original magnification ×100, scale bar represents 100 µm.

In the small intestine, the villi in the duodenum and jejunum are long, while in the ileum the villi are typically shorter. Villous blunting and eventually atrophy indicate histopathological changes in the small intestine of CD patients (**Figure 5A**, **5B**). Villous blunting or atrophy is abundant in all categories of IBD models exhibiting small bowel inflammation. Models mediated by disturbed immune cell homeostasis like: XBP1 ko [159], N-cadherin DN [111], Roquin ko [112], LIGHT tg [118], guanine nucleotide-binding protein subunit Gαi2 ko [123], IEC-specific deletion of caspase 8 ($Casp8^{\Delta IEC}$) [124] or CD40L/B tg [129], as well as some having a genetically altered cytokine balance like SAMP/Yit, SAMP/YitFc [157, 161, 162] and IL15 tg mice [160] exhibit villous blunting or villous atrophy like in $TNF^{\Delta ARE}$ mice [30]. Mechanisms directly interfering with the epithelial integrity as in mice lacking the murine multiple drug resistance gene Mdr1a (Mdr1a ko) [191] or enteric glia ko mice [194, 195] as well as transfer colitis models [116] show this feature. In antigen-specific models, villous blunting and atrophy in the HSP60-specific model [101] and after infection with *H. polygyrus* (**Figure 5C**), *Strongyloides ratti* [98] or 10 cysts of *T. gondii* (**Figure 5D**) consequently worsen to villous destruction after oral infection with 100 cysts of *T. gondii* (**Figure 5E**).

Tissue swelling due to edema is commonly seen in the submucosa of CD patients (**Figure 6A**). During disease progression, submucosal

