Genes Nutr (2007) 2:71–73
DOI 10.1007/s12263-007-0012-y

PROCEEDINGS

Uncoupling gene–diet interactions in inflammatory bowel disease (IBD)

Lynnette R. Ferguson · Ivonne Peterman · Claudia Hübner · Martin Philpott · Andrew N. Shellin

Published online: 19 September 2007

Keywords Nutrigenomics · Inflammatory bowel disease · Crohn's disease · Ulcerative colitis · Immune response · Transporter functions

Introduction

Inflammatory bowel disease (IBD) is a complex disorder characterised by chronic inflammation of the gastrointestinal tract [1, 2]. There are two main clinical subtypes, Crohn's disease (CD) and ulcerative colitis (UC). CD can affect any part of the intestine, and is associated with discontinuous, transmural lesions of the gut wall. In contrast, inflammation in UC is confined to the colon and rectum, and lesions are continuous and superficial. The overall prevalence of CD is 1:250–1:1,000 in European populations, and it affects men and women equally. It has long been recognized that there is a familial clustering, since ~20% of people with one form of IBD have a blood relative also with IBD (although not necessarily the same form). Twin studies indicate a genetic basis, and there is significant ethnic variability.

There is evidence that IBD is increasing in incidence throughout the Western world [2]. Although pharmaceutical approaches have been well investigated, prevention of the diseases would be highly desirable. CD is an important focus of research being done through Nutrigenomics New Zealand, since there is good reason to believe that there are a limited number of genes associated with the disease, and that its' incidence and severity could be modulated through diet.

L. R. Ferguson (✉) · I. Peterman · C. Hübner · M. Philpott · A. N. Shellin
Discipline of Nutrition and Nutrigenomics New Zealand, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand
e-mail: l.ferguson@auckland.ac.nz

Genetics of inflammatory bowel disease

A number of chromosome regions have been described as associated with IBD, as recently summarized by Schrieber et al. [3]. Since the definitive recognition of key area of the IBD1site as NOD2/CARD15, an increasing volume of literature has been published in the area. There are now a wide number of claimed associations of genes associated with IBD [3, 4]. It is of interest that those associated with IBD thus far generally fall into one of three classes: those affecting immune response, those affecting transport, and those affecting bacterial recognition.

Studies in more depth have been done on NOD2/CARD15, for which four common polymorphisms have been associated with CD susceptibility. The best characterised of these is a frameshift mutation at position 1,007. It seems that approximately 1% of the normal population, but around 14% of CD patients, are heterozygous for the variant allele. This implies that NOD2 acts as a susceptibility allele, rather than directly causing the disease.

Nutritional management of IBD

A considerable number of studies, especially in the clinical nutrition field, have attempted to define diets for IBD. As well as the direct effects that are reflected in the inflamed colon, there are a number of other nutritional requirements that are associated with the longer term effects of the disease process. Decreased oral intake, malabsorption, accelerated

nutrient losses, increased micronutrient requirements, and drug-nutrient interactions, are all important factors that result in many IBD patients typically developing symptoms of malnutrition, as well as the more direct symptoms of the disease. An important series of studies in this area was done by John Hunter and his group in Cambridge [5–7], who recognised the importance of individualising diet for these people. They utilised a systematic study approach where, in a carefully controlled fashion, they added new foods one at a time back into a polymeric diet, and only permitted the individual to continue with this dietary item if they were convinced they had no suggestion of a negative effect. While clearly efficacious, this approach had the disadvantage of not being time or cost-effective.

More generally, these early studies had one observation in common. Without individualising diets, it was not possible to control IBD in general, or CD more specifically, using nutritional approaches. Nutrigenomics New Zealand intends to utilise the knowledge of the genes involved in disease susceptibility, in order to design diets that may potentially overcome the disorder.

Dietary manipulation of immune response

Various nutrients are particularly important to the immune system, since they are either preferentially used by the system, or rapidly consumed during an immune response [8]. The amino acids arginine and glutamine are considered non-essential amino acids, but may be depleted during an immune response. Arginine is the sole substrate for nitric oxide synthase, necessary for the synthesis of nitric oxide that is secreted by macrophages to kill pathogens. Glutamine is a specific fuel for the proliferation of lymphocytes. Many sulphur amino acids act as substrates for acute phase protein and immunoglobulin synthesis, and the intake of these molecules is particularly important for glutathione production. An insufficient intake of sulphur amino acids will both exert a pro-inflammatory influence, and reduce the efficiency of the specific immune response.

