International Journal of Medical Microbiology 311 (2021) 151489

Contents lists available at ScienceDirect

International Journal of Medical Microbiology

journal homepage: www.elsevier.com/locate/ijmm

Modeling microbe-host interaction in the pathogenesis of Crohn's disease

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ARTICLE INFO

Keywords:
Inflammatory bowel disease
Crohn's disease
Microbial dysbiosis
Paneth cells dysfunction
Ileal inflammation
TNF$^{\Delta ARE}$mice

ABSTRACT

Alterations in the gut microbiota structure and function are thought to play an important role in the pathogenesis of Crohn's disease (CD). The rapid advancement of high-throughput sequencing technologies led to the identification of microbiome risk signatures associated with distinct disease phenotypes and progressing disease entities. Functional validation of the identified microbiome signatures is essential to understand the underlying mechanisms of microbe-host interactions. Germfree mouse models are available to study the functional role of disease-conditioning complex gut microbial ecosystems (dysbiosis) or pathobionts (single bacteria) in the pathogenesis of CD-like inflammation. Here, we discuss the clinical and mechanistic relevance and limitations of gnotobiotic mouse models in the context of CD. In addition, we will address the role of diet as an essential external factor modulating microbiome changes, potentially underlying disease initiation and development.

1. Introduction

1.1. Genetic and environmental triggers of Crohn's disease

Crohn's disease (CD) is one of the two main subtypes of inflammatory bowel diseases (IBD) characterized by patchy, transmural, chronically relapsing inflammation of the entire digestive tract in a discontinuous, segmental manner predominantly affecting the terminal ileum and proximal colon (Baumgart and Sandborn, 2012). Collectively, the total prevalence of IBD reached more than 6.8 million patients worldwide, with 1.5 million individuals in North America and more than 2 million in Europe (Alatab et al., 2020). The prevalence of CD is expected to increase globally due to high urbanization and the steadily rising life expectancy (Alatab et al., 2020; Ng et al., 2018, 2013).

While the understanding of CD pathophysiology substantially improved over the past decade, the causal cues responsible for the patchy initiation and progression of inflammatory responses towards the commensal gut microbiota remain poorly defined. Genome wide association studies (GWAS) have identified more than 71 susceptibility loci in the genome of CD patients (Franke et al., 2010) and 241 loci for Ulcerative Colitis (UC) and CD collectively (de Lange et al., 2017). These genetic risk loci identified various pathways involved in IBD pathogenesis, including aberrant innate immune mechanisms linked to microbial sensing and signaling, lack of adaptive mechanisms in the regulation of immune activation, intestinal epithelial cell dysfunction and barrier disruption, impaired resolution of endoplasmic reticulum (ER) stress, organelle-related unfolded protein responses (UPR) and autophagy (Graham and Xavier, 2020; Jostins et al., 2012; Liu et al., 2015). Interestingly, genes involved in microbial sensing such as nucleotide-binding oligomerization domain-containing protein 2 (NOD2), an intracellular pattern recognition receptor, have been strongly associated with IBD and mutations in NOD2 are observed in one-third of CD patients for at least one allele (Hugot et al., 2001; Ogura et al., 2001). Disruption of Paneth cell functionality affects epithelial stem cell homeostasis and anti-microbial defense in the small intestinal crypt region (Clevers and Bevins, 2013). Genetic variations in NOD2, Atg16l1, and Xbp1 support the hypothesis that disturbed Paneth cell activity contributes to the pathogenesis of CD at least in a subset of patients with ileal phenotype (Fritz et al., 2011; Khaloian et al., 2020). Phenotype mapping of IBD based on genotype association determined three groups of patients including ileal CD, colonic CD and ulcerative colitis without a link to individual disease behavior (Cleynen et al., 2016). A few monogenetic primary immunodeficiencies, including variants of the X-linked inhibitor of apoptosis protein (XIAP), are characterized by CD-like chronic inflammation often associated with severe early onset of the disease (Amininejad et al., 2018; Zeissig et al., 2015), however less than 30 % of the heritability to CD is explained by known genetic variants, emphasizing that environmental triggers play a

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https://doi.org/10.1016/j.ijmm.2021.151489
Received 14 September 2020; Received in revised form 19 January 2021; Accepted 23 February 2021
Available online 25 February 2021
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Table 1
Mouse models of CD-like ileitis.