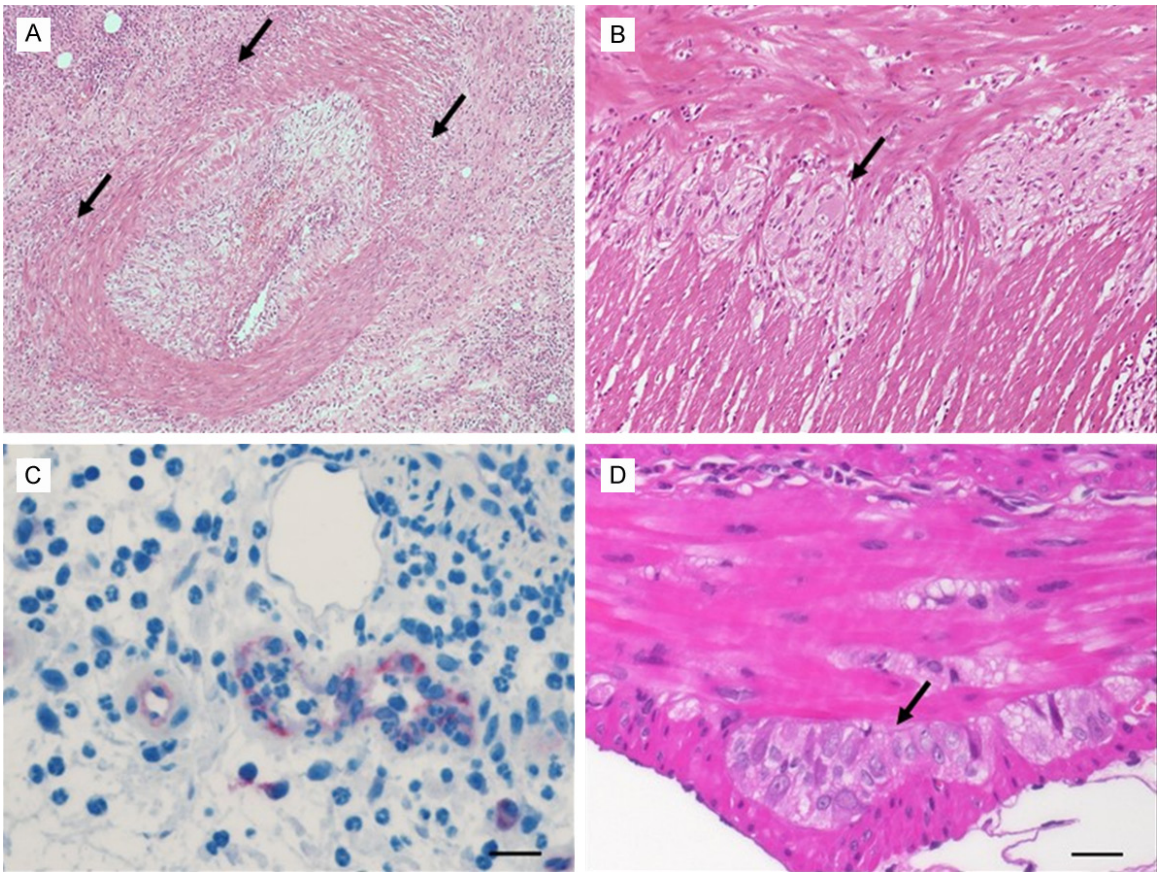

Figure 7. Vasculitis and hyperplastic nerves. Representative images of H&E stained tissue sections of (A, B) the ileum of a Crohn's disease patient showing (A) inflamed and obliterated vessel with inflammatory cell infiltrates within the vessel wall (arrows) and (B) neuronal hyperplasia with increased numbers of ganglion cells (arrow) between the striated muscle (above) and the longitudinal muscle (below); original magnification ×400. Representative images of an (C) immunohistochemically stained colon section of a mouse with severe DSS-induced colitis showing an inflamed vessel with inflammatory leukocytes between CD31-positive endothelial cells (red) with a normal lymphatic vessel above and a non-inflamed vessel (red) on the left and (D) H&E stained colon section of an IL2ko mouse with neuronal hyperplasia (arrow); original magnification ×400 (scale bar represents 20 µm).

edema will become fibrotic. Edemas with or without fibrosis occur in chemically inducible models like acute DSS-induced colitis (**Figure 6B**), but were not reported in carrageenan [87] or chronic DSS-induced colitis [95, 96]. In genetic models, fibrosis is an extremely rare event and so far only reported in the cecum of C3H/HeJBir mice [134], in the large intestine of Ahr ko mice haplodeficient for the transcription factor RORγt (Ahr ko) [136] or in the ileum of SHIP1 ko mice [164]. Edemas in genetic models occur in colons of Pofut$^{\Delta IEC}$ [121], apoptosis-related FAS villin-Cre [131], TLR5 ko [135], STAT4 tg [167], mice deficient for the transcription factor AP-1B (AP-1B ko) [168] or IL2 ko mice (**Figure 6C**). Neither edema nor fibrosis have been reported for any of the models with adoptive transfer of defined T-cell populations [143, 145], but submucosal edema develop in the colon of HSP60-specific mice [102].

Frequently observed in CD, inflamed lymphatics, vasculitis (**Figure 7A**) or neuronal hyperplasia (**Figure 7B**) is seldom described in mouse models. As a rare event, vasculitis can be detected in the ileum of SHIP1 ko mice [164] and in severe DSS-induced colitis (**Figure 7C**). Vessel dilatation with erythrostasis and formation of microthrombi are found in the small intestine of enteric glia ko mice [194]. Lymphatic vessels are enlarged in the small intestine of SAMP/Yit mice [157]. Neuronal hyperplasia with increased numbers of ganglion cells can be seen in SAMP/YitFc [161], TNF$^{\Delta ARE}$ (not shown) and IL2 ko mice (**Figure 7D**).

Lymphoid aggregates can be observed in all segments of the bowel wall and are generally located along the muscularis mucosae and muscularis propria in CD patients forming even in the absence of granulomas (**Figure 8A**). In

