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Pathogenesis of Inflammatory Bowel Diseases

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Abstract

Despite of the extensive spent efforts and money on research on Inflammatory Bowel Diseases (IBD) over the last sixty years, the aetiology of these diseases is still largely unknown. Subsequently no highly effective management has been designed yet.

It was proposed that IBD's were likely to be due to persistent intensified T-cell activation in response to bacterial components. However, the emergent information from the recently reported studies challenge this proposal and evidently prove its impracticality.

The immune system like other biological systems is subject to complex regulatory control. When a normal immune response is initiated by antigenic stimulation, mechanisms must be in place to control the magnitude of that response and to terminate it over time. Down-regulation should contribute to the homeostatic control of all immune responses serving to limit clonal expansion and effector cell activity in response to any antigenic stimulus.

The recent experience suggests that polymorphism of the suppressor genes of the immune responses is significantly contributing to the development of IBD.

Introduction

The etiology of Inflammatory Bowel Diseases (Crohn's disease and ulcerative colitis) is unknown. It is likely to be multifactorial, where the existence of environmental risk factors is quite essential. These diseases are also inherited by incomplete penetration.

In earlier publications, I explained how the overproduction of Free Radicals and lack of anti-oxidants due to life style over a long period of time could help developing genetic mutations[1,2]. Yet, the then played role by these mutations in the pathogenesis of inflammatory bowel diseases is still unclear. The purpose of this review is to examine the possible mechanism by which genetic polymorphism contribute in the pathogenesis of inflammatory bowel diseases.

Genetic Codes and Genetic Inheritance

A gene is made up of short sections of DNA which are contained on a chromosome within the nucleus of a cell. Genes control the development and function of all organs and all working systems in the body. A gene has a certain influence on how the cell works; the same gene in many different cells determines a certain physical or biochemical feature of the whole body. All human cells hold approximately 30,000 different genes Even though each cell has identical copies of all of the same genes, different cells express or repress different genes.

There are several definitions for the genetic codes. They were defined as "set of trinucleotides that make a protein" by Fernando Castro-Chavez[3] This means that different related proteins will have different related genes even if they originated in the same genomic locus. But Gerstein in 2007[4] described "Gene" as "A union of genomic sequences encoding a coherent set of potentially overlapping functional products".

Kane in 2004[5] defines a gene as "both the static chemical compound and the dynamic template executed through the genetic code"; she also provides highly related definitions for the genetic code: "the set of invariant relationships between DNA and protein", "the universal dictionary for the conversion of DNA to protein", and "the molecular dictionary of the cell", while, according to Voie[6], the genetic code is a time-independent language to build functional biomolecules.

Genetic Mutations

Genetic mutation is a change in the DNA sequence of a gene, ranging from a change in as little as a single nucleotide to changes that may affect many thousands of base pairs, but always on a scale too small to be even seen with high-resolution cytogenetic analysis[7].

Mutation is the ultimate source of evolutionary change; new alleles arise in all organisms, some spontaneously but others as a result of exposure to radiation and chemicals (mutagen) in the environment. The new alleles produced by mutation become the raw material for a second level of variation, effected by recombination. Recombination is the outcome of cellular processes that cause alleles of different genes to become grouped in new combinations. Mutagens usually act to increase the frequency of the occurrence of the mutations[8]. When a mutation occurs, the new form of the gene is inherited in a stable manner, just like the previous form. The nature of the residual activity of each mutant allele in heterozygote animals determines its phenotype. The relationship between two mutant alleles is, in principle, no different from that between the wild-type and mutant allele (a wild-type gene codes for a protein product that is functional but mutant allele codes for proteins that are non-functional)[9] One allele may be dominant, there may be partial dominance or there may be co-dominance. Genes that are on different chromosomes (or that are far apart on the same chromosome) recombine independently[9]. But genes on a chromosome form a linear linkage group which those genes near one another tend to be inherited together[9].