Mouse model	Inflammation phenotype	Germ-free/antibiotic treatment	Other housing (SPF/ conventional/ex-germ free)	Paneth cell phenotype	References
$TNF^{\Delta ARE}$	Acute and chronic CD-like ileitis accompanied by extra-intestinal manifestations (skin rashes, arthralgia)	No inflammation under GF condition Antibiotic treatment ameliorated intestinal inflammation – recurrence 6-weeks after antibiotic cessation.	Disease severity correlates with changes in gut microbial community structure. Transfer of the SPF disease-associated microbial communities transmits disease in ex-germfree mice (in contrary to disease-free microbial communities)	Disease severity coupled with the loss of Paneth cell function and antimicrobial production.	(Kontoyiannis et al., 1999; Roulis et al., 2016; Schaubeck et al., 2016)
SAMP1/YitFc	Spontaneous patchy transmural inflammation resembling CD's "cobblestone lesions" in the terminal ileum develops accompanied with extra-intestinal manifestations.	GF SAMP1/YitFc mice develop chronic attenuated ileitis when compared to their SPF counterparts.	SPF-housed SAMP1/YitFc mice show spontaneous cobblestone patchy ileitis from 10 weeks of age. IL-1α blockade in SAMP1/YitFc mice ameliorates ileitis severity and is reflected in distinct microbial profiles. IL-1α blockade does not influence the ileitis severity in GF SAMP/ YitFc mice.	Expansion of epithelial cells of the secretory lineage; Paneth and goblet cells prior to inflammation and persists during the inflammation.	(Bamias et al., 2017; Menghini et al., 2019; Pizarro et al., 2011; Rodriguez-Palacios et al., 2015)
$Caspase8^{\Delta IEC}$	Spontaneous ileitis and microbiota-dependent susceptibility to colitis driven by epithelial cells necroptosis.	Spontaneous small intestinal inflammation observed and Paneth cell death under GF conditions.	SPF-housed mice develop inflammation in all parts of the intestine, whereas mice housed under conventional conditions display ileitis.	Increased Paneth cells death.	(Günther et al., 2011; Stolzer et al., 2020)
$Xbp1^{IEC-KO}$	Spontaneous enteritis is driven by ER stress, autophagy, and Paneth cell loss in addition to increased colitis susceptibility.	No ileitis was observed in germ-free housing.	A patchy inflammatory pattern in the small intestine is accompanied by Paneth cell loss and minor defect in goblet cells with no effect on enteroendocrine cells nor barrier function under GF conditions.	Absence of Paneth cells	(Adolph et al., 2013; Kaser et al., 2008)
$Atg16l1^{IEC-KO}$	Transmural ileitis at an older age (35 weeks of age) driven by ER stress sensor IrE1α.	No germ-free/ antibiotic experiments reported	An age-dependent manifestation of ileitis was recorded in $Atg16l1^{IEC-KO}$ that showed strong inflammation at 35 weeks of age when compared with $Atg16l1^{IEC-KO}$ at 10 weeks of age.	Paneth cells showed a reduction in their size and granules numbers and Lysozyme expression was reduced at 10 weeks of age.	(Adolph et al., 2013; Tschurtschenthaler et al., 2017)
$XIAP^{-/-}$	Spontaneous ileitis is characterized histologically by villous edema and an increased influx of immune cells into the lamina propria.	No germ-free/ antibiotic experiments reported	It was reported that microbial dysbiosis in $XIAP^{-/-}$ mice was characterized by a higher abundance of *Deltaproteobacteria* and an increase in mucosa-adherent bacteria.	Loss of Paneth cells.	(Gopalakrishnan et al., 2019)
$Phb1^{IEC-KO}$ or $Phb1^{PC-KO}$	Spontaneous ileitis was observed in $Phb1^{IEC-KO}$. Interestingly deletion of Phb1 from Paneth cells only was sufficient to induce ileitis.	No germ-free/ antibiotic experiments reported	Decreased microbial diversity was observed in $Phb1^{IEC-KO}$ mice compared with $Phb1^{fl/fl}$ littermates. Also, there was a significant decrease in the abundance of *Roseburia*, *Coprococcus*, *Blautia*, and *Oscillibacter*.	Aberrant Paneth cells.	(Jackson et al., 2020))
SKG	Curdlan-treated SPF SKG mice develop ileitis with extra-intestinal manifestations. Also, ex-germfree SKG mice colonized with ASF consortia develop ileitis.	GF SKG mice are free from ileitis regardless of curdlan treatment. However, it developed extra-intestinal manifestations (peripheral arthritis and spondylitis)	Ileitis development was microbiota dependent, but not arthritis as it was suppressed when SKG mice co-housed with WT mice.	No Paneth cell phenotype was reported, but a loss of goblet cells and ER stress was described in SKG mice	(Rehaume et al., 2014)
$FADD^{IEC-KO}$	Spontaneously developed enteritis with severe erosive colitis characterized by transmural inflammation and abscess formation driven by epithelial cell necrosis.	GF $FADD^{IEC-KO}$ mice showed inflammation in the small intestine but did not reveal any or histological signs of colitis.	$FADD^{IEC-KO}$ and $FADD^{FL}$ were co-housed under SPF conditions, where $FADD^{IEC-KO}$ showed spontaneous enteritis and colitis at 10 weeks of age.	Loss of Paneth cells	(Welz et al., 2011)
$SHIP^{KO}$	Spontaneous inflammation and fibrosis in the terminal ileum.	The administration of antibiotics reduced the severity of inflammation.	$SHIP^{+/+}$ and $SHIP^{-/-}$ were cohoused together in the SPF facility, where $SHIP^{-/-}$ developed inflammation at 6 weeks of age.	It was not reported any Paneth cell phenotype in this model.	(Dobranowski et al., 2019)

(*continued on next page*)

Table 1 (*continued*)

