10

Animal Models of Colitis: Lessons Learned, and Their Relevance to the Clinic

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1. Introduction

The term 'Inflammatory Bowel Disease' (IBD) refers to conditions characterized by chronic inflammation of the gastrointestinal tract, including ulcerative colitis (UC) and Crohn's disease (CD). UC and CD have distinct pathologic features, for example the location, depth and severity of inflammation. For UC, inflammation is confined to the colon and rectum, is continuous, and is superficial, affecting only the mucosal layer of the intestinal wall. In contrast, the inflammation seen in CD can affect any part of the gastrointestinal tract from mouth to anus, is typically discontinuous or 'patchy', and involves all layers of the intestinal wall (Abraham and Cho, 2009). In spite of these differences, there is also overlapping pathology, suggesting some common causal factors and potential treatments.

The exact cause of IBD is still unclear, although it appears to involve a complex interaction between genetic susceptibility and environmental triggers including the resident microbial population of the intestinal tract (Abraham and Cho, 2009). The gastrointestinal tract uses a system of tolerance and controlled inflammation to limit the response to dietary or bacterially-derived antigens in the intestinal tract. When this complex system breaks down, either by a chemical or pathogenic insult in a genetically predisposed individual, the resulting innate immune response may lead to IBD. Although the aetiopathogenesis of IBD remains unsolved, current evidence indicates that increased activation of T cells, and an imbalance of Treg and Th1, Th2 and Th17 cells play important roles (Sanchez-Munoz et al., 2008). Activation of macrophages also seems to be important, with increased production of the macrophage-derived cytokines such as TNF-alpha, IL-1 and IL-6 contributing to the observed inflammation. The triggering factor(s) are still to be elucidated, although host response to microbial pathogens includes self-defense mechanisms including defensins, pattern recognition receptors and Toll-like receptors; this suggests there may be an element of "self" recognition triggering the immune response (Strober et al., 2002). Neuroimmunomodulation in IBD is another interesting possible mechanism with its

implications relating to the influence of the brain-gut axis on the perpetuation of intestinal inflammation (Tsianos and Katsanos, 2009).

Evidence for a genetic component comes from various sources such as twin studies and familial aggregation, which suggest that CD has a stronger genetic component than UC (Halfvarson et al., 2003). A number of genome-wide association studies (GWAS) have also identified several key gene variants which occur at a higher rate in people with IBD compared with controls who do not have any gastrointestinal symptoms (Barrett et al., 2008). These findings have led to significant recent progress in the understanding of the genetic component of IBD. Relevant genes and pathways have been well characterized for CD, such as innate immunity, adaptive immunity, and more recently autophagy (Massey and Parkes, 2007; Van Limbergen et al., 2009). The part played by autophagy had not been recognized prior to the comprehensive GWAS data, but these data have allowed research to focus on this pathway with a resultant significant increase in understanding of how it may contribute to IBD pathogenesis (Brest et al., 2010). There is also overlap with other diseases, particularly auto-immune diseases, showing genetic variants in the same pathways (Lees et al., 2011).

The genetic component of UC is less well understood than CD, but it seems likely that variants in mucosal barrier function genes (ECM1, CDH1, HNF4α, and laminin B1) are associated with increased risk of UC, and impaired IL10 signalling appears to be a key pathway in intestinal inflammation (Thompson and Lees, 2011). It has been observed that there are currently ninety nine published IBD susceptibility loci (Lees et al., 2011), and genetic variants contributing to both CD and UC have recently been reviewed (Paul et al., 2011).

Recent advances in understanding the genetic contribution to IBD have served to highlight the genetic complexity of the disease, as reflected by the large number of genes potentially implicated in disease pathogenesis or risk. The analysis becomes more complex as risk genes for one ethnic group may not be replicated in another. This has been shown several times, with gene variants identified in populations of European origin showing only limited agreement in, for example, North Indian (Juyal et al., 2011), Indian (Mahurkar et al., 2010), and Japanese (Nakagome et al., 2010) population groups. A combination of the genetic and pathological complexity has contributed to the relatively poor understanding of IBD. The widely varying phenotype suggests many different pathways for the disease, but attempts to sub-classify CD and UC in clinical terms have only been partially successful. This lack of clarity in clinical classification has hampered attempts at genotype-phenotype associations, which has in turn contributed to difficulties in establishing appropriate clinical interventions.

Recent studies have highlighted the relationship between disease and the intestinal microbiota, with the suggestion that an inappropriate immune/inflammatory response to normal intestinal bacteria may be a key triggering factor (Nell et al., 2010). Environment may also play an important role, with diet in particular having an influence, if not in the initiation of the disease, then certainly in the maintenance and/or amelioration of disease symptoms. As part of a long-term research project (Nutrigenomics New Zealand (NuNZ); www.nutrigenomics.org.nz) we have identified a number of foods which are perceived by people with IBD as being either detrimental or beneficial in terms of managing the symptoms of both CD and UC (Petermann et al., 2009b) or show evidence of ameliorating intestinal inflammation in animal studies (Knoch et al., 2009; Nones et al., 2009; Knoch et al., 2010).