There are different types of mutations. A loss of function mutation is the most common type. It results from inactivation of the gene and it is recessive because the mutant gene produces an altered protein or fails to produce any functional protein. Sometimes, a non-functional mutant polypeptide interferes with the function of the normal allele in a heterozygous person, giving a dominant negative effect. A null mutant is the extreme type that produces no protein. But a gain-of-function mutation results when a new property is conferred up a protein and it usually causes dominant phenotypes, because the presence of a normal allele does not prevent the mutant allele from behaving abnormally. Often this involves a control or signalling system behaving improperly. Signalling when it should not, or failing to switch a process off when it should. Sometimes, the gain of function involves the product doing something novel. However, some other mutations cannot easily be classified as either loss or gain[10], if the function of a single allele is sufficient in the diploid cell or wild-type allele, its activity would be dominant over a recessive mutant. Partial dominance occurs when gene functions are quantitative (two alleles produce twice the activity of one allele). Co-dominance results when different alleles have distinctive specifies, so that a heterozygote possess the properties of both parents. Mutations can be conditional, showing mutual phenotype under non permissive conditions but appearing wild-type in permissive conditions[9].

Inheritance of risk frequency

Inheritance of risk frequency can be determined by different factors including the position of the mutant allele and sex-threshold. For example, it was estimated that mutant alleles in the first or the second positions are more determinant than others[11]. Congenital pyloric stenosis is a representative example for the other determinant factor. Congenital pyloric stenosis is five times more common in boys than in girls. The threshold must be higher for girls than boys; therefore, relatives of affected girl have a higher average susceptibility than relatives of an affected boy[12]. The factors that govern the expression of pathogenic mutations are: the location of the mutation within the gene, the degree to which aspects of the aberrant phenotype are aberrant in the heterozygote, the degree to which expression of a mutant phenotype is influenced by other gene products, the proportion and nature of cells in which the mutant gene is present and the parental origin of the mutation[11].

Experimental studies on animal models (Evidence for cause-effect relationship)

In an interesting experimental study[12] aimed at identifying the contributing pathogenic alleles that could lead to the development of experimental colitis in mouse models with defined genetic background, the investigators used 1% Dextran Sodium Sulfate (DSS) in drinking water for seven days, as an environmental sensitising agent, in order to establish the cause-effect relationship It is known that low dose of DSS can convey insult to epithelial integrity comparable to many that occur in nature. A total of 15 transmissible mutations causing hypersensitivity to DSS have been discovered. Of these, five have been recognized as belonging to four gene categories concerned with: sensing microbes, prolifera-

tion of epithelial cells, accommodating Endoplasmic Reticulum (ER) stress and packaging specialized proteins within secretory vesicles. The characters of the identified mutant alleles (their locations, the changed amino acids, mode of inheritance and phenotypic category) are summarised in Tables 1.

More recently, another interesting experimental study on animal models has been published[13]. The objective of this study was to assess the status of colonic microcirculation in response to the administration of DSS. For that purpose, the investigators have used 9-10 weeks old-male C57BL/6J mice. DSS was administered to the mice as a 2% aqueous solution in their drinking water. But the control mice received normal tap water in a bottle. The DSS administered mice were killed each day and evaluated.

The findings of this study demonstrated that DSS administration initially injured the wall of vasculature in the deep layer of the lamina propria before mucosal epithelial cells were disorganized. Congestion of the affected lamina propria took place next and finally epithelial cells were exfoliated. During the course of the disease, Hypoxia-Inducible Factor 1α (HIF1α) and inducible nitric oxide synthase (iNOS) were expressed in the rows of the myenteric plexus.

The chronological changes that occurred in DSS administered mice were categorized into two phases, namely the early phase (days 2-3) and the late phase (days 4-5), and the pathogenic mechanism of DSS-induced colitis was discussed in each phase.

In the early phase of DSS-induced colitis, the vascular insufficiency occurred before the mucosal disorder. DSS administration increased vascular permeability before pathological changes in the mucosal epithelium have become detectable. Oxygen supply insufficiency was demonstrated by the enhancement of the expression of Hypoxia-Inducible Factor 1α (HIF1α) and inducible nitric oxide synthase (iNOS) in the colonic mucosa. DSS administration induced HIF1α expression in submucosal endothelial cells and vascular smooth muscle cells of the large vessels and the perikarya of myenteric plexus neurons, as well as iNOS expression in nerve fibres running in the lamina propria and in the muscular layer.

