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Lecture

Immune mechanisms and natural history of inflammatory bowel disease

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SUMMARY

The gastrointestinal tract uses a system of tolerance and controlled inflammation to limit the response to dietary or bacteria-derived antigens in the gut. The triggering factor for this and cascade whether it represents an auto-antigen or an heteroantigen is still to be elucidated. It has been also demonstrated that a serologic anti-microbial response in CD patients exists. This response includes antibodies against saccharomyces cerevisiae (ASCA), E.coli outer membrane porin C (Omp-C), flagelin (cBir1) and pseudomonas aeroginosa (I2). Host response to microbial pathogens includes self-defense mechanisms such as defensins, pattern recognition receptors (PRRs) and TLRs (Toll Like Receptors).

Natural history of IBD has been described mainly through studies in American and north European IBD cohorts. In general, 50-60% of IBD patients are in remission during any given year. The likelihood of steroid dependency remains high in IBD. The prediction of disease location seems quite safe as the location of the disease remains stable over time. By contrast the disease behaviour changes over time with increasing risk for structuring/penetrating disease with longer disease duration. The question whether currently available therapies are able to alter natural history of IBD still remains unanswered. The risk of colorectal cancer in UC patients begins to increase 8 years from diagnosis and high risk groups are patients with extensive colitis, young age at UC onset, familial cancer history and co-existing primary sclerosing cholangitis. In CD the risk of cancer seems to be comparatively smaller. Life expectancy of CD patients is slightly lower compared to healthy subjects while life expectancy in UC patients is generally normal.

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IMMUNE MECHANISMS IN IBD

The gastrointestinal tract uses a system of tolerance and controlled inflammation to limit the response to dietary or bacteria-derived antigens in the gut.[1-3] When this complex system breaks down, either by a chemical or pathogenic insult in a genetically predisposed individual the resulting immune response may lead to IBD.[4-8] Although the aetiopathogenesis of IBD remains unsolved, current evidence indicates that defective T-cell apoptosis and impairment of intestinal epithelial barrier function play important roles.[9-10] Difference in T-cell responses between CD and UC have been identified, with mucosal T-cell apoptosis being defective in CD but not in UC.[7] In both CD and UC activation of macrophages seems to be important as increased production of the macrophage derived cytokines TNF-alpha, IL-1 and IL-6 have been reported in both diseases.[11-12] Additionally, the symptomatic phases of IBD are characterized by migration of large numbers of neutrophils and accumulation in the intestinal lumen. The triggering factor for this cascade and whether it represents an auto-antigen or an hetero-antigen, is still to be elucidated i.e. a microbial component.[3-5] Dysbiosis is the disturbance of intestinal microflora resulting in the breakdown in the balance between 'protective' vs 'harmful' intestinal bacteria.[13] Dysbiosis is implicated in many chronic diseases such IBD which are associated with 'westernized' life style. It has been shown that enteric bacteria do not have equal capacities to induce or protect from inflammation and interestingly, H.pylori has also been implicated in CD pathogenesis.[14] It has been also demonstrated that a se-

rologic anti-microbial response in CD patients exists. This response includes antibodies against saccharomyces cerevisiae (ASCA), E.coli outer membrane porin C (OmpC), flagelin (cBir1) and pseudomonas aeroginosa (I2).[15-16] Host response to microbial pathogens includes self-defense mechanisms including defensins, pattern recognition receptos (PRRs) and TLRs (Toll Like Receptors). The leucocyte-epithelial interactions are of special interest as exposure of epithelial TLRs to microbial ligands has been shown to result in transcriptional upregulation of inflammatory mediators whereas ligation of leucocyte TLRs modulate specific antimicrobial responses.[17] Another issue of interest is that ASCA may develop before the obvious clinical diagnosis of CD according to a study using serum samples from the Israeli Defense Corp repository. In this study, 32% of patients were ASCA(+) 38 months before CD clinical diagnosis was made.[18] According to emerging data perinuclear antineutrophil cytoplasmic antibodies (pANCA) have a 60-80% sensitivity for UC and 10% for CD. Antibodies to baker's yeast (ASCA) hold a 60-65% sensitivity and 95% specificity for CD.[19-21]The target antigen for pANCA is currently unknown and there is still variation regarding the interobserver agreement with the several assays used for their determination. These serologic markers may be of great potential importance as they can inform more on the IBD pathogenesis, the differentiation between UC and CD, the further differentiation of indeterminate colitis, the prediction of pouchitis and prediction of response to therapies.[19-21] It is of importance that ASCA have a genetically-modulated expression as they are found in 20-25% of relatives of CD patients and are absent in spouses. In addition, pANCA are present in up to 20% of unaffected relatives of UC patients and they persist after colectomy indicating two points: that the target antigen in IBD is not fully eradicated and that it is not just the colon which is immunologically targeted in UC.[19-22] Neuroimmunomodulation in IBD is another interesting approach with implications on the influence of brain-gut axis on intestinal inflammation and its perpetuation.[23-25] It is probable that both UC and CD represent heterogenic groups of diseases that share similar mechanisms of tissue damage but have different initiating events and immunoregulatory abnormalities. A better understanding of all these events will hopefully provide new insights into the mechanisms of epithelial responses to microorganisms and ideas for therapies.

