Genetic factors in animal models of intestinal inflammation

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RB SARTOR. Genetic factors in animal models of intestinal inflammation. Can J Gastroenterol 1995;9(3):147-152. The critical importance of host genetic susceptibility in determining chronicity, aggressiveness and complications of intestinal inflammation is clearly demonstrated by studies of inbred rodents, transgenic rats and spontaneous mutants. Inbred Lewis rats challenged by purified bacterial cell wall polymers, indomethacin or small bowel bacterial overgrowth develop chronic granulomatous intestinal inflammation with fibrosis and extraintestinal manifestations, whereas Fischer (major histocompatibility complex identical to Lewis) and Buffalo rats identically stimulated demonstrate only self-limited enterocolitis with no chronic inflammation, fibrosis, granulomas or extraintestinal inflammation. Similar differential patterns of intestinal inflammation are apparent in inbred mouse strains challenged with trinitrobenzene-sulphonic acid, *Citrobacter freundii* or backcrossed with T cell receptor deficient (knockout) mice. The dominant role of genetic background in induction of intestinal inflammation is further documented by spontaneous colitis which develops in spontaneously mutant mice, cotton-top tamarins, human leukocyte antigen-B27/β2 microglobulin transgenic rats and mice with targeted deletions of certain immunoregulatory cytokine and T lymphocyte genes. Identification of the immunological mechanisms of host genetic susceptibility and the genetic basis of spontaneous colitis should provide new insights into the pathogenesis of human inflammatory bowel disease.

Key Words: *Animal models, Enterocolitis, Experimental colitis, Genetic susceptibility, Intestinal inflammation*

Facteurs génétiques dans des modèles animaux d'inflammation intestinale

RÉSUMÉ : La grande importance de la sensibilité génétique de l'hôte dans la détermination de la chronicité, de l'agressivité et des complications de l'inflammation de l'intestin est fortement mise en évidence par des études menées chez des

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CLINICAL INVESTIGATORS HAVE compellingly documented a genetic component in ulcerative colitis and Crohn's disease (1). There is an increased incidence of inflammatory bowel disease (IBD) in family members, a predilection for these disorders in certain genetically defined ethnic groups, higher concordance of disease in monozygotic versus dizygotic twins and familial patterns of clinical phenotypes. However, human genetic research has not yet provided clinically useful disease susceptibility markers nor an understanding of the immunopathogenesis of IBD.

The critical importance of host genetic susceptibility in determining chronicity, aggressiveness and complications of intestinal inflammation is clearly demonstrated by studies in inbred rodents, transgenic rats, gene knockout mice and spontaneous mutants (Table 1). This report summarizes evidence of genetic control of intestinal and extraintestinal inflammation in these models, briefly outlines possible immunological mechanisms of enhanced genetic susceptibility and discusses the relevance of these observations to the pathogenesis of human IBD.

SPONTANEOUS INFLAMMATORY MODELS

The cotton-top tamarin and the recently developed C_3H/HeJ Bir substrain mouse develop chronic, spontaneously relapsing colitis. The mechanisms of intestinal inflammation in

rats consanguins, des rats transgéniques et des mutants spontanés. Des rats Lewis consanguins, exposés à des polymères de la paroi cellulaire purifiée de bactéries, à l'indométhacine ou à des bactéries du grêle, ont développé une inflammation intestinale granulomateuse chronique avec fibrose et manifestations extra-intestinales, alors que des rats Fisher (complexe majeur d'histocompatibilité semblable à ceux des rats Lewis) et des rats Buffalo stimulés de la même façon n'ont manifesté qu'une entérocolite à résolution spontanée, sans inflammation chronique, fibrose, granulomes ni inflammation extra-intestinale. Des modèles différentiels semblables d'inflammation intestinale apparaissent chez des souches de souris consanguines exposées à de l'acide trinitrobenzènesulfonique, à *Citrobacter freundii* ou soumises à un croisement en retour avec des souris présentant un déficit en récepteurs des cellules T. Le rôle dominant des antécédents génétiques dans l'induction de l'inflammation de l'intestin s'appuie encore sur la présence de colite spontanée qui se développe chez des souris mutantes, chez des tamarins, chez des rats et de souris rendues transgéniques par une microglobuline de l'antigène B27/2 des leucocytes humains avec élisions ciblées de certains gènes des lymphocytes T et des citokines immunorégulatrices. L'identification des mécanismes immunologiques de la susceptibilité génétique de l'hôte et de la base génétique de la colite spontanée devrait offrir de nouveaux renseignements sur la pathogenèse de la maladie inflammatoire de l'intestin chez l'humain.