Mouse model	Inflammation phenotype	Germ-free/antibiotic treatment	Other housing (SPF/ conventional/ex-germ free)	Paneth cell phenotype	References
			$SHIP^{-/-}$ showed distinct microbial profile in the ileal compartment, but not fecal.		
$AGR2^{KO}$	Severe terminal ileitis and colitis	No germ-free experiments were reported for this mouse model	Mice demonstrated severe ileitis phenotype and less inflammation in the colon coupled with the disruption of the Paneth and goblet cells homeostasis driven by elevated ER stress.	Increase of Paneth cell compartment and abnormal Paneth cell localization was demonstrated	(Zhao et al., 2010)
$Nemo^{IEC-KO}$	Spontaneous severe chronic intestinal inflammation in the colon and milder inflammation in the ileum.	GF $NEMO^{IEC-KO}$ showed ileitis, but with reduced IEC apoptosis and tissue damage in ileal crypts, when compared to their SPF housed counterparts. Interestingly, it did not develop colitis and showed reduced numbers of apoptotic colonic IEC.	Under SPF conditions, $NEMO^{IEC-KO}$ showed ileitis characterized by mild immune cells infiltration, but without any epithelial erosion. However, it developed spontaneous colitis that depends on Myd88 and TNFR1 signaling.	Paneth cell numbers and functions were strongly reduced.	(Nenci et al., 2007; Vlantis et al., 2016)

dominant role in the etiology of IBD (Kaplan, 2015; Renz et al., 2011). The potential role of adverse environmental factors is further supported by low concordance rates in CD monozygotic twins (Halfvarson et al., 2003) and increased incidence of IBD in first-generation immigrants (Benchimol et al., 2015). Additionally, IBD-related genetic variants substantially penetrate healthy populations (Knights et al., 2013). Given that most IBD-related mouse models are disease-free under germ-free (GF) conditions, and that the re-introduction of distinct microbial communities is capable of driving disease pathology in these models, the complex interaction of gut microbiota with host genetic-susceptibility evolved as a central theme in the pathogenesis of IBD (Hörmannsperger et al., 2015).

1.2. Perturbations of microbe-host mutualism in CD

Parallel to understanding the mechanisms of microbe-host interactions, the vast advancement of high-throughput sequencing technologies allowed the identification of microbiome risk signatures linked to distinct disease phenotypes (Lloyd-Price et al., 2019; Pascal et al., 2017; Yilmaz et al., 2019), response to therapy (Ananthakrishnan et al., 2017; Metwaly et al., 2020) and geographic distribution of disease manifestation (Rehman et al., 2016). Although large population studies identified a remarkable variability of the human gut microbial community (He et al., 2018; Reitmeier et al., 2020), only 15–20 % of this variation is explained by host or environmental factors, such as genetics, physiology, diseases, geographic region, diet or medication. From an ecological standpoint, some of these alterations can be viewed in the context of transient adaptations, including diurnal fluctuations of bacterial abundance and activity (Reitmeier et al., 2020), with a high degree of resilience in the microbial communities of a healthy host. However, emerging evidence suggests that persistent perturbations of microbial communities (also often referred to as dysbiosis) are causally linked to a distortion of microbe-host homeostasis and human health (Ianiro and Hansen, 2018; Sartor and Mazmanian, 2012).

Faecal stream diversion and antibiotic treatment in subsets of patients with active CD provided first clinical evidence for a central role of bacteria in the pathogenesis of this chronic inflammatory disorder (Perencevich and Burakoff, 2006; Rutgeerts et al., 1991). Following these first observations, multiple cross-sectional studies on CD and UC patients confirmed significant microbial shifts throughout the course of the disease. Overall reduction of microbial community richness and diversity, together with an inversed *Firmicutes/Bacteroidetes* ratio and a remarkable increase in *Gammaproteobacteria* have been consistently reported (Gevers et al., 2014; Pascal et al., 2017). More specifically, the relative abundance of certain bacterial taxa known to exert beneficial functions for the host was found to be reduced in IBD patients. For instance, a reduction of *Faecalibacterium prausnitzii*, *Roseburia hominis*, *Bifidobacterium adolescentis*, *Clostridiales* and *Bacteroidales* were reported in IBD patients (Joossens et al., 2011; Quévrain et al., 2016; Sokol et al., 2008a). Conversely, an increase in the relative abundance of pathobionts belonging to *Enterobacteriaceae*, *Fusobacteriaceae*, *Veillonellaceae*, and *Pasteurellaceae* were described (Frank et al., 2007; Gevers et al., 2014; Pascal et al., 2017; Strauss et al., 2011). Besides bacterial dysbiosis, IBD patients showed fungal microbiota dysbiosis characterized by alterations in community diversity and composition, suggesting potential role of fungi in IBD pathogenesis. (Sokol et al., 2017). It was also reported that the ileal phenotype of CD is associated with an increased prevalence of invasive *Escherichia coli* (AIEC) (Baumgart et al., 2007; Darfeuille-Michaud et al., 2004; Lapaquette et al., 2010), but colonic CD showed higher levels of *Faecalibacterium*, unidentified *Ruminococceae* and *Clostridiales* (Naftali et al., 2016). In line with this high level of diversity, only few species were identified to be shared within different IBD studies (Schirmer et al., 2019), suggesting individual differences within similar CD phenotypes and disease courses (Metwaly et al., 2020). Intriguingly, assessment of intra-species resolution showed an increased strain diversity of potentially pathogenic species and, on the contrary, a reduced strain diversity in beneficial species in stool samples from patients with IBD or irritable bowel syndrome (IBS) compared with healthy controls (Vich Vila et al., 2018). These findings emphasize that strain-resolved metagenomic analyses are essential to connect intra-species variants to disease phenotypes (De Filippis et al., 2019; Metwaly and Haller, 2019).