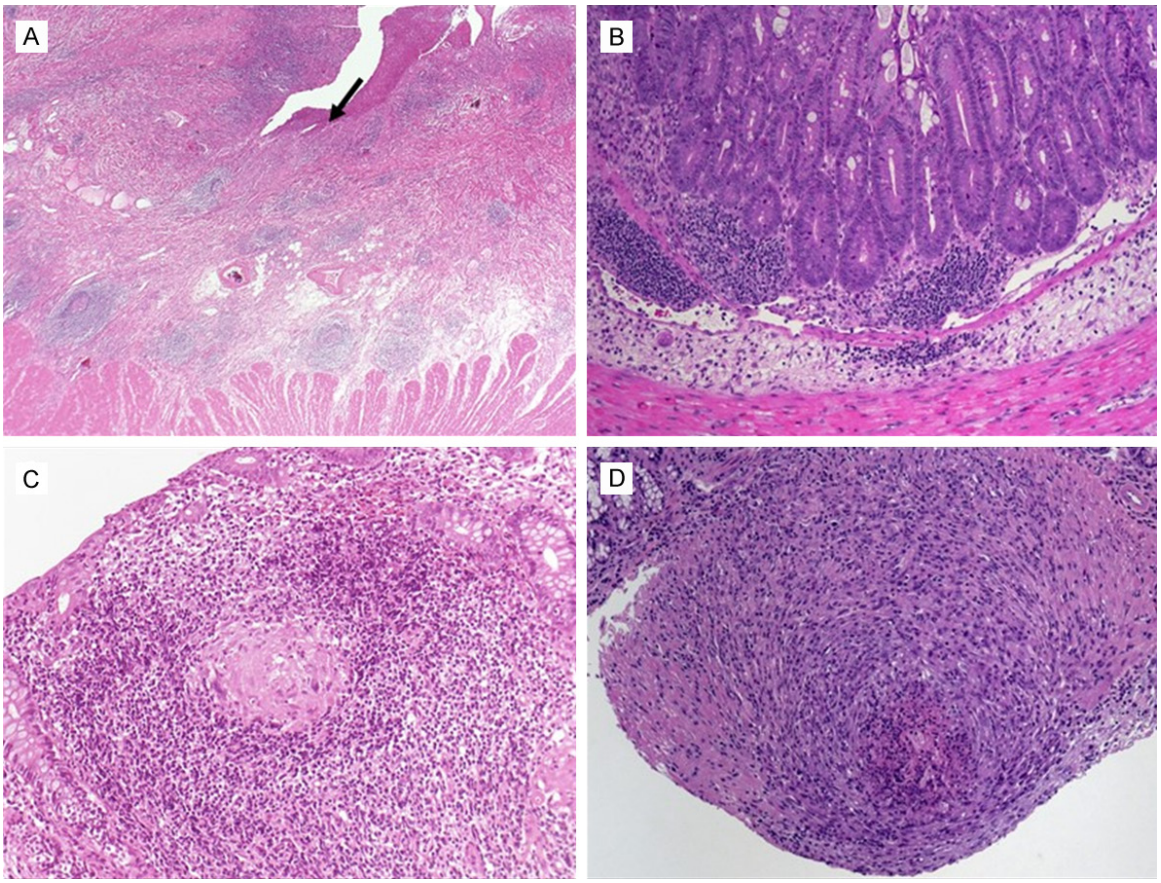

Figure 8. Lymphoid aggregates and granulomas. Representative images of H&E stained tissue sections showing (A, B) lymphoid aggregates and (C, D) granuloma in Crohn's disease and IBD mouse models. (A) Multiple lymphoid follicles at the muscularis mucosae and at the muscularis propria in the ileum of a patient with Crohn's disease; original magnification ×20. Note also the fissuring ulcer in the upper half of the picture (arrow). Formation of follicular aggregates without secondary follicles at the muscularis mucosae in (B) a colon of a mouse with chronic DSS-induced colitis; original magnification ×100. Granuloma in the (C) colon of a Crohn's disease patient with a cuff of inflammatory cells and (D) duodenum of a mouse after infection with *H. polygyrus*; original magnification ×100.

mice, lymphoid aggregates are reported in acute trinitrobenzenesulfonic acid (TNBS)-induced [89, 90] and chronic DSS-induced colitis (**Figure 8B**). They also occur in the ileum and the colon of Pofut$^{\Delta IEC}$ mice [121] and of mice deficient in the disulphide isomerase family member AGR2 (AGR2 ko) [196], in the small intestine of N-cadherin DN [111] and TNF$^{\Delta ARE}$ mice [30] as well as in the colon of LIGHT tg [120] or Ahr ko mice [136]. Lymphoid aggregates are also found in the colon of B7.2 tg [130] and following T-cell transfer into SCID mice [144], while they are missing in congenic models but occur in antigen-specific typhlocolitis [106]. In RUNX3 ko mice [153], reported lymphocytic cluster containing B cells as well as scattered T cells and granulocytes but no macrophages [34] are not considered lymphoid aggregates. Lymphoid aggregates are helpful in diagnosing CD, but granulomas are the main histopathologic criterion for differentiating CD from UC [35, 36]. Granulomas in CD consist of small, localized and well-formed aggregates of epitheloid histiocytes with a varying degree of hyalinization and fibrosis. They may contain Langerhans giant cells and are often surrounded by a cuff of lymphocytes (**Figure 8C**), increasing in numbers from the ileum to the rectum. They form mainly in the bowel wall, but are also found along blood vessels, lymphatics or nerves. Suppurative or necrotic granulomas are not specific for CD and may be caused by intestinal tuberculosis or other infections. Intramural granulomas were found in the model of *H. polygyrus* infection (**Figure 8D**). Granulomas in the small intestine were report-

