Genome Medicine

Musings

Musings on genome medicine: Crohn's disease

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Abstract

The inflammatory bowel diseases, Crohn's disease and ulcerative colitis, pose a fascinating challenge to specialists in gastroenterology, infectious diseases, immunology and genetics and an often crushing burden to patients and their families.

Approximately a half million children and adults deal with Crohn's disease (CD) in North America for a prevalence of about 170/100,000 [1], while the prevalence averages about 40/100,000 in Europe [2]. Curiously, the prevalence and incidence are higher in the northern parts of Europe and North America than in the southern parts [2].

There are well-established risk factors for CD, including being Ashkenazi Jewish, having a first-degree relative with CD, stress and smoking. Although there is female predominance in Canada, Europe and the United States report a small excess of males [2]. The incidence is much higher in developed than in less developed countries, leading to an hypothesis that improved hygiene may influence the onset of the disease. This concept has led to interesting experiments in which helminths are deliberately fed to patients with CD [3,4].

Crohn's disease was described first in 1904 by a Polish surgeon, Antoni Lesniowski [5], and more thoroughly by Burrill Crohn and his colleagues at the Mount Sinai Hospital of New York in 1932 [6]. The clinical presentation of CD and its pathology differs from that of ulcerative colitis (UC), in that the former may be far more widespread throughout the gastrointestinal tract, may extend deeply into the intestinal wall, is associated with granuloma formation and is characterized by skip areas. Hence the original and now unused name 'regional enteritis'. It tends to localize in the terminal ileum, where it may narrow the bowel and cause malabsorption of vitamin B_{12} and intestinal obstruction. The latter site is so frequently involved that the disease is also called terminal ileitis. The age of onset is usually in the teens or twenties and another peak is said to occur in the fifties to seventies, but CD may occur (or be correctly diagnosed) at any age. The major symptoms include abdominal pain, diarrhea (occasionally bloody), constipation, vomiting, and weight loss. CD is often associated with various skin rashes (including erythema nodosum), rheumatoid arthritis and uveitis, strongly suggesting an autoimmune basis for the disease to some, but the result of chronic stimulation of cytokine production and T cell activation to others. When CD is active, it is usually associated with microcytic anemia, the so-called 'anemia of inflammation' induced by excessive hepcidin synthesis in the liver and resultant inactivation of ferriportin. The latter diminishes iron transport from the gut lumen and the macrophage to the blood [7]. There are three primary types of CD, called mucosal disease, fistulizing disease and structuring disease. The search is on for the genetic factors that influence the three types. New classification schemes have been developed to aid in the latter process [8].

The etiology of CD has been a complete mystery until recently. In the mid 20th century, when Freudian theory held sway in academic medicine, CD, UC and peptic ulcer were all thought to be psychosomatic illnesses. The data supporting that argument were very thin at the time and the discovery of *Helicobacter pylori* as the cause of peptic ulcer [9] and *Tropheryma whipplei* as the inciter of Whipple disease [10] drove a very large nail into the coffin of psychosomatic medicine. Thus far, however, no specific micro-organisms have been isolated and shown to be the inciters of either CD or UC. Some studies suggest that *Mycobacterium avian paratuberculosis* could play an important role, and it is known to cause a similar disease called Johne's disease in cattle [11]. However, this lead and the inciting roles of other investigated bacteria have not been confirmed in human CD. Nonetheless, the possibility remains that such an organism may well be found as new molecular detection methods are developed. Open and receptive minds are essential in medicine for, as the Good Book emphasizes, 'idolatry blindeth the eye'.

At present the general consensus regarding the etiology of both CD and UC is that they are the result of very

CD, Crohn's disease; IL23R, receptor for interleukin 23; NOD2, nuclear-binding oligomerization domain containing 2; PTPN2, protein tyrosine phosphatase non-receptor 2; TNF, tumor necrosis factor; UC, ulcerative colitis.

unfavorable and persistent inflammatory reactions induced by confrontations betwixt normal resident (commensal) gut flora (largely bacteria) and the local host immune responses to their carbohydrate, protein and lipid antigens (for a broader review of inflammation see the recent *Nature* 'Insight' series edited by Weiss [12], and for the human 'microbiome' see the recent work of Segre and co-workers [13]).