The need to define the functional relevance and specificity of single bacteria (pathobiont) (Buttó et al., 2015; Jochum and Stecher, 2020) or dysfunctional bacterial networks (dysbiosis) (Buttó and Haller, 2016; Dalal and Chang, 2014) is indispensable to develop a mechanistic understanding of microbe-host interactions in the pathogenesis of IBD. At present, the implementation of germ-free IBD-related mouse models is of great relevance in dissecting the complex interplay between microbes and the genetically susceptible host. Under gnotobiotic conditions, the mouse models are selectively colonized with single bacterial strains, minimal bacterial consortia or defined complex gut microbial ecosystems from human stool or other donor material. In this context, we recently showed that humanized mice captured key features of the patient-specific microbial dysbiosis, and reproducibly transferred the different disease states into GF IL10-deficient mice after colonization with CD-derived stool microbiota (Metwaly et al., 2020). These findings show that despite the known limitation of incomplete human bacterial transfer into GF mice (Walter et al., 2020), humanized mice could be used as a tool for functional validation of bacterial communities in vivo.

Table 2
Histological and Immunological features of Crohn's disease in human and commonly used mouse models.

	Endoscopy and histological presentation	Immunological phenotype	Epithelial alterations	Microbiota dysbiosis	Extra-intestinal manifestations	References
Feature description in CD patients	- Patchy, discontinuous, transmural inflammatory infiltrates with independent granulomas and irregular crypts. - Protruding cobblestones lesions over the gut mucosa. - Complications over time such as abscesses, fistulas, or strictures.	- Th1 and Th17 immune response characterized by high production of TNF-α, IL-1ß, IL-6, IFNɣ, IL-22, and IL-17 among other cytokines in the mucosa - Reduced numbers of Treg in the peripheral circulation - Increased numbers of innate immune cells such as neutrophils, mature DCs, ILCs, and macrophages.	- Paneth cells loss and dysfunction - Impaired epithelial and tight junction barriers - Aberrant goblet cell numbers and function (ileocolonic CD) - Reduced intestinal epithelial stem cells	- Microbial dysbiosis is a disease hallmark characterized by a reduction of community diversity and an increase of specific taxa such as *Enterobacteriaceae* or *Fusobacteriaceae* and reduction of beneficial ones such as *Faecalibacterium*, and Bifidobacterium.	Extra-intestinal manifestations such as arthritis, ankylosing spondylitis, and psoriasis.	(Annunziato et al., 2007; Baumgart and Sandborn, 2012; Bernink et al., 2013; Brand et al., 2006; Eastaff-Leung et al., 2010; Geremia et al., 2011; Gevers et al., 2014; Haberman et al., 2019; Hart et al., 2005; Kamada et al., 2008; Khaloian et al., 2020; Middel et al., 2006; Sokol et al., 2008; Torres et al., 2017; Vavricka et al., 2011; Zeissig et al., 2007; Zhou and Liu, 2017)
Examples of mouse models showing similar phenotype	- $TNF^{\Delta ARE}$, SAMP1/YitFc, $Atg16l1^{IEC-KO}$, and $FADD^{IEC-KO}$ - SAMP1/YitFc - Some SAMP1/YitFc mice showed perineal fistulas and stricture phenotype	Most available mouse models	$TNF^{\Delta ARE}$, $Caspase8^{\Delta IEC}$, $Xbp1^{IEC-KO}$, $Atg16l1^{IEC-KO}$, $FADD^{IEC-KO}$, $NEMOI^{EC-KO}$, $Phb1^{\Delta PC}$, and $Xiap^{-/-}$ - SAMP1/YitFc - $TNF^{\Delta ARE}$	Germ free $TNF^{\Delta ARE}$, SKG, and $Xbp1^{IEC-KO}$ showed no ileitis phenotype.	$TNF^{\Delta ARE}$, SAMP1/YitFc, and SKG mice	(Adolph et al., 2013; Khaloian et al., 2020; Pizarro et al., 2011; Rehaume et al., 2014; Rodriguez-Palacios et al., 2015; Schaubeck et al., 2016; Tschurtschenthaler et al., 2017; Welz et al., 2011)

Using a toolbox of multi-omics technologies, a network of interacting bacterial taxa and metabolites involving sulfur metabolism was identified to be linked to progressive disease in CD patients after autologous hematopoietic stem cell transplantation (Metwaly et al., 2020).