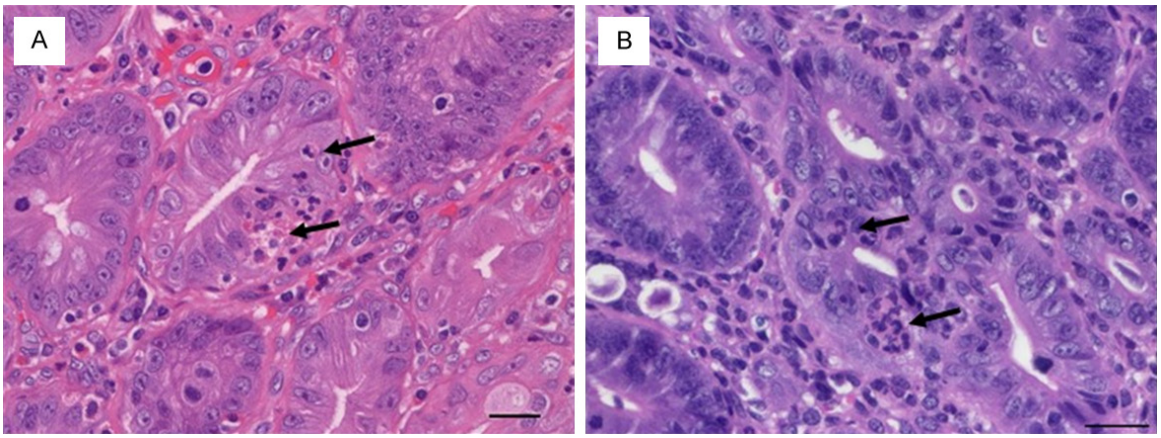

Figure 9. Inflamed crypts in the colon mucosa. Representative images of H&E stained colon sections showing cryptitis (neutrophils interspersed in crypt epithelium, arrows) in (A) ulcerative colitis and (B) transfer colitis; original magnification x400, scale bar represents 20 µm.

ed in LIGHT tg [119], SHIP1 ko [164], SAMP/YitFc [161], $TNF^{\Delta ARE}$ [165] and AGR2 ko mice [196] as well as in the colon of mice with OVA-induced colitis [104] and following transfer of $CD4CD45RB^{hi}$ into SCID mice [143].

Mouse models histomorphologically resembling human ulcerative colitis

The majority of the IBD mouse models listed in **Table 2** present diffuse (sub)mucosal inflammation. Aggregation of lymphocytes and plasma cells at the crypt base referred to as basal plasmacytosis in UC is described only in SAMP/YitFc mice [161]. In active inflammation, neutrophils migrate into the crypt epithelium resulting in cryptitis (**Figure 9A**). Cryptitis was reported in the colon of Ahr ko mice [136] and TRUC mice [156] as well as in the small intestine of N-cadherin DN [111] and SAMP/YitFc mice [161]. In experimental models of colitis induced by luminal antigens cryptitis is only reported after application of OVA [104]. We frequently found cryptitis upon transfer of $CD4^{+}CD45RB^{high}$ T cells into syngeneic Rag1 ko mice (**Figure 9B**).

Denuded mucosa, erosions and ulcerations are characteristic for human UC (**Figure 10A**), but ulcerations occur also in CD (**Figure 10B**). Erosions and ulcerations are a typical feature in colitis models dependent on erosive chemicals except for butyric acid-induced colitis (**Table 2**/part A.1) (**Figure 10C**). They are also found in the majority of the models mediated by luminal antigens (**Table 2**/part A.2) or most models with a "first hit" from the inside (**Table 2**/part B) as exemplified by IL2 ko mice (**Figure 10D**). In cell transfer models, only SCID mice develop ulcerations [143, 144]; RAG1 ko mice rather display erosions [146]. The C3H/HeJBir mice exhibit ulcerations in the cecum [134].