Since the bacterial antigens responsible for CD and UC are currently unknown, both illnesses are considered 'auto-immune' diseases, as are multiple sclerosis, psoriasis, rheumatoid arthritis, juvenile diabetes mellitus and Hashimoto's thyroid struma. But such a term is misplaced and incorrect if the inciting antigen is not a self antigen but rather a bacterial antigen. The term 'autoimmunity' is bandied about in the medical literature as loosely as psychiatric terminology was tossed around in the mid 1900s.

CD and UC are probably better considered as examples of hyper-reactivity in which patients with certain polymorphisms of the genes that control autophagy, phagosome assembly, the so-called inflammasome, interleukin 23 receptors, epithelial barriers, Paneth cells of the gut, the NFkB/IRF system, and other pathways interact with genetic imbalances of Th1/Th17 cells [14], and defects in innate immunity and both systems confront a host of commensal bacteria. The risk of CD or UC is the result of the interaction between the genetic hand that is drawn and the bacteria residing in the gut. In this model, CD is seen as a disorder arising from both the environment (including micro-organisms, smoking and 'stress') and one's individual reactive genotype, including variations in *NOD2*, *PTPN2*, *IL23R*, *ATG16L1*, *IRGM*, *NCF4*, *TNFSF15* and *MST1*, three of which are described in more detail below.

Genome-wide association studies conducted by Mark Daly and his very large group of collaborators have revealed more than 30 susceptibility loci for CD [15]. Daly's group has evaluated 3,230 CD cases and compared them to 4,829 controls, all of European descent. The studies were well powered to detect alleles with odds ratios of 1.3 to 1.5 and had a 74% power to detect odds ratios of 1.2. Eleven previously reported single nucleotide polymorphism associations were again detected, including *NOD2* (nuclear-binding oligomerization domain containing 2; usually associated with structuring disease), *IL23R* (receptor for interleukin 23) and *PTPN2* (protein tyrosine phosphatase non-receptor 2) with odds ratios of 3.99, 2.50 and 1.35, respectively; but 21 other associations with odds ratios between 1.08 and 1.31 were also detected. Only a minority of the variance in risk (about 10%) is explained by the sum of all 32 of these alleles, strongly suggesting that other risk alleles will be detected in the future. Indeed, the sum of these alleles contributes only a factor of 2 to sibling relative risk, and a very large proportion of that contribution is derived from *NOD2*, the originally described risk factor gene. Clearly, delineation of the genetic basis of CD requires considerably more study. As emphasized above, it also remains possible that most of the risk is not inherited but is instead related to infection with a particular set of organisms. That infectious disease is the result of an interaction between micro-organisms and host response genes is scarcely a unique notion confined to inflammatory bowel disease. Casanova and his colleagues have successfully pointed out that infectious disease susceptibility is highly influenced by host response genes [16,17].

It is fervently hoped that more genetic information or the discovery of inciting bacteria will lead to improved therapy. Until that day arrives, clinicians utilize rather blunt tools designed to suppress a broad array of the members of the inflammatory response, such as methotrexate and corticosteroids or more targeted monoclonal antibodies to effecter proteins like TNF (tumor necrosis factor). It is surprising and gratifying that many CD patients, like cancer patients, do very well when treated by these non-specific drugs. But CD patients are not often, if ever, cured by such treatments. They are instead held in very acceptable remissions that may be punctuated by short bursts of symptoms that disappear as they came. Thus the treatments are effective holding actions while we await more practical applications of genetic information and (hopefully) the identification of unique bacterial pathogens, the removal of which would (as in peptic ulcer) truly produce cures.