There is a very real importance in seeking answers to the effective treatment of IBD because it is such a debilitating condition, and its prevalence is increasing (Cosnes et al., 2011). There is reduced quality of life from continuing disease activity and significant long-term complications that develop with persistent intestinal inflammation. There is clearly an as-yet

unmet clinical need due to limitations of current treatments. These tend to rely on the use of non-specific anti-inflammatory agents (such as 5-aminosalicytic acid and corticosteroids) and immunosuppressive drugs that may cause severe side effects, and in a significant percentage of the patients do not provide appreciable benefits (Grimm, 2009). Other approaches such as targeted interruption of the inflammatory cascade using anti-TNF monoclonal antibodies have been very successful, but greater understanding of the inflammatory process is required to identify other pivotal points in the relevant pathways that may be blocked by similar monoclonal antibodies. Surgical removal of diseased portions of the gastro-intestinal tract can be effective but highlights the failure of medical treatment to prevent the long-term consequences of chronic inflammation.

IBD may represent a heterogenic group of diseases that share similar pathologies and mechanisms of tissue damage, but are initiated by different events and characterized by a variety of immune abnormalities (Tsianos and Katsanos, 2009). A variety of mouse models of IBD have been used. This chapter will discuss if this represents the complexity and heterogeneity of IBD or if the multiple models simply reflect the failure of any one model to truly recreate the human disease. Research using these models has attempted to better understand disease pathogenesis and treatment, and to investigate the complex interactions that may be contributing to the pathogenesis. A better understanding of all these factors will provide new insights into the mechanisms by which intestinal inflammation is inappropriately triggered, and provide new targets for medical therapies.

In this chapter, we will review some of the key animal models used in IBD research, consider some of the findings from this research, and finally and most importantly discuss whether these research findings are being applied in a clinical setting to make a real impact for people with IBD.

2. Animal models of IBD

Animal models of IBD have been used for over fifty years. Early models resulted from the observation that a variety of laboratory animals fed extracts from certain species of seaweed displayed similar symptoms to human IBD (Marcus and Watt, 1969). Subsequent refinement and development of this model led to a variety of chemically-induced models. More recently, gene variants relevant to IBD have been incorporated into animal models (primarily mice and rats) and these have been used extensively (Jurjus et al., 2004). These models have recently been comprehensively reviewed in the context of the role of intestinal bacteria in the development of IBD (Nell et al., 2010).

Clinical features in animal models that are of relevance to human IBD include weight loss, anaemia, diarrhoea, visible or occult blood, and sometimes mucus in the faeces. Pathologically there are similarities such as ulceration of variable extent and largely confined to the mucosa, some loss of haustration (i.e., disappearance of the horizontal folds of the colon), granularity of the mucosa along with pseudo-polyps and polypoidal formations (UC features), as well as strictures leading to intestinal obstruction (a feature of CD). Histological features in common are acute, subacute, and chronic inflammatory changes in the mucosa, with occasional crypt abscesses and cystic dilatation or distortion of mucosal glands, mucosal ulceration in various stages of progression and healing, and hyperplastic changes of the glandular epithelium.

Animal models of IBD have significant advantages – one can investigate not only factors concerned in pathogenesis, but also the secondary effects of ulceration, e.g., liver changes,

effects on protein metabolism, electrolytic changes in the cellular and extracellular spaces, and other systemic complications. They may also be used to study the influence of drugs or other potential therapies on the pathogenesis and course of the disease process. However, none of the current IBD models in itself constitutes a faithful equivalent for the human diseases (this will be discussed in more detail in the final section of this chapter). It may therefore be essential to evaluate the effect of any candidate therapies in several IBD models. The wide variety of models of IBD includes chemically-induced models, adoptive transfer models, and genetically modified models such as gene knockouts and transgenic animals. We will consider each of these types of model as they apply to IBD, focusing in particular on those models with a genetic basis, describing some of our work using the *Il10*$^{-/-}$and Mdr1a models and, more recently, the *Nod2*^{2939iC} model.

2.1 Chemically induced models of IBD

A variety of agents have been used as inducers of colitis in animal models, including carragenin (Moyana and Lalonde, 1990), acetic acid (MacPherson and Pfeiffer, 1978), and very recently, sodium hydroxide (Kocak et al., 2011). While predominantly used in rodents, compounds such as these have also been used to develop colitis models in dogs (Shibata et al., 1993) and rabbits (Depoortere et al., 2004). The two most widely used chemicals used to induce IBD in such models are 2,4,6-trinitrobenzene sulfonic acid (TNBS) and dextran sodium sulphate (DSS). Both act via acute destruction of the intestinal barrier, although TNBS more closely mimics CD, and DSS UC (Alex et al., 2009). We will consider these two compounds in greater depth as examples of chemically-induced models of colitis.

2.1.1 DSS

DSS, $(C_6H_7Na_3O_{14}S_3)_n$, is a polyanionic derivative of dextran, and is used for such diverse applications as selective precipitation of lipoproteins (Burstein et al., 1970), acceleration of probe hybridization to membrane-immobilized DNA (Wahl et al., 1979), and the release of DNA from DNA-histone complexes (Kent et al., 1958). Its use in animal models is more recent, and it has been widely used in both mice and rats in the context of colorectal cancer (Ishioka et al., 1987) in addition to its role as a model of intestinal colitis (Okayasu et al., 1990) which we are considering here.