The loss of goblet cells, a distinctive feature in the colon of UC patients (**Figure 4C**) is found in the majority of the IBD mouse models though not in congenic models. Goblet cells are lost in the small and large intestine upon adoptive transfer as exemplified here for $CD4CD45RB^{hi}$ T cells into RAG1 ko mice (**Figure 4D**) and in half of the genetic models interfering with immune cell homeostasis (**Table 2**/part B.1), cytokine balance (**Table 2**/part B.2) or epithelial/mucus integrity (**Table 2**/part B.3). Lost goblet cells in cecum and colon are reported upon infection with *E. falciformis* [103] and in the OVA-colitis model [105, 107]. In chemically induced models, goblet cell loss shown here for chronic DSS-induced colitis (**Figure 4E**), is not found in carrageenan [87], oxazolone [88] or in chronic TNBS-induced colitis [92].

Changes in the mucosal architecture like crypt distortion due to excessive epithelial cell regeneration reflected by crypt hyperplasia are common alterations in the colon during human UC (**Figure 11A**) but also in experimental transfer colitis (**Figure 11B**) up to crypt distortion (**Figure 11C**) and the eventual loss of crypts (**Figure 11D**). Crypt loss is also nicely represented in the colon mucosa of mice with DSS-induced colitis (**Figure 11E**) as well as in acute carrageenan-[87] and TNBS-induced colitis [89]. In