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References

1. Loftus EV Jr, Schoenfeld P, Sandborn WJ: **The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America: a systematic review.** *Aliment Pharmacol Ther* 2002, **16:**51-60.
2. Bernstein CN, Wajda A, Svenson LW, MacKenzie A, Koehoorn M, Jackson M, Fedorak R, Israel D, Blanchard JF: **The epidemiology of inflammatory bowel disease in Canada: a population-based study.** *Am J Gastroenterol* 2006, **101:**1559-1568.
3. Weinstock JV, Elliott DE: **Helminths and the IBD hygiene hypothesis.** *Inflamm Bowel Dis* 2009, **15:**128-133.
4. Rook GA: **Review series on helminths, immune modulation and the hygiene hypothesis: the broader implications of the hygiene hypothesis.** *Immunology* 2009, **126:**3-11.
5. Lichtarowicz AM, Mayberry JF: **Antoni Lesniowski and his contribution to regional enteritis (Crohn's disease).** *J R Soc Med* 1988, **81:**468-470.
6. Crohn BB, Ginzburg L, Oppenheimer GD: **Regional ileitis: a pathologic and clinical entity. 1932.** *Mt Sinai J Med* 2000, **67:** 263-268.
7. Lee PL, Beutler E: **Regulation of hepcidin and iron-overload disease.** *Annu Rev Pathol* 2009, **4:**489-515.
8. Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, Caprilli R, Colombel JF, Gasche C, Geboes K, Jewell DP, Karban A, Loftus Jr EV, Peña AS, Riddell RH, Sachar DB, Schreiber S, Steinhart AH, Targan SR, Vermeire S, Warren BF: **Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a**

Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005, **19(Suppl A):**5-36.

9. Cover TL, Blaser MJ: ***Helicobacter pylori* in health and disease.** *Gastroenterology* 2009, **136:**1863-1873.
10. Marth T, Schneider T: **Whipple disease.** *Curr Opin Gastroenterol* 2008, **24:**141-148.
11. Naser SA, Collins MT: **Debate on the lack of evidence of *Mycobacterium avium* subsp. *paratuberculosis* in Crohn's disease.** *Inflamm Bowel Dis* 2005, **11:**1123.
12. Weiss U: **Inflammation.** *Nature* 2008, **454:**427-477.
13. Grice EA, Kong HH, Conlan S, Deming CB, Davis J, Young AC; NISC Comparative Sequencing Program, Bouffard GG, Blakesley RW, Murray PR, Green ED, Turner ML, Segre JA: **Topographical and temporal diversity of the human skin microbiome.** *Science* 2009, **324:**1190-1192.
14. Korn T, Bettelli E, Oukka M, Kuchroo VK: **IL-17 and Th17 cells.** *Annu Rev Immunol* 2009, **27:**485-517.
15. Barrett JC, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, Brant SR, Silverberg MS, Taylor KD, Barmada MM, Bitton A, Dassopoulos T, Datta LW, Green T, Griffiths AM, Kistner EO, Murtha MT, Regueiro MD, Rotter JI, Schumm LP, Steinhart AH, Targan SR, Xavier RJ; NIDDK IBD Genetics Consortium, Libioulle C, Sandor C, Lathrop M, Belaiche J, Dewit O, Gut I, Heath S, *et al.*: **Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease.** *Nat Genet* 2008, **40:**955-962.
16. Zhang SY, Boisson-Dupuis S, Chapgier A, Yang K, Bustamante J, Puel A, Picard C, Abel L, Jouanguy E, Casanova JL: **Inborn errors of interferon (IFN)-mediated immunity in humans: insights into the respective roles of IFN-alpha/beta, IFN-gamma, and IFN-lambda in host defense.** *Immunol Rev* 2008, **226:**29-40.
17. Al-Muhsen S, Casanova JL: **The genetic heterogeneity of mendelian susceptibility to mycobacterial diseases.** *J Allergy Clin Immunol* 2008, **122:**1043-1051; quiz 1052-1043.

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