On day 3 (changes in the intestinal blood supply): (1) the blood vessels that ran from the submucosa to the lamina propria appeared constricted as they passed through the muscularis mucosa, and αSMA. Immune-reactivity at the vascular wall was decreased in the lamina propria; (2) The arrangement of PECAM1-positive endothelial cells was disorganized in the blood vessels and demonstrated RITC-gelatin leakage; (3) The αSMA-positive vascular wall was thinning and occasionally ruptured; (4) αSMA immunofluorescence in spindle-shaped cells was diminished; (5) RITC-gelatin leaked into the intercellular space of the vascular wall and the surroundings of the vessels; (6) The crypts became shortened or lost, the arrangement of cells in crypts was distorted,

Table 1. The identified mutant genes in response to 1% DSS in drinking water for 7 days.

Gene	Allele/amino acid change	Chr	Chromosome (chr) Loci	Mode of inheritance	Phenotypic category
Muc2	*Schlendrian*/ Cysteine changed to Phenylalanine	7	141744616-141754694 bp(+)	Autosomal Semidominant	Immune system inflammatory bowel disease phenotype
Muc2	*Muskatenwein* Isoleucine changed to Asparagine	7	141744616-141754694 bp(+)	Autosomal Semidominant	Immune system inflammatory bowel disease phenotype
Tlr9	*Cpg7* Arginine to a leucine	9	106222598-106226876 bp (+)	Autosomal semidominant	Immune system, inflammatory bowel disease phenotype TLR signaling defect: TNF production by macrophages
Aqp3	*Phoebus* Valine changed to Alanine	4	41,092,722-41,098,183 bp (-)	Autosomal recessive	Immune system, inflammatory bowel disease phenotype
Yipf6	X-linked Klein-Zschocher (KLZ) mutation	X	98936316-98949017 bp, (+)	Autosomal recessive	Immune system, inflammatory bowel disease phenotype

and goblet cells were decreased in number; (7) The number of KI67-positive cells in the remaining crypts was drastically reduced, and their immune reactivity markedly diminished, whereas KI67-positive free cells appeared in the deep layer of the lamina propria; (8) HIF1α immune reactivity spread from the mucosal surface to the bottom of remaining crypts; (9) Endothelial cells of the large vessels in the submucosa and myenteric neurons demonstrated immune positivity for HIF1α; (10) HIF1α was most prominent on day 3 and decreased thereafter; (11) Mucosal epithelial cells demonstrated iNOS immune reactivity; (12) Peripherin-positive nerve fibers were running in the lamina propria, submucosa, and myenteric plexus were also immune positive for iNOS; (13) gene expression of HIF1α was observed in the goblet cells of all crypts and in myenteric neurons that also expressed iNOS mRNA; (14) iNOS expression in epithelial cells intensified compared with day 0; (15) HIF1α mRNA in the colonic extract was up-regulated significantly on days 2 and 3; (16) mRNA levels and protein contents of iNOS rapidly increased from day 2

On day 5 (advanced mucosal changes): (1) RITC gelatin leakage occurred throughout the distal colon over the lamina propria and accumulating in the sub-epithelial region; (2) The epithelium as well as crypts were lost, and most blood vessels became dense in the lamina propria, and some were tortuous; (3) The number of αSMA-positive cells was increased in comparison with day 3; (4) The mucosal epithelium had completely disappeared,

and inflammatory cells increased and accumulated in the submucosa as well as the lamina propria; (5) Likewise, KI67-positive cells increased in the lamina propria and submucosa; (6) no cells in the lamina propria demonstrated a positive reaction to HIF1α and the thinning epithelium and myenteric neurons were faintly immune reactive for HIF1α; (7) iNOS immune reactivity was scarce in peripherin positive nerve fibres in the lamina propria, whereas nerve fibers and perikarya in the myenteric plexus were still positive; (8) iNOS-positive stromal cells in the lamina propria were more abundant than on day 4; (9) HIF1α expression was decreased similar to HIF1α protein immune reactivity; (10) In contrast, iNOS expression in mucosal epithelial cells and neurons were intensified with the progression of DSS administration; (11) HIF1α mRNA in the colonic extract was reverted to the level of day 0; (12) mRNA levels and protein contents of iNOS rapidly increased from day 2.