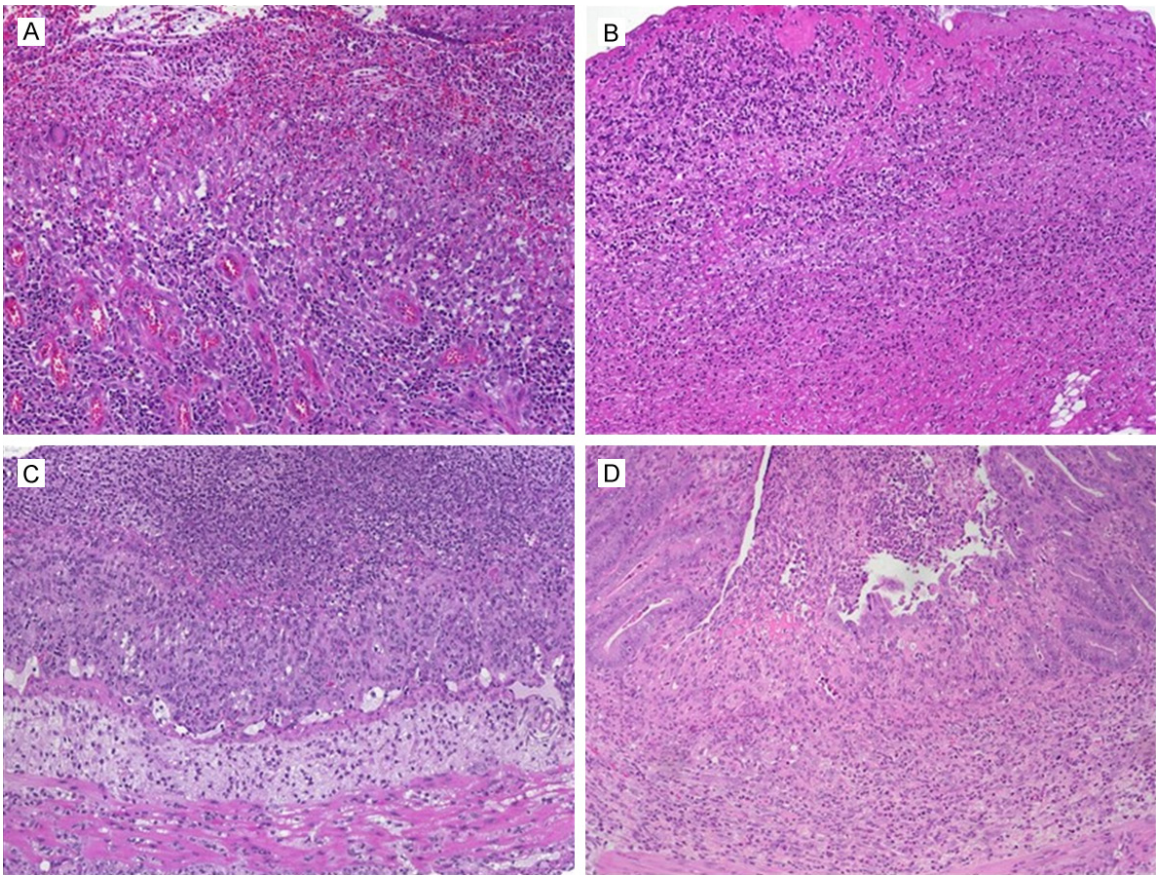

Figure 10. Ulcerations. Representative images of H&E stained tissue sections showing ulcerations in (A) the colonic mucosa of a patient with ulcerative colitis, (B) the ileum of a patient with Crohn's disease, (C) the colon of a mouse with DSS-induced colitis and (D) the colon of an IL2ko mouse; original magnification ×100.

genetic models, crypt distortion is found in mice deficient in the ubiquitin-editing protein A20 (A20 ko) [107], Common γ chain ko [115], JAK3 ko [115], CD4/PDK1 ko [117], TCRα ko mice [44, 45], CD4/TSC1 ko [141], RBP-J$^{\Delta IEC}$ [152], T/Blimp1 ko [154], STAT4 tg [167], AP-1B ko [168], CD4/TGFβ1 ko [173], IL2 ko [177], mice with IEC-specific deletion of the endoplasmic reticulum stress sensor IRE (IREα$^{\Delta IEC}$) [181], STAT3 ko [186] and IL1RAxRAG2 DKO [189] as well as in the small intestine of LIGHT tg mice [118, 120]. While crypt loss occurs in the colon of Pofut$^{\Delta IEC}$ [121], Casp8$^{\Delta IEC}$ [124], FAS villin-Cre [131], Ahr ko [136], RBP-J$^{\Delta IEC}$ [152], IL2 ko (**Figure 11F**) and TRUC mice [156] as well as in some models mediated by luminal antigens like OVA-induced colitis [107] and upon *E. falciformis* infection [103].

While the surface of the small intestine is enlarged by villi protruding into the gut lumen, the colon surface appears flat but shows the openings of numerous crypts. An irregular or villiform surface of the colon as seen in about 60% of UC patients [37] as well as the thickening of the muscularis mucosae is not represented in any of the IBD mouse models.

Discussion

A comprehensive comparison of the intestinal histomorphology of more than 90 IBD mouse models of different genesis to human IBD is presented herein. The most common forms of IBD are Crohn's disease and ulcerative colitis, although up to 20% are classified as indeterminate colitis, since the clinical, endoscopical and histomorphological parameters do not suffice for distinguishing UC from CD [38]. None of the experimental models reflects all histomorphological characteristics of either CD or UC. So there is always the problem to choose the most appropriate model for testing a hypothesis. A recent review focused on the preclinical