1.3. Mouse models of CD-like ileal inflammation

Numerous mouse models are currently available to study molecular mechanisms of IBD. However, most of these models are suitable to study chronic colonic inflammation (colitis) (Hörmannsperger et al., 2015) and only a few models develop CD-like inflammation resembling the transmural ileal pathology frequently seen in CD patients (Table 1). Most of these models are generated by either chemical or immunologic manipulation, or genetic modification, and thus do not ideally mirror the spontaneous and multifactorial nature of human CD (Cominelli et al., 2017; Mizoguchi et al., 2020). Genetically engineered mouse models mostly represent specific aspects of the clinical phenotype or mechanism of the human disease. As such, these models can be extremely useful for understanding the functional role of a specific gene mutation in IBD. Targeted mouse models include $Caspase8^{\Delta IEC}$, $FADD^{\Delta IEC}$, $NEMO^{\Delta IEC}$, $Xbp1^{\Delta IEC}$ and $Atg16l1^{\Delta IEC}$ with often conditional deletions of death-related, ER stress or autophagy mediators in intestinal epithelial cells (IEC). In addition, mouse models with gene mutations involved in tumor necrosis factor (TNF) and PI3K signaling ($TNF^{\Delta ARE}$ and $SHIP^{-/-}$) developed CD-like inflammation, suggesting that a variety of different pathways contribute to the pathology in the ileum (Cominelli et al., 2017). For instance, the SAMP1/Yit mouse strain develops spontaneous ileal inflammation resembling histologic features of human CD. A genome-wide scan of SAMP1/YitFc mice identified four susceptibility loci on chromosomes 9, 6, and X, which are linked to epithelial and immunological functions (Kozaiwa et al., 2003). In humans, chronic and progressive gut inflammation leads to patchy, discontinuous, transmural ileal inflammation characterized by protruding lesions resembling 'cobblestones' over the gut mucosa (Rodriguez-Palacios et al., 2015). CD patients might additionally show extra-intestinal manifestations, such as arthritis, ankylosing spondylitis, and psoriasis, some of which have been reported in CD-relevant mouse models (Kontoyiannis et al., 2002; Pizarro et al., 2003; Rodriguez-Palacios et al., 2015). Together, SAMP1/YitFc and $TNF^{\Delta ARE}$ mice represent two of the most important models to study the development of non-infectious, CD-like inflammation (Table 2).

1.4. Pros and cons of mouse models for studying CD-like ileitis

Among the rarely available mouse strains modelling ileal inflammation, SAMP/Yit and $TNF^{\Delta ARE}$ mice show remarkable similarities to CD-like ileitis, making them extremely useful in modelling human CD. In contrast to the genetically engineered $TNF^{\Delta ARE}$ mouse model of tumor necrosis factor overexpression, the SAMP1/YitFc inbred mouse strain develops spontaneous ileal inflammation without exogenous manipulation. Both mouse strains show patchy inflammation localized mostly to the terminal ileum, transmural intestinal inflammation, with the presence of mucosal and submucosal granulomas. However, in contrast to SAMP1/YitFc mice, $TNF^{\Delta ARE}$ mice do not show the characteristic mucosal cobblestone structure, frequently seen in CD patients. Ileal inflammation in SAMP1/YitFc mice originates from a non-hematopoietic source and is characterized by epithelial barrier disruption followed by downstream mucosal inflammation. In contrast $TNF^{\Delta ARE}$ mice, SAMP1/YitFc mice show alterations in epithelial cell function, where the expansion of Paneth cells is evident before the onset of gut inflammation and persists through disease manifestation (Pizarro et al., 2011). We previously suggested that stochastic occurrence of focal lesions in the intestinal epithelium generates local sites of erosions that allow bacterial translocation and subsequent inflammation in $TNF^{\Delta ARE}$ mice (Buttó and Haller, 2017). Of note, the role of dysbiotic microbial communities in driving disease was only demonstrated in $TNF^{\Delta ARE}$ mice, which remained disease-free under GF housing conditions (Schaubeck et al., 2016), making them particularly relevant for studies aiming at the identification of microbial aggressive traits and underlying microbe-host interactions. In this review, we focus on the $TNF^{\Delta ARE}$ mouse model as a

CD-like ileitis mouse model driven by gut microbial alterations.

$TNF^{\Delta ARE}$ mice bear a targeted deletion of a 69 base pair region of the adenosine-uracil (AU)-rich elements (ARE) in the 3′- untranslated region of the TNF-encoding gene. The resulting aberrant TNF production due to enhanced TNF mRNA stability leads to the development of spontaneous joint and gut-associated immune pathologies (Baur et al., 2011; Kontoyiannis et al., 1999; Schaubeck et al., 2016). Interestingly, the selective overexpression of TNF in the intestinal epithelium is sufficient to trigger CD-like ileitis (Roulis et al., 2011), supporting the important role of the epithelium in the pathogenesis of ileal inflammation in $TNF^{\Delta ARE}$ mice. Tissue pathology of $TNF^{\Delta ARE}$ is characterized by progressive diffuse inflammation with transmural involvement that extends into the muscular layer involving CD8αβ+ intraepithelial lymphocytes (IEL) and a Th1-driven immune activation (Apostolaki et al., 2008; Chang et al., 2012; Ivanov et al., 2009; Roulis et al., 2011). Progressive pathology results in complete loss of villous structures and granulomas with extensive immune cell infiltration in aging mice. Interestingly, TNF-driven pathology follows a gene dosage effect, where homozygous mice show rapid and severe wasting and die within 1–3 months of age, while heterozygous littermates show slower onset of disease and develop severe ileal inflammation at 8 weeks of age. In support of $TNF^{\Delta ARE}$ mice relevance to human disease, TNF neutralizing antibodies used for the treatment of CD patients could ameliorate inflammation in $TNF^{\Delta ARE}$ mice (McNamee et al., 2013).