TABLE 1
Genetic influence on animal models of intestinal inflammation

Spontaneous mutations (presumed)
Cotton-top tamarin
C_3H/HeJ Bir mouse
Genetically engineered models
Human leukocyte antigen-B27/β2 microglobulin transgenic rats
Interleukin (IL)-2, IL-10, transforming growth factor-beta, alpha-beta-T cell receptor , $G_{i\alpha 2}$ knockout mice
Differential susceptibility of inbred rodent strains to induced inflammation
Peptidoglycan-polysaccharide enterocolitis
Indomethacin enterocolitis
Small bowel bacterial overgrowth-induced hepatobiliary inflammation
Trinitrobenzene sulphonic acid/ethanol colitis
Alpha-beta-T cell receptor-deleted colitis
Citrobacter freundii colitis

these animals are unknown, but presumably are the result of a spontaneous genetic mutation because closely related strains do not develop colitis and aggressive searches have not identified environmental microbial pathogens.

At least 11 different species and hybrids of tamarins, a group of New World monkeys, spontaneously develop mild chronic colitis with mucosal atrophy (2). Cotton-top tamarins are unique in that they exhibit acute relapsing colitis complicated by adenocarcinoma of the colon (2-4). Captive cotton-top tamarins frequently develop a wasting syndrome characterized by weight loss, anorexia and diarrhea. An age-related chronic colitis is almost universally present by two years of age. Underlying chronic colitis is relatively mild, characterized by a thickened mucosa with hyperplastic, elongated crypts, pseudopolyps and mild mononuclear cell infiltration of the lamina propria. At any given time approximately one-half to two-thirds of marmosets have histological evidence of acute colonic inflammation, with neutrophilic infiltration, crypt abscesses and goblet cell depletion, but rarely have ulceration. Adenocarcinoma that complicates chronic colitis is not preceded by epithelial cell dysplasia or adenomatous polyps. Some tamarins develop chronic periportal inflammation with fibrosis.

The mechanism(s) of intestinal inflammation in cotton-top tamarins remains unclear. The inflammatory mediator profile of increased interleukin (IL)-1 and eicosanoids is characteristic of intestinal inflammation, and the colitis responds to sulfasalazine and a 5-lipoxygenase inhibitor (5). These marmosets share several biochemical and immunological alterations with ulcerative colitis patients. They have a selective reduction in mucus glycoprotein fraction IV which does not correlate with inflammatory activity (6). In addition their serum contains antineutrophil cytoplasmic autoantibodies which react with human, but not marmoset, neutrophils (7), and slightly increased concentrations of serum antibodies which stimulate cell-mediated cytotoxicity to colonic epithelial cell-associated components (8). However, the precise genetic alteration that predisposes these marmosets to chronic, relapsing colitis with associated adenocarcinoma remains uncharacterized.

C_3H/HeJ Bir SUBSTRAIN MOUSE COLITIS

Birkenmeier and colleagues (9) have recently described a heritable form of murine colitis. It had become apparent that sporadic diarrhea and perianal ulceration were frequent in individual members of the Jackson Laboratory C_3H/HeJ mouse breeding colony but that no microbial pathogens were demonstrable. Selective breeding of mice that developed diarrhea resulted in a pedigree of mice in which there is a 50% incidence of spontaneous colitis. Colitis is more frequent in males (67% incidence) than females (31% incidence) and exhibits a seasonal variation (occurring more often in winter than summer). Inflammation follows a biphasic time course with onset around the time of weaning (three to five weeks of age), spontaneous resolution in most mice and a less predictable chronic phase. Clinical manifestations include occasional diarrhea, fecal blood (not grossly apparent) and perianal ulceration. Inflammation is most frequently found near the ileocecal valve but can involve the entire colon. Histological findings include focal linear ulcers and a mixed mononuclear and neutrophilic infiltration. Extraintestinal manifestations have not been described.

Attempts to identify the presumed spontaneous genetic mutation are in progress. Like the parent C_3H/HeJ strain, monocytes from mice with spon-

taneous colitis are unresponsive to lipopolysaccharide (endotoxin) (10). Comparison of in vitro reactivity of T lymphocytes derived from parent strain and substrain mice with colonic cytokine profiles has not been reported. In preliminary studies, serum antibodies from 50% of C_3H/HeJ Bir mice react with luminal bacterial extracts compared with no detectable antibacterial antibodies from serum of C_3H/HeJ mice (11).