DSS is most commonly administered in the drinking water, often as a 3% solution (Johansson et al., 2010), although it can also be administered rectally. This compound results in inflammation in wild-type animals that starts distally after about five days and is confined to the colonic mucosa (Fig.1, [A–C]). How DSS initiates the colonic inflammation is not well understood despite its wide use, although a recent study investigating DSS both *in vitro* (effect on the inner mucus layer secreted by mucosal explants) and *in vivo* (mice given a 3% DSS solution) showed that DSS has a direct effect on the inner mucus layer, allowing bacteria to penetrate this layer before any signs of inflammation could be observed. The authors concluded that a lack of the inner colon mucus layer may be an initial event in the development which allows bacteria to reach the epithelial cells and thus trigger the characteristic inflammatory reaction (Johansson et al., 2010).

As well as being used in wild-type mice, DSS is also used in some genetic models of IBD, which while being genetically predisposed to inflammation still require this challenge in order to trigger an inflammatory response. This is the case for the *Nod2*^{2939iC} mouse model (described in more detail in section 2.3.3) in which DSS treatment led to more severe colonic inflammation and ulceration than wild-type mice (Maeda et al., 2005).

2.1.2 TNBS

TNBS is a nitroaryl oxidizing acid with extreme oxidising properties. TNBS dissolved in ethanol induces severe colonic damage, which is characterized by areas of necrosis surrounded by areas of acute inflammation. The damage is associated with high myeloperoxidase activity, mainly as a reflection of neutrophilic infiltration into the damaged tissue (Veljaca et al., 1995) and caustic injury to the colonic epithelium and interstitium as measured by the rapid and dramatic increases in mucosal permeability (Yamada et al., 1992). It has been assumed that interstitial TNBS initiates the inflammatory response via macrophage-mediated recognition and degradation of TNBS-modified mucosal cells and proteins (Grisham et al., 1991). TNBS may reduce mucosal hydrophobicity by reacting with the surface-active phospholipids of the colonic mucosa. Reduced hydrophobic integrity of the colonic mucosa may contribute to TNBS-induced colonic inflammation (Tatsumi and Lichtenberger, 1996). TNBS causes necrosis and deeper tissue damage (somewhat akin to transmural inflammation seen in CD).

2.2 Adoptive transfer models

The adoptive transfer model involves transferring T cells or immune tissue from one mouse into a histocompatible, adoptive host which results in colitis. A variety of donors and hosts have been used, including CD4+ T cells transferred into severely immunodeficient (SCID) mice (Rudolphi et al., 1996), hsp60-specific CD8 + T-lymphocytes into *TCR*$^{-/-}$ or SCID mice (Steinhoff et al., 1999) and CD4+CD25- T cells into SCID mice (Kjellev et al., 2006).

Adoptive transfer models represent well-characterized models of chronic colitis induced by disruption of T cell homeostasis. The colitis is characterised by transmural inflammation, epithelial cell hyperplasia, polymorphonuclear leukocyte (PMN) and mononuclear leukocyte infiltration, crypt abscesses, and epithelial cell erosions. The disease model is responsive to a variety of treatment protocols (Ostanin et al., 2009). The adoptive host can influence the severity and location of colitis, with the recombinase activating gene-1-deficient (*RAG*$^{-/-}$) deficient mouse showing both small bowel inflammation and colitis, and therefore being the model most relevant for CD (Ostanin et al., 2009).

Because these models rely on the transfer of T cells, they are particularly useful in understanding how different T cell populations might contribute to the pathogenesis of IBD.

2.3 Genetic models of IBD

Recent research using novel genetic technologies has resulted in the identification of a large number of genes, variants of which may be related to increased susceptibility to IBD. Tools such as GWAS have identified susceptibility genes such as those encoding the autophagy protein ATG16L1, the receptor for prostaglandin E2 (CD), and the intestinal barrier protein ECM1 (UC) (Paul et al., 2011). Existing mouse and rat models containing relevant genetic variants, or those incorporating these newly identified variants, have been used to further investigate the genetic contribution to IBD. Gene variant models include knockouts (interleukin-2 KO/IL-2 receptor (R)α KO mice, T cell receptor (TCR) mutant mice, TNF-3' untranslated region (UTR) KO mice, interleukin-22 KO mice) and transgenic models (IL-7 transgenic mice, signal transducer and activating transcription (STAT)-4 transgenic mice, HLA B27 transgenic rats), and have been comprehensively reviewed elsewhere (Jurjus et al., 2004; Mizoguchi and Mizoguchi, 2010). Some of these models develop spontaneous colitis as a result of the genetic variant, others can require additional intervention to act as a trigger for the onset of inflammation (Mizoguchi and Mizoguchi, 2010). For the

purposes of this chapter, we will consider three models with which we have some experience; the interleukin 10 gene-deficient, multi-drug resistant gene-deficient, and *Nod2*^{2939iC} mouse models.