The immunological response and Inflammatory Bowel Diseases

Because it has been proposed that inflammatory bowel disease are likely due to over activation of the immune-response, the researches over the last thirty years until recently had concentrated on elucidating the molecular basis of antigen recognition by T cells. However, it has become clear that antigen engagement is insufficient to activate T cells and that co-stimulation through receptors such as CD28 was also required[14]. Co-stimulation has proved to be of fundamental importance. For example, the preliminary and major activity of Toll-like receptor (TLR) commitment by microbial molecules was to upregulate on antigen presenting cells (APCs)[15] (the ligands for CD28, known as B7-1 and B7-2). In addition, it soon became apparent that the activation of T cells was only one side of co-stimulation; the other being the capacity of co-stimulatory molecules to inhibit T cell activation by engaging an alternative receptor. For example, cytotoxic T lymphocyte antigen (CTLA)-4 is upregulated on activated T cells and competes with CD28 for B7 molecules, thereby attenuating the effector T cell response.

Polymorphism ofBTNL2 and the development of inflammatory bowel diseases

Butyrophilins (Btns) and butyrophilin-like (Btnl) molecules are emerging as novel regulators of immune responses in mice and humans. Several indications direct to their probable importance: (1) many of the genes are located within the MHC; (2) they are structurally related to B7-co-stimulatory molecules; (3) they are functionally implicated in T cell inhibition and in the modulation of epithelial cell-T cell interactions; and (4) they are genetically associated with inflammatory diseases.

Within the extended butyrophilin superfamily, most information is currently known about BTNL2. Three lines of evidence have recently united to identify BTNL2 as a molecule involved in the control of immune-related disorders:

1. **Human polymorphism of BTNL2 link with inflammatory diseases**
   Polymorphism of the human gene of BTNL2 (BTL-II) have been linked to a growing number of inflammatory diseases, all of which can be characterized by inappropriate T cell activation. Following the initial reports linking BTNL2 and sarcoidosis, the impact of BTNL2 polymorphism has been queried in several additional inflammatory diseases. Polymorphisms of BTNL2 have now been identified in ulcerative colitis,

rheumatoid arthritis, spontaneous inclusion body myositis, systemic lupus erythematosus, type I diabetes, tuberculoid leprosy and antigen-specific IgE responsiveness[16-22].

2. **BTNL2 shares homology and protein structure with the B7 family, a family with known functions in the immune system**
   The gene encoding BTNL2 is contained in the MHC locus. Similar to the B7 family members, BTNL2 contains two Ig-like domains (IgV and IgC), and has more recently been described to also bear a transmembrane domain and a cytoplasmic tail that lacks a B30.2 domain. Multiple variants and polymorphisms have been identified at the genomic level in both mouse and human BTNL2, which are each encoded by eight exons[23].
3. **BTNL2 inhibits the proliferation of T cells**
   Recent publications have explored a functional role for BTNL2 revealing that BTNL2 can inhibit proliferation of T cells in response to a T cell receptor (TCR) activating signal[24,25]. *In vitro*, the extracellular domain of mouse BTNL2 is sufficient to inhibit T cell proliferation and cytokine production in response to anti-CD3 and other costimulatory molecules[24]. IL-2 is one of the cytokines whose production is inhibited by BTNL2, and is critical for T cell survival and function. Addition of IL-2 to the T cell cultures in the presence of BTNL2 is capable of restoring some, but not all, proliferative capacity[25].
   Although the cutting-edge receptor for BTNL2 on T cells has not yet been identified, mouse BTNL2 induces a similar inhibitory response on primary T cells in both human and mouse[24] suggesting that their binding partner and conferred function on T cells may be preserved across species. In mouse T cells, BTNL2 binding to T cells leads to a decrease in activation of NFAT, NFkB, and AP1, pathways known to dampen activation signals in the lymphocytes[25].

Polymorphism of NOD2 and the development of Crohn's disease

Nod2 is a member of the NLR family of proteins that initiate inflammatory responses when exposed to ligands derived from bacterial components that gain access to the intra-cellular environment. Evidences exist to prove that NOD2 activation by its ligand, muramyl dipeptide (MDP), usually down-regulates responses to TLR stimulation and hence the cells lacking NOD2 shows increased responses to such stimulation. This explains the reason for why the mice that bear a NOD2 transgene have showed decreasing responses to TLR stimulation and have showed resistant to experimental colitis induction. This is because pre-stimulation of cells with NOD2 ligand results in the elaboration of IRF4, an inhibitor of TLR-induced inflammatory pathways. These findings explain the played role of the NOD2 polymorphisms in subjects with Crohn's disease[26].