GENETICALLY ENGINEERED MODELS

Molecular engineering techniques permit selected genes to be overexpressed (transgenic) or deleted (embryonic stem cell recombination) in rodents. These methods have been powerful tools to determine the in vivo function of a targeted gene, and at times have provided unanticipated results. Deletion of several immunoregulatory cytokines, including IL-2, IL-10, transforming growth factor (TGF)-beta-1, $G_{i\alpha 2}$ and alpha or beta T cell receptor (TCR) chains, induces spontaneous colitis (12-15). These studies show that a single mutation of a key immunoregulatory cytokine, signalling molecule or T lymphocyte protein can lead to spontaneous intestinal inflammation, and that the colon is particularly susceptible to injury in immunodeficient hosts.

Overexpression of human leukocyte antigen (HLA)-B27/β2 microglobulin (β2μ) in transgenic rats induces a systemic inflammatory syndrome in which the first manifestation is diarrhea, followed by arthritis, dermatitis, hair loss, psoriatic nail changes, epididymitis and a wasting syndrome (16,17). Histological patterns of inflammation include focal chronic gastritis and duodenitis, and diffuse infiltration of the colonic lamina propria by mononuclear cells. Severely inflamed rats exhibit focal mucosal ulcerations and crypt abscesses in the colon. Cell transfer experiments demonstrate that HLA-B27/β2μ expressing bone marrow cells mediate the disease, and that B27/β2μ protein expression by nonimmune cells is neither necessary nor sufficient to cause disease (18). The absence of colitis, gastritis and arthritis in germ-free B27/β2μ transgenic rats, attenuated inflammation in specific pathogen-free rats and inhibition by metronidazole clearly demonstrate the importance of luminal bacteria in initiation and perpetuation of intestinal inflammation and associated extraintestinal disease (19,20). The incidence and onset of colitis and systemic inflammation depend on high copy numbers of HLA-B27/β2μ (17). Compared with induced rat models of enterocolitis (see below), the incidence of intestinal inflammation in Lewis and Fischer rats expressing equivalent copy numbers of the HLA-B27/β2μ transgene is similar, although extraintestinal inflammation is somewhat more frequent and rapid in onset in Lewis than Fischer rats (17).

TABLE 2
Differential susceptibility of inbred rats to experimental enterocolitis and systemic inflammation

High responder	Intermediate responders	Low responders
Lewis	Sprague-Dawley	Fischer F344
	Wistar	Buffalo

TABLE 3
Differential host susceptibility of inbred mice to experimental colitis

Model	High responders	Low responders
Trinitrobenzene sulphonic acid/ ethanol	Balb/C, C_3H/HeN	DBA/2, C57/BL
Citrobacter freundii	C_3H/HeJ	DBA/2J
T cell receptor alpha knockout	C_3H/He	Balb/C, C57BL/6

INDUCED INFLAMMATION IN INBRED RODENT STRAINS

Differential susceptibility of inbred rodents to intestinal and systemic inflammation powerfully illustrates the key role of genetic regulation of chronic inflammation and its complications, including fibrosis.

Inbred rat strains: The author used three experimental models to demonstrate that, with identical stimuli, inbred Lewis rats develop chronic relapsing enterocolitis with extraintestinal inflammation and fibrosis whereas inbred Buffalo and Fischer F344 (major histocompatibility complex matched with Lewis) rats develop only transient intestinal inflammation and no systemic manifestations (Table 2). Lewis rats injected subserosally with the bacterial cell wall polymer peptidoglycan-polysaccharide (PG-PS) develop chronic, spontaneously relapsing, granulomatous enterocolitis with fibrosis and associated polyarthritis, granulomatous hepatitis, leukocytosis and anemia which persists for at least 16 weeks (5,21). With identical exposure to PG-PS, Buffalo or Fischer rats exhibit only transient local inflammation, which resolves by 14 days, with residual damage and no chronic enterocolitis or extraintestinal manifestations. Outbred Sprague-Dawley rats develop chronic granulomatous enterocolitis, but the chronic intestinal inflammation is less pronounced and there is no extraintestinal disease (22).