2.3.1 The interleukin 10 gene-deficient (*Il10*$^{-/-}$) mouse model

The *Il10*$^{-/-}$ mouse model has been widely used as a model of IBD (Kuhn et al., 1993; Berg, D. J. et al., 1996; Barnett et al., 2010). This mouse model lacks a functional version of the important anti-inflammatory cytokine interleukin 10. When originally developed, these mice were observed to be anaemic and underweight, and showed a chronic enterocolitis involving the entire intestinal tract. The intestinal pathology (Fig.1 [D–E]) was characterized by variable mucosal inflammation, abnormal crypt and villus structures, inflammatory cell infiltration and epithelial destruction (Kuhn et al., 1993).

The precise mechanism that results in inflammation in *Il10*$^{-/-}$ mice is unclear although, as is the case in human IBD, there is evidence of an inappropriate inflammatory response to normal intestinal flora (Sydora et al., 2003). This was seen in studies where mice raised in germ-free conditions showed no colitis (Sellon et al., 1998), while those under specific-pathogen free conditions showed a local colitis, and not the general enterocolitis seen in animals raised under conventional conditions (Kuhn et al., 1993). More specific studies of bacterial interactions have shown that clinical isolates of *Enterococcus faecalis* induce IBD-like symptoms in germ-free *Il10*$^{-/-}$ mice (Balish and Warner, 2002; Kim et al., 2005). Enterococcus species are a common component of the intestinal flora of healthy humans and animals (Jett et al., 1994), with *E. faecalis* and *E. faecium* being the most commonly detected species in the human bowel (Noble, 1978; Tannock and Cook, 2002). Both carry a variety of virulence factors which may play a role in the establishment of inflammation (Jett et al., 1994).

We have utilized *Il10*$^{-/-}$ mice inoculated with normal intestinal bacteria, including *Enterococcus* species (Barnett et al., 2010), to investigate the role of diet in intestinal inflammation. We have shown that food components such as polyunsaturated fatty acids (Knoch et al., 2009; Knoch et al., 2010) can prevent or ameliorate the level of intestinal inflammation, and have characterized changes in gene expression in association with this change in inflammation to better understand the mechanisms through which such food components might be acting.

We have also used metabolomic analysis to measure urinary metabolite differences between *Il10*$^{-/-}$ and wildtype C57BL/6 mice, and to determine which of these differences were associated with intestinal inflammation (Lin et al., 2010). Eleven metabolites, including glutaric acid, 2-hydroxyglutaric acid and 2-hydroxyadipic acid, were significantly different in *Il10*$^{-/-}$ compared with C57 mice, but these differences were not related to the severity of inflammation, and were possibly associated with the genetic manipulation that produced these animals, rather than any inflammatory-related function of IL-10. In contrast, fucose, xanthurenic acid and 5-aminovaleric acid were among fifteen metabolite differences associated with intestinal inflammation (Lin et al., 2010). The presence of defined metabolites associated with inflammation may be of benefit in enabling a non-invasive measurement of the severity of inflammation in human IBD.

2.3.2 The multi-drug resistant (Mdr1a) mouse model

Mdr1a (otherwise known as ATP-binding cassette, sub-family B (MDR/TAP), member 1A (Abcb1a)), is a member of a family of proteins that actively transport a wide range of