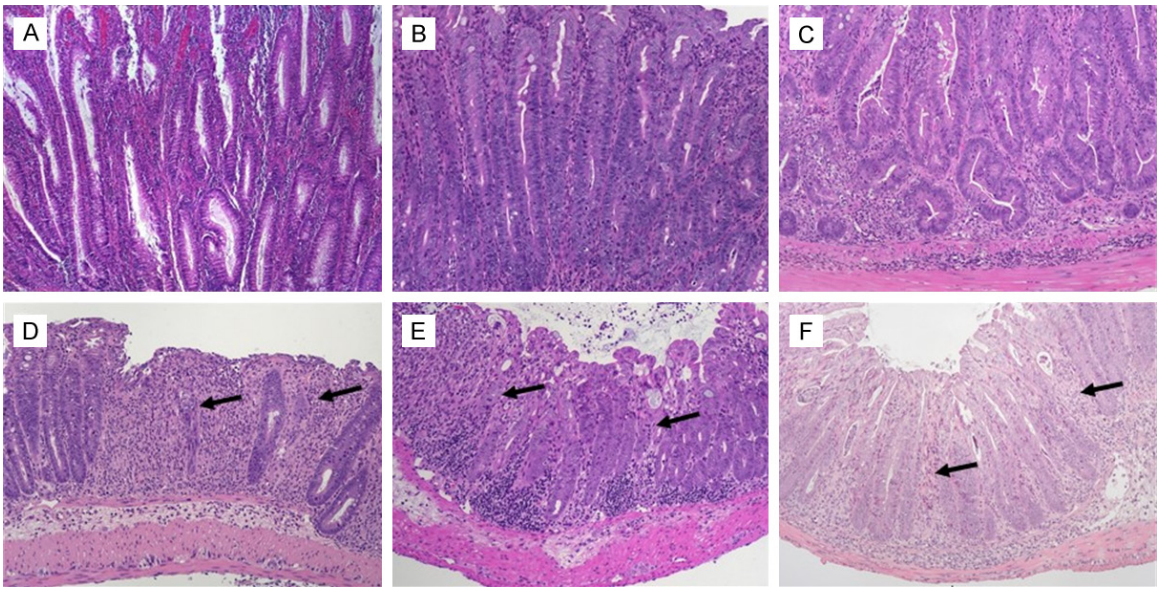

Figure 11. Altered crypt morphology. Representative images of H&E stained colon sections of (A) an ulcerative colitis patient exhibiting elongated and slightly distorted crypts and (B) crypt hyperplasia as well as (C) irregularly shaped, distorted crypts in transfer colitis. Crypt loss (arrows) in the colon mucosa of a mouse with (D) transfer colitis, (E) DSS-induced colitis and (E) deficiency in IL2 (IL2 ko mouse); original magnification ×100.

efficacy of the commonly used mouse models of DSS- or TNBS-induced colitis, transfer of $CD45RB^{hi}$ T cells, IL10 ko mice as well as $TNF^{\Delta ARE}$ or SAMP1/Yit mice [20]. It states, that a suitable model for a particular scientific question should be chosen by the dominant pathological response, e.g. damaged epithelium, intestinal architecture or the participating immune cells [20]. This was followed by a review of Jones-Hall and Grisham, who discussed the same mouse models with respect to immunopathology with emphasis on the mouse strain and the role of the microbiota [39]. This study includes other pathogenetic factors in IBD and highlights histopathology as an important tool. We focused on mouse models of IBD as these constitute the major part. As a result, some characteristics of the human disease are not represented, e.g. "creeping fat". In CD, mesenteric fat often wraps around the bowel presenting as "creeping fat" [40]. This feature is not represented in any mouse model, but can be found in indomethacin-induced colitis in rats (not shown). Keeping in mind, that human IBD depends on genetic predisposition, excessive immune responses to the commensal microbiota triggered by urbanization stress, not all characteristics of the human diseases are found in these models.

The most commonly used mouse models resembling CD are the $TNF^{\Delta ARE}$ [41] and SAMP1/Yit mice [42]. Both models present with small bowel inflammation, while the $TNF^{\Delta ARE}$ mouse comprises more CD-like features [41, 43]. For example, the inflammation in $TNF^{\Delta ARE}$ mice is transmural compared to (sub)mucosal inflammation in SAMP/Yit mice. Additionally, $TNF^{\Delta ARE}$ mice develop lymphoid aggregates and granulomas, which are missing in SAMP/Yit mice [44]. SAMP/Yit mice display a hyperplastic epithelium, which is rather an UC-like feature. The SAMP1/YitFc substrain (SAMP1/Fc) was developed by the group of Fabio Cominelli [44] and shares more histomorphological features with human CD than SAMP1/Yit mice like transmural inflammation, goblet cell and neuronal hyperplasia as well as the development of granuloma, fistulae and strictures [161-163]. Other rarely used mouse models like N-cadherin DN [45] and LIGHT tg mice [46-48] share histomorphological characteristics with CD. Both develop transmural inflammation of the small intestine as well as lymphoid aggregates and villous shortening. LIGHT tg mice also present intramural granuloma and fissures. Like SAMP/Yit mice, they share UC-like characteristics like goblet cell loss [42, 47, 48].