Several micronutrients are especially important for immunonutrition, and three examples will be used to illustrate this. Zinc is a critical component of many of the enzymes involved in DNA replication and transcription. Since immune cells are rapidly dividing, especially during infection, they therefore have heightened sensitivity to impaired DNA replication. Zinc is also a component of proteins involved in signal transduction during T-cell activation and interaction with B-cells. A deficiency raises blood glucocorticoid levels, decreases thymulin activity and affects many cytokine concentrations. Selenium deficiency decreases antibody production by B-cells and decreases neutrophil chemotaxis and activity, while selenium supplementation enhances T-cell responses by upregulation of the T-cell IL-2 receptor and increases antibody synthesis. It acts as an antioxidant, protecting host tissues from damage by reactive oxygen species (ROS) generated by the inflammatory response. It is also a key component of glutathione peroxidase, which detoxifies the ROS hydroperoxide and hydrogen peroxide.

Less clear is the example of iron, where the effects on immune function and benefits of supplementation are heavily debated. Iron deficiency does lead to reduced neutrophil function, depression of T-cell numbers with thymic atrophy, defective Tcell proliferative response, and impaired interleukin 2 production by lymphocytes. However, iron is a requirement of many pathogens, and the net effect of iron supplementation can be increased susceptibility to some infections, such as malaria.

None of these nutrients is unique to the immune system, but all are important to many other cell types. They are incorporated into proteins and may act as normal protein substrates. That is, these are compounds with a defined physiological role. However, their deficiency will often impact the immune system first due to the relatively high proliferation rate of immune cells, or the heightened demands placed on the immune system during infection. More intriguing are the immunonutrients with no previously defined role in nutrition, and whose role is currently less well defined. Examples here are green tea (reduces immune stimulation) or echinacea which is claimed to enhance it.

Dietary manipulation of transporter functions

Of the various genes identified as probable IBD susceptibility genes, MDR1 is the best characterised. The human gene encodes P-glycoprotein (Pgp), a 170 kDa phosphorylated glycoprotein, that is vulnerable to inhibition, activation, or induction by herbal constituents [9]. For example, curcumin, ginsenosides, piperine, some catechins from green tea, and silymarin from milk thistle were found to be inhibitors of Pgp, while some catechins from green tea increased Pgp-mediated drug transport. St. John's wort induced the intestinal expression of Pgp in vitro and in vivo.

Conclusions

It is the major aim of Nutrigenomics NZ to determine how foods and food components affect health at the molecular genetic level by using nutritional genomic methods. Identifying SNPs involved in the development of IBD is an important first step in the Nutrigenomics Research Programme. Relating these to dietary restrictions

and preferences will permit the development of hypotheses relating diet and genotype. Ultimately, it is hoped that we can use this information to come up with practical solutions to IBD. Milk shakes or muesli bars might provide a useful vehicle for bringing specific changes into a diet. Application of a wide range of techniques in systems biology will be necessary to fully uncouple gene–diet relationships.

Acknowledgments Nutrigenomics New Zealand is a research collaboration between The University of Auckland, AgResearch, HortResearch, and Crop and Food Research. It is financially supported with funding from the Foundation for Research, Science and Technology.

References

1. Rogler G (2004) Update in inflammatory bowel disease pathogenesis. Curr. Opin Gastroenterol 20:311–317
2. Macdonald TT, Monteleone G (2005) Immunity, inflammation, and allergy in the gut. Science 307:1920–1925
3. Schreiber S, Rosenstiel P, Albrecht M, Hampe J, Krawczak M (2005) Genetics of Crohn's disease, an archetypal inflammatory barrier disease. Nat Rev Genet 6:376–378
4. Russell RK, Nimmo ER, Satsangi J (2004) Molecular genetics of Crohn's disease. Curr Opin Genet Dev 14:264–270
5. Workman E, Jones VA, Wilson AJ, Hunter JO (1984) Diet in the management of Crohn's disease. Appl Nutr Hum Nutr 38A:469–473
6. Jones VAA, Workman E, Freeman AH, Dickinson RJ, Wilson AJ, Hunter JO (1985) Crohn's disease: maintenance of remission by diet. Lancet 22:177–180
7. Jones VAA (1987) Comparison of total parenteral nutrition and elemental diet in induction of remission of Crohn's disease. Dig Dis Sci 32:100S–107S
8. Philpott M, Ferguson LR (2004) Immunonutrition and cancer. Mutat Res 551:29–42
9. Zhou S, Lim LY, Chowbay B (2004) Herbal modulation of P-glycoprotein. Drug Metab Rev 36:57–104