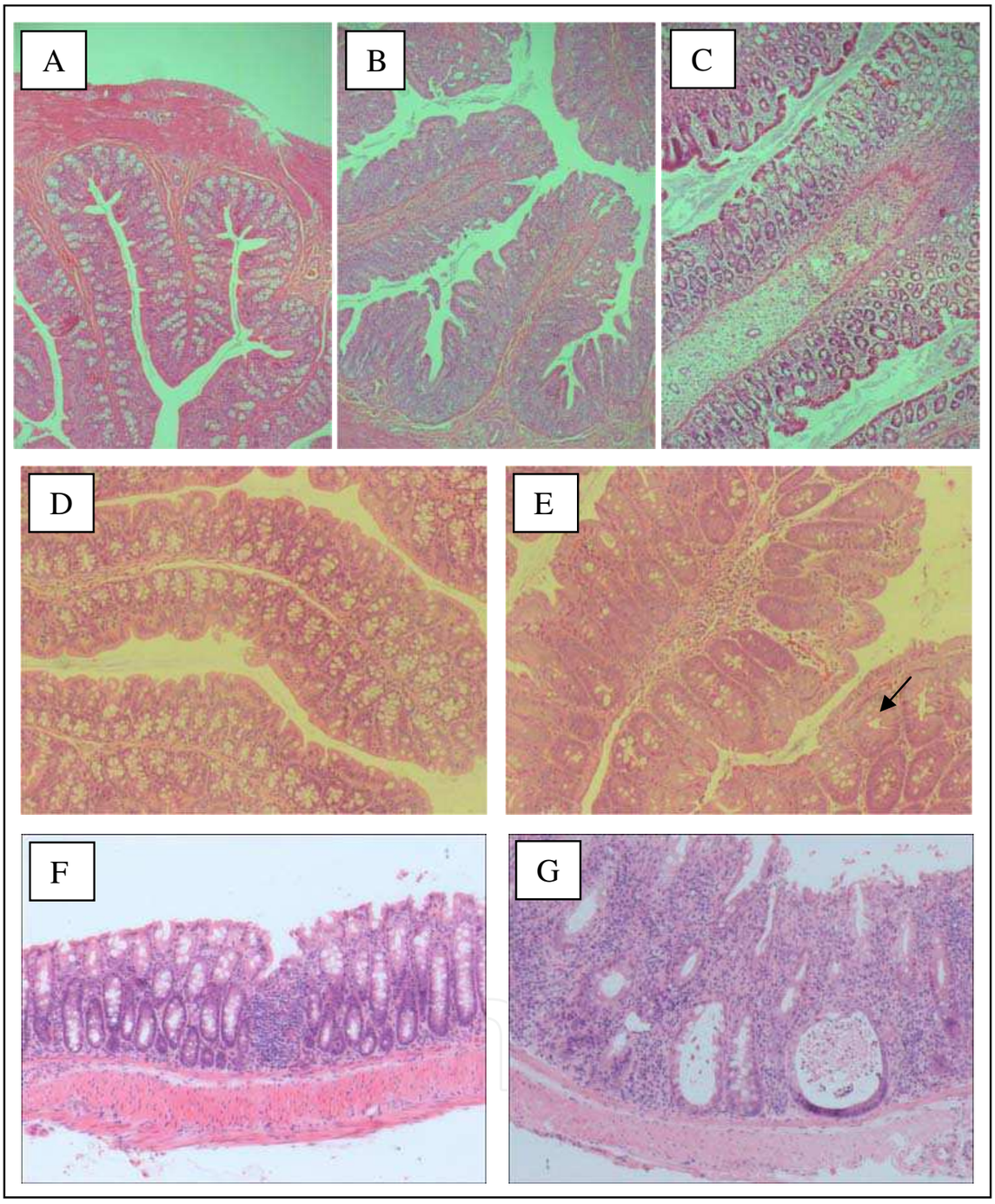

Fig. 1. Comparison of microscopic features of colon inflammation in a variety of animal models. DSS rat: Panels [A] to [C]. An untreated rat in panel [A] exhibits normal crypt distribution, high numbers of goblet cells, and intact surface enterocytes. There are noinflammatory aggregates, and immune cells present are well within normal limits. Sub mucosa and muscularis region are of normal size and proportion to the mucosa region. In a moderately inflamed colon [B], crypt loss, crypt shortening and aberrant crypts can be seen along with the associated loss of goblet cells, and some loss of integrity of the surface

enterocyte layer. An increasing number of inflammatory cells in the mucosa and submucosa region can also be seen. In a severely inflamed colon [C], the surface enterocyte layer is severely impaired. There is loss of crypts, and the majority of those still present are aberrant in structure, showing severe shortening. The number of goblet cells visible is significantly reduced and infiltrating inflammatory cells are evident throughout all definable regions of the tissue. Thickening/swelling/oedema of the submucosa region can also be observed.
Panel [D] shows a control C57 mouse which exhibits the intact enterocyte layer, abundant goblet cells, and normal crypt definition of a healthy mouse colon. In contract, the *Il10*$^{-/-}$ mouse in panel [E] shows aberrant crypts (black arrow) and crypt hyperplasia (swelling), an increase in inflammatory cells in the lamina propria and the presence of RBCs in the mucosa region of the tissue. There is also a decrease in goblet cell number and loss of surface enterocyte integrity. In panel [F], the FVB/N mouse is generally normal, although there is a lymphoid aggregate (arrow). In contrast, the Mdr1a mouse colon [G] shows significant inflammatory cell infiltration, aberrant crypts and some loss of surface enterocyte integrity

structurally unrelated, amphiphilic hydrophobic drugs from the cell, many of which are toxic compounds (Panwala et al., 1998). There is evidence that single nucleotide polymorphisms (SNPs) of the *MDR1* gene in the human population are associated with changes in the risk of UC (Huebner et al., 2009). Mice with a homozygous disruption of the *mdrla* gene were originally developed to better understand the physiological significance and other possible biological roles of this protein (Panwala et al., 1998). It was subsequently shown that these mice spontaneously develop intestinal inflammation (Fig.1, [F–G]) similar to that seen in human IBD, with infiltration of intestinal cells into the lamina propria, increased crypt length, goblet cell loss, interstitial oedema, ulceration (ranging from superficial to transmural) and crypt abscesses (Banner et al., 2004). These mice have since been used as an experimental model of colitis in a number of studies.
As in the case of the *Il10*$^{-/-}$ mice, we have used the Mdr1a mouse model to investigate potential beneficial effects of food components on intestinal inflammation (Nones et al., 2009). These studies have shown that the polyphenolic compound curcumin, but not rutin, significantly reduced colonic inflammation in Mdr1a mice. Microarray analyses suggested that curcumin reduced colon inflammation by up-regulating xenobiotic metabolism and down-regulating pro-inflammatory pathways, possibly through the pregnane X or retinoid X receptors (Nones et al., 2009).