1.5. Paneth cells defects in CD: key target of underlying pathology

Several lines of evidence suggest that dysfunctional or loss of Paneth cells play an important role in ileal CD pathology specifically linked to NOD2 mutations (Hugot et al., 2001; Wehkamp et al., 2005) and microbial community alterations (Liu et al., 2016). Paneth cell alterations were also linked to autophagy and ER stress-related mechanisms (Adolph et al., 2013; Cadwell et al., 2008). We have previously shown that TNF-driven inflammation in $TNF^{\Delta ARE}$ mice is characterized by the loss of lysozyme-positive Paneth cells, subsequent to but not preceding the onset of ileal inflammation, suggesting epithelial re-modeling rather than Paneth cell-specific apoptosis (Khaloian et al., 2020; Schaubeck et al., 2016). In this context, we also showed that impaired mitochondrial function is linked to CD-associated loss of stemness and the generation of dysfunctional Paneth cells in $TNF^{\Delta ARE}$ mice. The translational importance of these findings in relation to the human disease was demonstrated in ileal tissue biopsies from patients being predictive for post-surgical recurrence of CD (Khaloian et al., 2020). Notably, GWAS identified several IBD-associated genetic risk factors that are involved in regulating UPR and organelle stress (Rath et al., 2018). For example, mutations in genes including (XBP1 (endoplasmic reticulum (ER) stress response), IGRM and ATG16L1 (autophagy), or NOD2 (bacterial sensing) impair Paneth cell functionality, anti-microbial peptides (AMP) production and bacterial evasion (Adolph et al., 2013; Cadwell et al., 2008; Kaser et al., 2008). In line with these findings, CD patients with ileal phenotype exhibit reduced levels of AMP, for example alpha-defensin (Wehkamp et al., 2005), which has been linked to reduced numbers of segmented filamentous-bacteria (SFB) (Salzman, 2010)., a mucosal adherent bacterium involved in ileal inflammation Taken together, these observations put Paneth cells forward as a key target to understand Crohn's disease underlying pathology.

1.6. Microbiota-related mechanisms of ileal inflammation

The presence of commensal bacteria proved to induce ileal inflammation in several models, including $TNF^{\Delta ARE}$, SKG and $Xbp1^{IEC-KO}$ (Adolph et al., 2013; Rehaume et al., 2014; Roulis et al., 2016; Schaubeck et al., 2016). In the frame of this Priority Program, we showed that GF $TNF^{\Delta ARE}$ mice are completely disease-free, and following Koch's postulates, the transmission of disease-associated dysbiotic gut microbial communities re-established CD-like inflammation in these mice. These results emphasize the essential role of gut bacteria *per se* and demonstrate the functional importance of disease-associated dysbiosis in the pathogenesis of ileal inflammation (Schaubeck et al., 2016). Interestingly, $TNF^{\Delta ARE}$ mice kept under specific pathogen-free (SPF) conditions developed inflammation at 18 weeks of age with a gradient of disease activity including few mice without any sign of inflammation despite their genetic susceptibility (non-responder mice). Microbiota profiling using 16S rRNA amplicon sequencing revealed a clear separation of bacterial communities, with a strong correlation to disease severity. The functional relevance of dysbiotic gut microbial communities in the initiation of disease has been confirmed in a set of experiments, where distinct microbial communities have been transplanted into GF $TNF^{\Delta ARE}$ mice. Most importantly, disease-associated microbiota induced transmissible CD-like ileitis in ex-GF $TNF^{\Delta ARE}$ mice, while the transfer of non-responder microbiota failed to induce disease, supporting the concept of specific, disease-triggering microbial communities in CD. Analysis of differentially abundant bacterial species identified distinct molecular taxa (operational taxonomic units; OTUs) that correlate positively or negatively with disease severity. In search of single bacterial strains capable to induce CD-like ileitis in $TNF^{\Delta ARE}$ mice, *Alistipes spp.* were found to correlate positively with enhanced inflammation in responder mice. However, mono-association of GF $TNF^{\Delta ARE}$ mice with *Alistipes spp* (unpublished data) or *Escherichia coli LF82* (Schaubeck et al., 2016), as a potential pathobiont in human CD, failed to induce inflammation. In this context, the isolation and identification of disease-relevant bacterial taxa is of paramount importance with the aim of having cultured bacteria for further functional validation *in vivo*.

Given that the intestinal epithelium is the first line of defense against luminal microbial stimuli (Clavel and Haller, 2007; Stange and Schroeder, 2019), bacteria residing in close contact to the intestinal mucosa have been of great interest (Conte et al., 2006; Donaldson et al., 2016; Mann et al., 2014). Research efforts in our laboratory have focused on the isolation and identification of mucosa-associated bacteria from inflamed ileal samples obtained from $TNF^{\Delta ARE}$ mice (Clavel et al., 2009; Kläring et al., 2013). The generation of potential disease-causing or disease-free minimal bacterial consortia could facilitate the study of molecular mechanisms underlying microbe-host interactions. In this aspect, we previously proposed "disease-related" and "disease-unrelated" bacterial taxa based on experimental antibiotic treatment in $TNF^{\Delta ARE}$ mice (Schaubeck et al., 2016). To assess changes in microbiota biodiversity and composition, we performed a 16S rDNA-based high-throughput sequence analysis of ileal mucosa and cecal content from antibiotic treated and control $TNF^{\Delta ARE}$ mice Expectedly, microbiota profiling revealed a significantly reduced bacterial diversity and altered microbiota composition in the antibiotics treated animals. Here, we identified six genera that correlated with the disease-free phenotype of antibiotic treated $TNF^{\Delta ARE}$ mice. Three genera (*Oscillobacter*, *Alistipes, Rikinella*) showed reduced relative abundance under antibiotic treatment, and were referred to as "disease-related" bacteria. On the other hand, *Lactobacillus*, *E. coli*, *Akkermansia* showed an increased relative abundance under antibiotic treatment, and were referred to as "disease-unrelated" bacteria. To assess the functional relevance of disease-related bacterial strains in initiating CD-like ileitis, we tested the pathogenic role of *Alistipes spp*. by means of mono-association experiments in GF $TNF^{\Delta ARE}$ mice. However, it showed no impact on disease initiation, and the mice remained disease-free. To test the role of *Lactobacillus spp*. with respect to their ability to prevent recurrent CD-like ileitis, we inoculated antibiotic treated $TNF^{\Delta ARE}$ mice with the probiotic *Lactobacillus murinus*, however it showed no impact on reversing inflammation (Unpublished data).