In a second model, Lewis rats injected subcutaneously with indomethacin (7.5 mg/kg/day for two days) developed chronic mid-small bowel longitudinal ulcers with fibrosis and associated hepatobiliary inflammation, anemia and leukocytosis which persisted for at least 77 days, whereas Fischer rats had no residual inflammation 14 days after indomethacin (23). Similarly, Lewis rats – but not Buffalo or Fischer rats – developed chronic, fibrotic hepatobiliary inflammation in response to experimental small intestinal overgrowth of anaerobic bacteria following surgical creation of jejunal self-filling blind loops (24). In this model, Lewis rats develop clinical (hepatomegaly), biochemical (increased plasma aspartate aminotransferase), histological and cholangiographic evi-

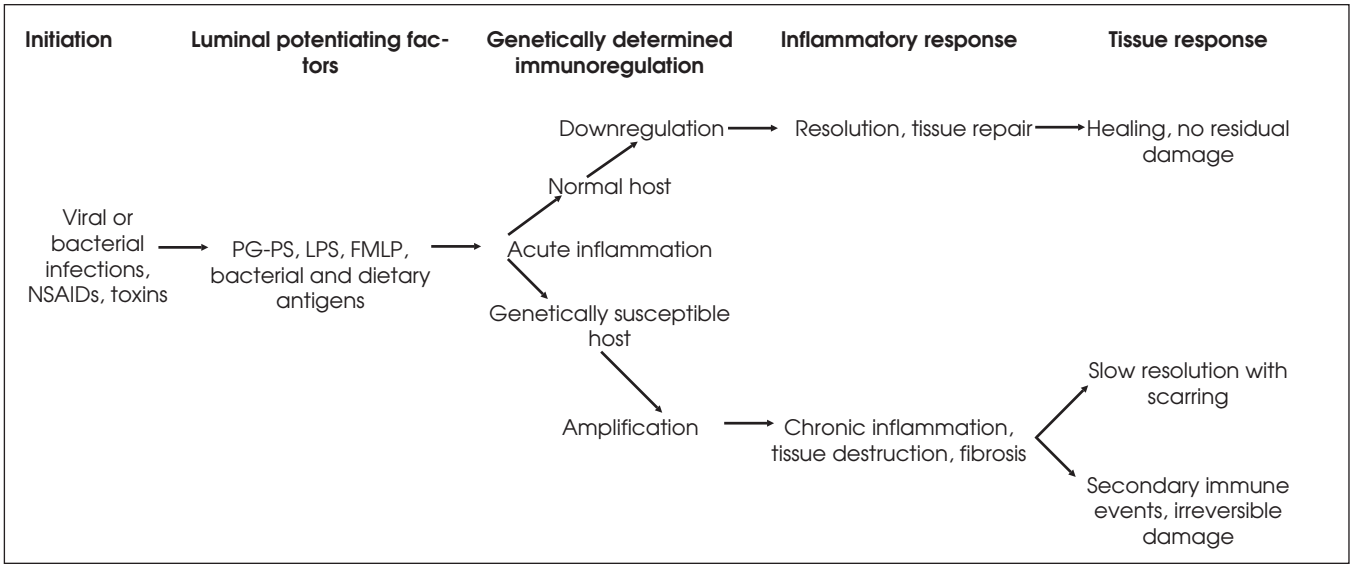

Figure 1) *The influence of genetic susceptibility on chronicity of inflammation is presented. Episodic enteric infections, environment toxins and enhanced mucosal uptake of ubiquitous bacterial constituents induce transient injury in all hosts. The normal response is appropriate suppression of inflammation with no residual damage (upper arm). However, genetically susceptible hosts amplify the inflammatory response, which leads to chronic tissue damage. FMLP n-formyl-methionyl-leucyl phenylalanine; LPS Lipopolysaccharide, endotoxin; NSAIDs Nonsteroidal anti-inflammatory drugs; PG-PS Peptidoglycan-polysaccharide. Reprinted with permission from: Sartor RB. Microbial factors in the pathogenesis of Crohn's disease, ulcerative colitis and experimental intestinal inflammation. In: Kirsner JB, Shorter RG, eds. Inflammatory Bowel Disease, 4th edn. Baltimore: Williams & Wilkins, 1995:96-124*

dence of hepatobiliary inflammation two to four weeks after formation of the self-filling blind loops. Wistar rats develop similar lesions by eight and 12 weeks, but Fischer and Buffalo rats fail to develop hepatobiliary injury despite very similar luminal bacterial concentrations in all rat strains. Thus, with identical stimuli, Lewis rats develop chronic, spontaneously relapsing inflammation with extraintestinal inflammation, but Buffalo and Fischer rats develop transient, self-limited inflammation with no local or systemic complications.