2.3.3 The *Nod2*^{2939iC} mouse model

The NOD2 protein is important in the discrimination between normal intestinal flora and pathogenic bacteria (Inohara et al., 2002). It belongs to a class of pattern recognition receptors of the innate immune system that recognise evolutionarily conserved pathogen-associated molecular patterns. Pattern recognition by NOD2 initiates the signal transduction that leads to translocation of nuclear factor-kappa B (NF-κB) to the nucleus, transcription of specific genes and eventual activation of appropriate innate and adaptive immune responses (Inohara et al., 2002).
In humans, the most common CD susceptibility allele is 3020insC, which encodes a truncated NOD2 protein lacking the last 33 amino acids (Ogura et al., 2001). It has been established that this SNP, and possibly others in the *NOD2* gene, are important genetic determinants of CD risk in the NZ population (Leung et al., 2005). Variants of the NOD2

gene have also been shown to interact with other genes influencing bacterial recognition which results in an increased risk of IBD (Petermann et al., 2009a).

A mouse model has been generated containing a susceptibility allele homologous to that in humans (Maeda et al., 2005). These mice (*Nod2*^{2939iC}) express a protein truncated by 33 amino acids, which by itself does not alter the phenotype: homozygous *Nod2*^{2939iC} mice were healthy, not showing abnormalities of the gastrointestinal tract or other organs (Maeda et al., 2005). However, when 8-12 week old mice were exposed to DSS treatment (3% in drinking water), they exhibited increased body weight loss, increased colonic inflammation and ulceration and more apoptotic cells in the lamina propria when compared to similarly treated wild-type mice. The intestinal inflammatory response to DSS was dramatically reduced by oral antibiotics, suggesting that enteric bacteria elicit the inflammatory response to DSS, and without bacterial exposure, *Nod2*^{2939iC} mice have the same reaction as WT counterparts (Maeda et al., 2005).

We have inoculated these mice with intestinal bacteria, including *Enterococcus* strains, using the same protocol as previously applied to *Il10*$^{-/-}$ mice (Barnett et al., 2010). While there was some evidence of reduced body weight associated with the *Nod2*^{2939iC} mutation (WT > *Nod2*^{2939iC} heterozygotes > *Nod2*^{2939iC} homozygotes), there was no data to suggest an effect of either genotype or bacterial inoculation on intestinal phenotype, as assessed by assigning a histological injury score (Barnett et al, "unpublished observations"). It therefore seems likely that disruption of the epithelial barrier, for example with DSS, is necessary to enable bacterial infiltration which leads to altered NF-kB activation and IL-1β secretion in the *Nod2*^{2939iC} mice (Maeda et al., 2005).

This preliminary evidence suggests that the *Nod*^{22939iC} mutation is not, of itself, sufficient to lead to increased intestinal inflammation, requiring a simultaneous disruption of the epithelium. This is an example of an interaction between an environmental trigger, genetic susceptibility and inappropriate response to normal bacteria leading to intestinal inflammation. This model may therefore be particularly relevant for individuals in the human population carrying the homologous gene variant, and metabolomics approaches applied to this model may enable, for example, early detection of susceptibility to IBD and therefore earlier and more effective responses.

3. Lessons learned from mouse models

The body of evidence using mouse models of IBD is large, and there is no doubt that much has been learned by using such models. A selection of some key observations is shown in Table 1. This is clearly not an exhaustive list, but it serves to demonstrate some of the important areas in which animal models have contributed. In addition to more precisely defining the pathogenesis of IBD, insights have been gained into the inflammatory process itself, and this is relevant both in terms of colitis *per se* as well as being useful for the complications or systemic effects that may arise from a prolonged period of inflammation occurring within the intestine. There has also been progress in understanding the complex interactions occurring within the intestinal tract between the resident microbial population and the host.

Models such as the *Il10*$^{-/-}$ and adoptive transfer models have been particularly helpful in terms of generating deeper understanding of the inflammatory process itself. This has included better defining some of the leukoctye-epithelial cell interactions and the importance of cell adhesion, as well as the roles of the Th1 response in CD and the Th2 response (albeit an atypical one) in UC (Strober et al., 2002).

Model	Observation	Reference
TNBS	Fatty acid amide hydrolase (FAAH) inhibitors are promising targets for IBD treatment.	(Andrzejak et al., 2011)
DSS	DSS makes the inner colon mucus layer permeable to bacteria, which reach the epithelial cells and trigger an inflammatory reaction. Altered inner colon mucus layer may be an early event in colitis development.	(Johansson et al., 2010)
Various	IBD is much more complicated than currently predicted. Cell-specific, tissue-specific, or personalized approaches may be required for effective IBD therapy.	(Mizoguchi and Mizoguchi, 2010)
Various	A significant (as-yet not precisely defined) role for IL-10 in orchestrating intestinal immune homeostasis.	(Paul et al., 2011)
SAMP1/Yit	A hypothesis that CD is caused by a dysregulated immune response to an unknown (bacterial?) antigen in a genetically susceptible host.	(Pizarro et al., 2011)
TNFΔARE	Deregulation of TNF gene leads to spontaneous development of chronic ileitis similar to that of CD.	(Pizarro et al., 2011)
Various	Response in IBD takes the form of either a Th1 or Th2 T cell-mediated inflammation driven by antigens associated with normal mucosal microflora ("self" antigens).	(Strober et al., 2002)
Il10$^{-/-}$	Importance of *Enterococcus* bacterial strains in development of intestinal inflammation.	(Balish and Warner, 2002; Barnett et al., 2010)
Il10$^{-/-}$	Omega-3 and -6 polyunsatured fatty acids reduce intestinal inflammation in the *Il10*$^{-/-}$ mouse, in the case of n-3 via peroxisome proliferator-activated receptor a.	(Knoch et al., 2009; Knoch et al., 2010)
CD4+ SCID mice	Flagellins act as antigens that stimulate pathogenic intestinal immune reactions.	(Lodes et al., 2004)
Mdr1a	Reduction of inflammation associated with diets enriched with polyphenolic compounds.	(Nones et al., 2009)