1.7. Dissecting the role of pathobiont-driven CD-like inflammation

While our data clearly demonstrated the importance of dysbiotic microbial communities in initiating CD-like inflammation in $TNF^{\Delta ARE}$ mice, specific aggressive bacterial traits and host related mechanisms

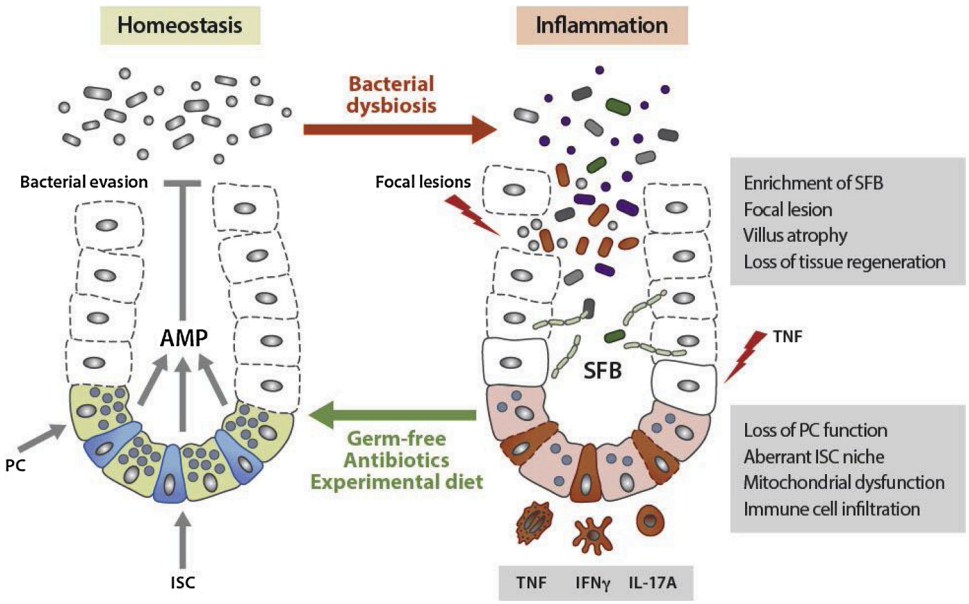

Fig. 1. Host and microbial (mechanisms) drivers of CD-like inflammation in TNF $^{\Delta ARE}$ mouse.
Under homeostatic conditions, Antimicrobial peptides (AMPs) produced by Paneth Cells (PC) at the crypt base avert the luminal bacteria from interacting with the surface of the Inter-epithelial cells (IECs). Few pathobionts such as segmented filamentous bacteria (SFB) can breach the mucus barrier and interact with the IECs. Stochastic appearance of focal lesions in the intestinal epithelium creates local sites of inflammation in a genetically susceptible host. TNF-driven inflammatory milieu drives dysbiotic luminal gut bacterial of varying complexity (complex to single pathobionts) to evade host defense mechanisms and promote pro-inflammatory signals and subsequent tissue pathology. CD-like ileitis precedes loss of Paneth cells function in TNF^{DARE} mouse model. Impaired mitochondrial function was shown to control loss of stemness and the generation of dysfunctional Paneth cells. Antibiotic treatment, as well as semi-synthetic diet (as an analogue for exclusive enteral nutrition in CD patients) ameliorates inflammation leading to resolution of epithelial injury leading to tissue homeostasis.