Lewis rats are high responders in a number of inflammatory models, including autoimmune encephalitis, thyroiditis, uveitis and arthritis (adjuvant, collagen and PG-PS-induced) (25,26). Experimental data support two theories to explain mechanisms of enhanced susceptibility to inflammation in Lewis rats: defective acute hypothalamic/pituitary/adrenal responses to IL-1 and PG-PS (27); and disordered regulation of the immune response. In support of the latter theory, Lewis rats have an increased ratio of cecal IL-1:IL-1ra MRNA during the chronic phase of PG-PS-inducted inflammation relative to resistant Buffalo and Fischer rats (21). Moreover, noninflamed intestinal tissues from Lewis, but not Fischer and Buffalo, rats constitutively express MRNA for tumour necrosis factor and an IL-8-like molecule (28), suggesting that the mucosal immune system of the Lewis rat is in a 'primed' state. The author has also demonstrated that T lymphocytes regulate the chronic, relapsing granulomatous phase of PG-PS-induced enterocolitis and systemic inflammation based on observations that Lewis athymic (nude) rats fail to develop enterocolitis and arthritis, and that cyclosporin A prevents and treats chronic intestinal and systemic inflammation (29). These results complement the author's observations in IBD patients and observations by Bristol et al (30) that PG-PS stimulated peritoneal macrophages from Lewis rats have an increased IL-1:IL-1ra ratio relative to Buffalo rats. Patients with active Crohn's disease and ulcerative colitis have significantly increased tissue IL-1:IL-1ra and MRNA protein ratios compared with controls (31,32).

Inbred mouse strains: Beagley and coworkers (33) have reported that Balb/C and C_3H/HeN mice developed a chronic colitis upon repeated weekly administration of trinitrobenzene sulphonic acid/ethanol enemas, but DBA/2 and C57/BL mice were resistant to chronic inflammation (Table 3). Similarly, C_3H/HeJ mice developed more extensive colonic inflammation and ulcerations than DBA/2J mice following experimental infection with *Citrobacter freundii*, although the two strains developed similar degrees of epithelial hyperplasia (34). However, inbred mouse strain susceptibility is not entirely consistent because Mombaerts et al (15) found that TCR-alpha chain-deficient mice on the 129/SV background and 129/SVxC_3H/He crosses develop severe intestinal inflammation more rapidly (four to six months of age) and with a higher incidence than those 129/SV mice crossed with C57BL/6 or Balb/C strain, which develop a less severe disease with a slower onset. The only mouse strain that displayed consistent high susceptibility in these models was the C3H/He background (C3H/HeN or C3H/JHeJ), which is the parent strain for the C3H/HeJ Bir mice that spontaneously develop colitis (9).

SUMMARY AND CONCLUSIONS

The studies discussed above clearly demonstrate that the chronicity, ag-

gressiveness and complications of induced intestinal inflammation depend on host genetic susceptibility. Furthermore, spontaneous mutation or altered expression of a single gene can induce spontaneous colitis. Genetically engineered models demonstrate that alteration of any of a number of key immunoregulatory cytokine or T lymphocyte gene products can lead to phenotypically similar intestinal inflammatory conditions. Furthermore, inbred rodent strains susceptible to induced intestinal inflammation exhibit immunoregulatory defects (Lewis rats increased IL-1:IL-1ra ratio and C3H/HeJ lipopolysaccharide-unresponsiveness). These observations in animal models suggest that human IBD can arise from a number of mutations of immunoregulatory molecules, supporting the concept of genetic heterogeneity for ulcerative colitis and Crohn's disease.

The author suggests that genetically determined defects in immunoregulation or perhaps mucosal barrier integrity can alter the delicate balance among phlogistic luminal bacterial constituents, dietary antigens and mucosal protective forces, and proposes that the genetic susceptibility of high responding hosts (Lewis rats and perhaps IBD patients) is due to an inability to downregulate appropriately the inflammatory response to ubiquitous luminal antigens, probably of bacterial origin (35). This theory predicts that events initiating inflammation may be nonspecific (self-limited infection, nonsteroidal anti-inflammatory drugs, toxins) and produce acute inflammation of similar degree in all hosts (Figure 1). The normal, genetically resistant host appropriately downregulates inflammation, which heals with no residual damage. However, the genetically susceptible host (Lewis rat, IBD patient), due to defective immunosuppression, amplifies the inflammatory response to develop aggressive tissue injury, fibrosis and extraintestinal inflammation. Better understanding of genetically determined defects in immunoregulation of the Lewis rat, and C3H/HeJ and C3H/HeN mice, and identification of the spontaneous genetic mutation(s) of the C3H/HeJ Bir mouse should lead to valuable insights into the genetic regulation of experimental chronic intestinal and extraintestinal inflammation that can be rapidly tested in IBD patients.

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