Table 1. Some key observations from studies using mouse models of IBD

A variety of models have contributed to progress in understanding the complex interactions occurring within the intestinal tract between the resident microbial population and the host. A number of studies using *Il10*$^{-/-}$ mice have highlighted the importance of specific intestinal bacteria such as *Enterococcus* strains in triggering inflammation (Balish and Warner, 2002; Barnett et al., 2010). In terms of relevant components of bacteria which may be important, flagellins are molecules of the bacterial flagellum which are known to activate innate

immunity via toll-like receptor 5 (TLR5), and act as critical targets of the host's acquired immune system. These have been shown to elevated Th1 T cell responses in mice with colitis, and to thus be dominant antigens which may trigger the immune response in genetically susceptible individuals, leading to IBD (Lodes et al., 2004).

Potential therapeutic benefits include such molecules as superoxide dismutase 1 (SOD1), which has been shown to ameliorate colonic inflammatory changes in experimental colitis. Down-regulation of adhesion molecule expression, reduction of lipid hydroperoxidation, and recruitment of leukocytes into the inflamed intestine contribute to this beneficial effect (Segui et al., 2005). Our own studies have demonstrated the potential beneficial effects of dietary compounds such as polyunsaturated fatty acids (Knoch et al., 2009; Knoch et al., 2010) and polyphenols (Nones et al., 2009) on intestinal inflammation. A greater understanding of cell to cell adhesion has led to the development of monoclonal antibodies against α4 and α4β7 integrins that have been shown to have clinical efficacy (Lanzarotto et al., 2006), although there has been some debate as to the safety and efficacy of this approach (Davenport and Munday, 2007).

4. Relevance to the clinic

We will conclude our chapter by considering how information derived from these models has been applied to human IBD, and understanding both the value and limits of the lessons that have been learned from animal models. Finally, we will discuss the potential role of these models in the future of IBD research, and whether there are other alternatives to assist in translating fundamental research into a clinical setting.

4.1 Limits of animal models of IBD

Animal models can be an important tool in understanding complex diseases such as UC and CD, but it is important to remember that they are simply models. As such, they by definition will have some limitations, and while there are many similarities between experimental ulcerative disease of of the colon and human IBD, there are also differences. These can be either morphological (e.g., initial site of involvement of the bowel) or clinical. An example of a clinical difference is that spontaneous remission is sometimes seen in human disease (particularly with UC) but this is not seen in chemically-induced models unless exposure to the chemical is ceased. Mice may not be truly representative of other mammalian systems as has been observed with respect to early development (Berg, D. K. et al., 2011), and the inherent differences between mice and humans must be borne in mind when using such models.

The relevance of chemically-induced models has been called into question. It was noted early in the development of these models that there was a lack of any evidence that human ulcerative colitis is produced by the ingestion of compounds related to carrageenan, the chemical used to induce colitis (Watt and Marcus, 1973). Such evidence is still lacking, and it has also been observed that the acetic acid and TNBS models may have significant limitations in understanding events that initiate inflammation of the intestine in human IBD (Yamada et al., 1992). More recently, the relevance of the DSS-induced model has also been questioned (Petersen et al., 2009). To balance this, it should be noted that ulcerative disease of the colon can be caused by ingestion of certain chemical compounds in at least four different animal species, which suggests that this mechanism should not be completely disregarded with respect to human disease.

4.2 Application in a clinical setting

While animal models have clearly contributed to our knowledge of IBD, particularly in terms of understanding disease pathogenesis, the presence of useful progress in terms of treatment is less clear. There is an apparent lack of integration of mouse model data into the clinical setting, a so-called "missing link" between models and clinic (Petersen et al., 2009). This is seen in the conclusions to many studies incorporating such models, or indeed articles reviewing the use of these models, which tend to finish with statements referring to future, rather than current, therapeutic advances. Some examples of such conclusions are as follows (note that italics are not in the original references): "*...promising target* for the Inflammatory Bowel Diseases (IBD) treatment" (Andrzejak et al., 2011); "substantial investment from the pharmaceutical industry *should deliver* novel therapies arising from gene discovery to the clinic within the next 5 years" (Lees et al., 2011); "...recently established genetically engineered mouse models lacking IBD susceptibility gene *should be promising tools* to develop novel therapeutic measures for IBD" (Mizoguchi and Mizoguchi, 2010).