driving disease initiation and progression in this model are still unclear. TNF$^{\Delta ARE}$; Myd88$^{-/-}$ mice show an attenuated inflammatory phenotype compared to TNF$^{\Delta ARE}$ littermates under SPF conditions, supporting microbial triggers to be involved in the initial activation of TNF-mediate tissue pathology. Mucosa-associated microbial communities of TNF$^{\Delta ARE}$ mice are characterized by the expansion of segmented filamentous bacteria (SFB) (Roulis et al., 2016). Of note, Casp8$^{IEC\text{-}KO}$ mice developed ileal inflammation under GF conditions, suggesting that increased SFB levels under normal housing condition are a consequence rather than cause of inflammation (Stolzer et al., 2020). SFB are spore-forming, anaerobic commensal bacteria of the phylum Firmicutes that attach mainly to the ileal mucosa at the time of weaning and are responsible for the regulation of immune cell differentiation, including IL-17 producing innate and adaptive lymphocytes (Al Nabhani et al., 2019; Gaboriau-Routhiau et al., 2009; Lécuyer et al., 2014; Schnupf et al., 2015). SFB have been shown to colonize the small intestine of many species, including humans (Klaasen et al., 1993). More recently it was reported that biopsies from the terminal ileum of UC patients showed higher SFB load during active disease when compared with healthy controls (Finotti et al., 2017). In mice, SFB contribute to mucosal immune maturation via inducing Th17 differentiation, secretory immunoglobulin A (IgA) production, and antimicrobial peptides secretion (Ivanov et al., 2009; Suzuki et al., 2004). Further,they protect against some pathogens such as *Citrobacter rodentium* or *Salmonella typhimurium* (Edelblum et al., 2017; Gaboriau-Routhiau et al., 2009; Ivanov et al., 2009; Lécuyer et al., 2014). However, SFB mono-colonization in 2 different mouse models of multiple sclerosis and arthritis induced the respective disease phenotypes, while their germ-free counterparts revealed mild disease activity (Lee et al., 2011; Wu et al., 2010), suggesting a pathogenic role of SFB under certain conditions. Further, SFB were reported to induce colitis in a murine model of T cell transfer into SCID mice, however mono-association of GF mice with SFB did not lead to a disease phenotype (Stepankova et al., 2007). In TNF$^{\Delta ARE}$ mice, we identified a novel pathogenic role of SFB mono-association in driving severe ileo-colonic disease characterized by the loss of Paneth and goblet cell function (Calasan et al., 2019). In complex microbial conditions, SFB abundance correlate strongly with the severity of inflammation. Conversely, SFB does not seem to play a role in the IL10-defecient mouse model of chronic colitis. Parallel to high tissue levels of TNF and IL-17, SFB-mediated inflammation was associated with neutrophil infiltration and the expansion of IFNγ expressing Th1 cells in the mucosa. (Metwaly et al., Manuscript in preparation). Collectively, these data suggest that SFB acts as a double-edged sword, capable of promoting mucosal barrier integrity and mucosal immune homeostasis, but also act as a pathobiont, depending on the host genotype and potentially other environmental factors.

1.8. Dietary interventions in CD – the exclusive enteral nutrition (EEN) case

Several longitudinal studies from various cohorts proposed specific dietary patterns to be associated with IBD, including higher consumption of sugar and animal fat as well as a reduced vegetable intake (Ananthakrishnan et al., 2014, 2013; Racine et al., 2016). Consistent with these findings in human cohorts, we showed in mouse experiments that high-fat diet disrupts the barrier function, aggravates inflammation, and induced substantial shifts in the gut microbiota composition in TNF$^{\Delta ARE}$ mice, independent of the metabolic effects of obesity (Gruber et al., 2013). Similarly, iron, and sulfur-containing amino acids typically found in meat stand as risk factors for IBD. In this context, we previously showed that deprivation of oral iron intake in TNF$^{\Delta ARE}$ mice prevented ileitis development (Werner et al., 2011). This protective effect correlated with changes in microbiota profiles in TNF$^{\Delta ARE}$ mice confirming iron replenishment studies in IBD patients (Lee et al., 2017).

Exclusive enteral nutrition (EEN) is one of the most effective ways to treat pediatric CD, capable of inducing remission, mucosal healing, and nutritional enhancement. At present, EEN is the first line of therapy in Europe for pediatric CD (Day and Lopez, 2015; Grover et al., 2014; Ruemmele et al., 2014). EEN is a liquid-based diet that is provided either in elemental, semi-elemental, or polymeric formula, which is given to patients to be their sole source of energy for weeks. Genetic and environmental triggers of Crohn's disease in gut microbiota composition upon EEN therapy have been demonstrated, suggesting EEN as an effective dietary intervention ameliorating inflammation through gut microbiota modulation (Lewis et al., 2015; Schwerd et al., 2016). Consistent with the impact of EEN on gut inflammation in pediatric CD patients, we showed that semi-synthetic experimental diet prevented the development of CD-like ileitis in TNF$^{\Delta ARE}$ mice (Wagner et al., 2013)

Interestingly, dietary intervention using semi-synthetic experimental diet eradicates mucosal SFB and ameliorate inflammation in SFB-mono-associated TNF$^{\Delta ARE}$ mice, suggesting a role of microbiome modulation through controlling SFB-mediated immune regulation (Metwaly et al., Manuscript in preparation). Collectively, these data demonstrate the role of diet as a key environmental factor that targets CD-driving inflammatory mechanisms in the host, either directly or indirectly via changes in the structure and function of the gut microbiota (Schaubeck and Haller, 2015).

2. Conclusion

The development of numerous mouse models of intestinal inflammation has allowed significant progress in understanding the underlying etiology of chronic intestinal inflammation. Each of these models is suitable to address different host or microbiota-related mechanisms. Perturbations of a tightly controlled symbiotic relationship between the microbiota and host potentially leads to bacterial dysbiosis and gut inflammation. High-throughput sequencing of microbial communities confirmed that changes in gut microbiota structure and function can highly impact human health associated with a variety of pathologies, including ileal inflammation in CD. To better understand the pathologic role of single pathobionts and complex microbial communities, gnotobiotic mouse models are indispensable to dissect the functional relevance of gut microbiota to disease initiation and progression. In this Priority Program (SPP 1656), we generated GF TNF$^{\Delta ARE}$ mice and identified mechanisms related to the expansion of pathobionts in a highly dysbiotic microbiota to be critically relevant for the development of CD-like inflammation (Fig. 1) (Buttó and Haller, 2016; Hiergeist et al., 2016; Khaloian et al., 2020; Lengfelder et al., 2019; Metwaly et al., 2020; Rausch et al., 2016; Schaubeck et al., 2016).

Author contributions

All authors listed have made substantial, direct, and intellectual contribution to the work, and approved it for publication.

Funding

Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Priority Program SPP1656.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

None.

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