Matrix metalloproteinases (MMPs) and Inflammatory Bowel Diseases

Ulcerative colitis (UC) affects the colon and rectum. This disease is typically limited to the mucosa, manifesting as continuous areas of inflammation, crypt abscesses, and ulceration and extra intestinal manifestations. Ulceration of the mucosa involves many different pathways. Infiltrating neutrophils in UC secrete large amounts of the serineproteinase neutrophil elastase. In addition they secrete neutrophil collagenase enzyme (MMP-8) and there is marked overexpression of matrix metalloproteinases (MMPs) made by macrophages and fibroblasts, such as MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-10 and MMP-12[27]. The MMPs are a family of zinc and calcium dependent, highly regulated peptidases that function in the degradation of the extracellular matrix and collectively can cleave most of its constituents[28]. MMPs can also degrade other pro-inflammatory cytokines and chemokines, cleave tumour necrosis factor (TNF) from the cell membrane, and activate transforming growth factor (TGF)[19]. MMPs differ in their substrate specificity. The collagenases (MMP-1, MMP-8, and MMP-13) degrade mainly structural type I and III collagens, and the type IV collagenases/gelatinases, (MMP-2 and MMP-9) act on the basement membrane components and partially degraded collagen and the stromelysins, (MMP-3, MMP-10, and MMP-11) have broad substrate specificity, as do the matrilysins (MMP-7); and the metalloelastase (MMP-12) degrades mainly elastin. The 6 membrane-type MMPs (MT-MMPs) are integral trans-membrane proteins. Four are type 1 trans-membrane proteins (MMP-14, MMP-15, MMP-16, and MMP-24) and 2 are glycosyl phosphatidyl inositol (GPI) anchored proteins (MMP-17 and MMP-25). MMP expression is controlled at multiple levels, including transcription regulation, activation of the proenzymes and the binding to inhibitor proteins, such as tissue inhibitor of metalloproteinase (TIMP)[29,30] Disruption of control in any of these steps may result in a disease.

The identified inter-individual differences in UC susceptibility may be related to the genetic variation in the MMPs. MMP-8 has been found to be upregulated in a murine model of IBD[31] and it has been suggested that MMP-8 may participate in remodelling and homeostasis of the epithelial layer as well as in ulcer formation due to extensive type I collagen degradation[31]. MMP-10 has been found to be upregulated in IBD[32] and has been shown to be involved in macrophage movement, epithelial cell shedding, and wound healing[31,33,34]. MMP-3 has been found to be upregulated in IBD[35,36] and is believed to play an important role in IBD with roles in fistula formation, tissue damage, and neutrophil migration[37-39]. MMP-14 has also been found to be upregulated in IBD[40].

The Dendritic Cells and Inflammatory Bowel Disease

Antigen-presenting cells such as dendritic cells (DCs) are likely to play a central role in the host response to intestinal flora, both in innate responses to bacteria and by shaping the character of the host's adaptive immune response. In healthy mice, lamina propria DCs in the distal ileum showed evidence of bacterial sampling[41].

In mice with genetic abnormalities involving the function of antigen-presenting cells, intestinal inflammation occurs. Myeloid-specific Stat3-deficient animals that have a defect in the response of their macrophages and DCs to Stat3-dependent cytokines such as interleukin (IL)-10 develop intestinal inflammation characterized by enhanced production of pro-inflammatory IL-12, IL-6, and tumour necrosis factor (TNF)[42,43] Furthermore, studies in categories of murine models of colitis suggest that DCs are important in the initiation[44] and perpetuation of intestinal inflammation[45].