This is not to detract from some excellent research in the field, and the recently established genetically engineered mouse models lacking IBD susceptibility genes should indeed prove to be promising tools to develop novel therapies. For example, based on the numerous studies involving the *Il10*$^{-/-}$ mouse model demonstrating the importance of this anti-inflammatory cytokine in IBD, several human clinical trials have been carried out using IL-10. However, these have not shown a clear beneficial effect of IL-10 therapy. This has been attributed to polymorphisms of IL-10 receptors hampering effectiveness of this therapy for patients, or to the instability and short half-life of IL-10. More promisingly, engineered lactic acid bacteria have successfully delivered biologically active IL-10 into the intestine of both animal models (Wells and Mercenier, 2008) and some CD patients (Braat et al., 2006) indicating a potential bio-therapeutic application for IL-10.

4.3 Future relevance of animal models of IBD

It has been observed that differences between animal models may reflect the different subgroups of patients with IBD (Jurjus et al., 2004). This may be the case for some models, although the chemically-induced models may in fact be less relevant in terms of the clinical situation. Nevertheless, it seems clear that some of the genetically-based models may be of particular relevance for certain forms of IBD. In future, studies may utilise a specific mouse model targeted at the most appropriate subgroups and thus provide more relevant data. However, this will in turn rely on establishment of more clearly defined clinical phenotypes and the widespread application of genetic tests in clinical medicine to enable accurate matching of mouse model to patient thereby leading to the most appropriate therapy. The identification of appropriate diagnostic biomarkers would be of particular benefit in this case, both in terms of classification and subsequent monitoring of the effectiveness of therapies.

This potential 'matching' of model to patient sub-group may be constrained by financial considerations, nonetheless this personalised approach to treatment may be the most effective due to the heterogeneity of IBD. Recent evidence showing potential gene-diet interactions in IBD (Petermann et al., 2009b) and the potential for diet to modulate IBD through anti-inflammatory action or alteration of the microbiota (Issa and Saeian, 2011) suggests that dietary intervention appropriately matched to patient genotype may be an important aspect of successful therapy.

Mouse models will continue to be a pivotal part of IBD research. The complexity of the disease cannot currently be adequately modelled by *in vitro* or *in silico* approaches and requires an *in vivo* approach. Some novel therapies have shown promising initial data in limited human clinical trials, for example administration of viable eggs from the porcine whipworm, *Trichuris suis*, to patients with CD and UC, which may act to down-regulate the chronic Th1 immune response (Summers et al., 2003). However, more convincing safety and efficacy data derived from animal models are required before further human clinical trials using these novel treatments are conducted, particularly as some proposed treatments may have adverse effects on normal immune homeostasis (Grimm, 2009).

It has been observed that IBD may result from inappropriate responses to normal bacteria in a genetically susceptible host, which may arise due to some sort of environmental trigger. This situation is clearly seen in the *Nod2*^{2939iC} mouse, where the animals do not develop an inflammatory phenotype unless challenged with DSS, an insult which appears to damage the epithelial barrier and allow bacteria to infiltrate the mucosa, leading to an inappropriate response in the *Nod2*^{2939iC}, but not the wild-type, mouse. The requirement for a trigger in the form of DSS may make this model more relevant, as it could reflect the situation seen in human patients with this gene variant, who may have been exposed to some form of intestinal insult (dietary, or an infection) which has enabled the interaction with bacteria to occur. However, the fact that DSS is the trigger could be a weakness; as already observed, this particular compound has been questioned in terms of its relevance, and it may be that a more relevant trigger (e.g. dietary) needs to be found before such a model could be truly relevant.

The current comprehensive knowledge of the potential genetic component of both CD and UC, and rapid decreases in the cost of techniques to accurately measure these on an individual level, mean that more accurate classification of disease based on both clinical and genetic factors is achievable. The presence of multiple animal models, which may reflect these more accurately classified subgroups, means that a more targeted use of these models can be made. There is a growing body of evidence on the interactions between drugs (pharmacogenomics) or foods (nutrigenomics) and an individual's genotype. A truly personalised approach to managing IBD using appropriate preventive or therapeutic pharmacological or nutritional interventions is a future prospect if continued advances are made in this area.

In summary, there is clearly still a role for animal models of IBD, however more appropriate use of new information and technologies, better classification of IBD based on both phenotypic and genetic information, and closer alliances between fundamental biological researchers and clinicians are required to ensure that the key lessons from these models are effectively moved into clinical practice. This should enable more successful strategies for the prevention and amelioration of this debilitating condition.

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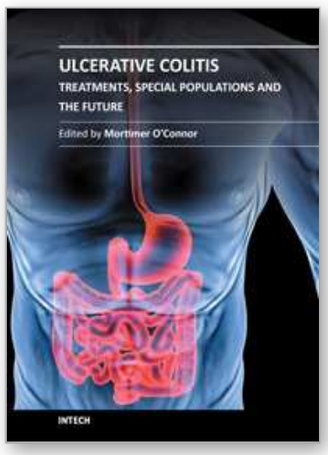

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