Although all models summarized in **Table 2** present themselves with intestinal damage and/or inflammation and are in the literature considered as IBD models, intestinal histomorphology

does not classify all these models as suitable for preclinical studies or for evaluation of IBD pathogenesis. For example, Cb1-b ko mice show infiltrations of activated B- and T cells into multiple organs and also into the large intestine [49]. Though this mouse model is suitable for studying the maintenance of peripheral immunological tolerance, it is not sufficient for an IBD model from the histopathological point of view [49]. Additionally, an increasing spectrum of monogenic diseases that present with very early and early onset of IBD-like intestinal inflammation not directly compare to the multifactorial "classical" IBD [50]. For example, $NEMO^{IEC}$ ko mice having disrupted nuclear factor-κB signalling in intestinal epithelial cells present with dense infiltrates of $CD4^+$ T cells, $CD11c^+$ cells and MPO-expressing cells in the colon mucosa and submucosa as well as erosions [51]. Patients with the NEMO syndrome develop systemic inflammation and atypical enterocolitis [52]. Hence, while a suitable model for studying monogenic diseases, the $NEMO^{IEC}$ ko mouse is not a suitable model for the complex interactions in IBD. In line with this, IL10 ko mice were first developed as an IBD model [53]. Fifteen years later, this deficiency was linked to mutations in genes encoding the IL10R subunit proteins in patients with early onset enterocolitis [54].

Many of the recently developed IBD models are based on modification of intestinal epithelial cells abrogating their function in the epithelial barrier [51, 55-60] emphasizing the crucial role of the gut microbiota in intestinal inflammation. This role also manifests in the environment of the animal facility. Not only studies using different mouse strains but also studies with the same strain in different environments within a given animal facility might produce discrepant results. For example, ulcerations are reported for transfer colitis [61, 62], but never occurred in our animal facility. Hence, histopathological features listed in **Table 2** might not be fully reproduced by the experimenter using a specific model. In line with this, some mouse models did not develop colitis in a germ-free environment [63, 64] and antibiotic treatment ameliorated experimental colitis [56, 60, 65]. IBD patients have an altered composition of the gut microbiota (dysbiosis) though it is not known whether this change is cause or a consequence of the disease [66]. Due to major differences in the diet of mice and men, the human and murine gut microbiota differ with respect to the microbial genera and species as well as in ratios of the species [67]. Gnotobiotic mice reconstituted with a defined humanized microbiota are widely employed in gut microbiota research [68-71], and might be a promising tool for IBD studies. Not only humanized gnotobiotic mice are advancing but also humanized mice in which various types of human cells and tissues are engrafted. These humanized mouse models are used for the analysis of graft-versus-host disease [72], cancer [73], infection [74], arthritis [75] and most recently for autoimmune diseases [76]. A humanized IBD model was not reported, but should evolve in order to overcome the significant differences between mouse and human immunology, preventing the direct transfer of data obtained from mouse models into the human disease. These differences for example encompass the distribution of peripheral leukocytes. In mice 24-50% of the peripheral leukocytes are neutrophils as compared to 45-70% in humans [77, 78]. About 50% of intraepithelial T cells in mice are γδ T cells *versus* less than 10% in men [79, 80]. Alternatively activated macrophages in mouse but human inflammatory macrophages express the eosinophil chemotactic factor-lymphocyte CHI3L3 [81, 82]. Additionally, the following anatomical dissimilarities between mice and men can exacerbate the interpretation of histopathological findings from mouse models in the light of human IBD. A large cecum without appendix in mice does not easily compare to a small cecum with appendix in men. In mice, Paneth cells are restricted to the small intestine and the goblet cell numbers decrease from proximal to distal colon and rectum, while Paneth cells are also present in the cecum and proximal colon in humans. The villi are taller, while the muscularis mucosae are smaller in mice compared to men. The Brunner's glands in murine duodenum are restricted to the submucosa and can extend into the mucosa in men. Finally, the mouse rectum is smaller than the human rectum and prone to prolapse.

Despite considerable limitations of IBD mouse models in reflecting the complex multifactorial human diseases, they remain invaluable tools to study specifics of and therapeutic options for CD and UC. We here summarized how histomorphology can contribute to testing the validity of

an IBD model for a planned experimental setup and the experimental performance. Specifics of the histopathology in intestinal inflammation clearly help to decide for the most relevant mouse model to understand human disease.

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Disclosure of conflict of interest

None.

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