In Crohn's disease, a subgroup of patients possesses variants of the NOD2 protein. NOD2 is expressed by myeloid cells, including DCs, and is involved in innate bacterial recognition and regulation of the inflammatory cascade[46-48], suggesting that altered responses to the microflora by DCs may contribute to the inflammatory response in Crohn's disease. DCs are present in the intestine in the gut-associated lymphoid tissue and the lamina propria and lie in close proximity to the large and dynamic antigenic load in the gut lumen[49-52]. DCs in Peyer's patches sample commensal bacteria[53], but this is not the only site at which antigen uptake occurs. Lamina propria DCs pass their dendrites between epithelial tight junctions and interact directly with luminal antigens[54] and can sample luminal antigens that have passed through the epithelium. Intestinal DCs have different properties from their non-mucosal counterparts, probably because of their with the external environment. They are involved in both non-responsiveness or tolerance induction and responsiveness to antigens in the gut[55,56]. For example, DCs isolated from murine Peyer's patches produce more IL-10 than splenic DCs and have a tendency to induce Th2/3 responses[50]. DCs sense microbes by a series of surface receptors, including Toll-like receptors (TLRs) that recognize structural elements displayed on the surface of microbes[57]. TLR4 is required for recognition of lipopolysaccharide from *Escherichia coli*, and TLR2 recognizes peptidoglycan and lipoteichoic acid from gram-positive bacteria and lipoproteins from both gram-positive and gram-negative organisms[58-63]. DCs control microbial driven T-cell polarization in part through the ligation of TLRs[64]. After interaction with microbial products or other maturation stimuli such as cytokines, immature DCs in peripheral tissues change their pattern of chemokine receptors and migrate to the draining lymphoid tissue[65]. During this process, DCs down-regulate their antigen acquisition machinery, up-regulate the cell surface expression of major histocompatibility complex/peptide antigen complexes and maturation/co-stimulatory molecules such as CD40, and acquire their characteristic ability to stimulate naive T cells. The type of effector T-cell response is influenced by the cytokines produced by the activated DCs. For example, production of IL-12 by DCs polarizes a Th1 response[66], production of IL-10 by DCs influences a regulatory response[10], and production of IL-6 plays a role in overcoming the suppressive effect of regulatory T cells[67].

Evidence exists to prove that DCs in the human colonic mucosa are altered in IBD[68]. DCs from diseased tissue showed enhanced expression of TLR2 and TLR4, which may contribute to altered microbial recognition and increased proportion of activated DCs that release pro-inflammatory cytokines.

Discussion

Most biological systems are subject to complex regulatory control and the immune system is not an exception. In addition to T cells that up-regulate (help), other populations down regulate (suppress) the immune response. Once a normal immune response is initiated by antigenic stimulation, mecha-

nisms must be in place to control the magnitude of that response and to terminate it over time. Down-regulation should contribute to the homeostatic control of all immune responses serving to limit clonal expansion and effector cell activity in response to any antigenic stimulus.

This review demonstrates that the polymorphisms resulting from environmental exposures significantly affects gene down-regulation. These findings support the results of previous experiments in animal models. Transferring $CD4^{+}$ $CD45RB^{high}$ cells to SCID mouse recipients resulted in the development of a wasting disease and colitis 6-8 weeks after T cell transfer[69]. This disease was characterized pathologically by epithelial cell hyperplasia, goblet cell depletion, and transmural inflammation[70]. There was a 20- to 30-fold accumulation of Th1 cells in the intestine in comparison to normal mice. Treatment of recipients with anti-IFN-α, anti-TNF-α, or anti-IL-12 inhibited the induction of the disease. Transfer of $CD45RB^{low}$ cells did not induce colitis and co-transfer of RB^{high} and RB^{low} cells prevented the development of colitis. A ratio of 1:8 RB^{low} to RB^{high} was able to prevent the disease. When $CD45RB^{low}$ cells were fractionated into $CD25^{+}$ and $CD25^{-}$ fractions, control of intestinal inflammation was mediated primarily by the $CD25^{+}$ fraction[71]. $CD45RB^{low}$ $CD25^{-}$ did exert any suppressive function when transferred at high cell concentrations.

Treatment of recipients of $CD45RB^{high}$ cells with IL-10 inhibited the development of colitis. This treatment inhibited the accumulation of Th1 cells in the intestine but did not induce regulatory T cells, in as much as colitis developed when IL-10 administration ceased. RB^{high} T cells from mice that expressed IL-10 under the control of the IL-2 promoter failed to induce colitis and were also able to prevent disease when co-transferred with RB^{low} cells. The administration of anti-IL-10 R mAb revoked the ability of regulatory T cells to inhibit colitis. Furthermore, $CD45RB^{low}$ cells from $IL\text{-}10^{-/-}$ mice were unable to protect recipients from colitis when co-transferred with $CD45RB^{high}$ cells and induced colitis when transferred alone[72]. The ability of regulatory T cells to inhibit colitis was dependent on TGF-β[73].

Conclusions

Inflammatory Bowel Diseases are due to complex genetic defects which resulted from the long exposure to environmental risk factors. Gene polymorphism controlling the suppression of T-cell response to antigens play a significant role in the development of these diseases.

Conflict of Interests:

The Authors declare that they have no conflict of interests.

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