The natural history of IBD

Natural history including the likelihood of a flare in any given year has been investigated in a restricted number of IBD cohorts. As CD is concerned, it has been shown that after the first year of diagnosis, the majority of patients with CD in any population has mild disease activity or is in remission[26] while another study showed that in 65% of follow up time IBD is characterized by medical or surgical remission.[27] It has also been demonstrated in CD that after a flare there is a 30% chance of remission in the following year whereas when the patient achieves remission for one year there is an 80% chance of remission in the following year.[28] For UC, in a study with 1,161 patients with 25 years follow up after diagnosis it has been shown that 50% of patients were in clinical remission every year at any time while the cumulative probability of a relapsing course was 90% after 25 years of follow up. In addition, activity in the first 2 years after diagnosis indicated 70-80% probability of 5 consecutive years of active disease.[29] In general, 50-60% of IBD patients are in remission during any given year. The likelihood of steroid dependency remains high in IBD as 40-50% of CD and 30% of UC patients will need steroids during the first year. In detail, according to the study from Copenhagen county[29], 56% of IBD patients required steroids while the Olmstead county study[30] showed that 34% of UC and 43% of CD patients required steroids. The prediction of disease location seems quite safe as the location of the disease remains stable over time. Only 15% of patients will have a change in location over a 10 year period.[31] The natural history of esophageal CD follows three patterns of evolution with the complete remission pattern being the most prevalent in such cases.[32] By contrast the disease behaviour changes over time with increasing risk for structuring/penetrating disease with longer disease duration. As far as the natural history of fistulizing CD is concerned, it seems that the cumulative incidence of anal fistulas approximates 23% while fistula incidence is increased with more distal intestinal disease location according to the Stockholm and Olmstead population-based studies.[33-34] According to another study, over a 20-year follow up in CD patients there is an 88% cumulative risk of developing structuring (18%) or penetrating (70%) disease.[35] It is noteworthy that it seems that location of the disease determines the behavior. Thus, ileal disease seems to correlate more with structuring behavior while colonic and ileocolonic disease correlates more with inflammatory or penetrating disease phenotype.[36] The cumulative risk of surgery 15 years after diagnosis is generally 80% for CD and 30% for UC.[30] It is of interest that the likelihood of surgical intervention at 1 year following start of steroid therapy shows that 40% of CD and 30% of UC patients will need surgery.[30] Risk factors for surgery are small bowel disease

and perianal fistulas while risk factors for recurrence after surgery are female sex (RR 1.2), small bowel disease (RR 1.8) and the existence of perianal fistulas (RR 1.4).[37] Another study with 770 patients undergoing intestinal resection for perforating or non-perforating indications has shown that rapid recurrence is more probable in perforating compared to structuring disease.[36] It is of importance that recurrence of CD almost always develops in the first year after an ileocolonic anastomosis operation.[38] Strictureplasty does not seem to alter the natural history of the disease.[39] Smoking has been found to protect against UC and to deteriorate the CD course in pre- and post operated patients.[40-41] Appendectomy has been suggested to protect against UC and it has also been shown that appendectomy may delay onset but not course of the disease while previous appendectomy (OR 0.4) and current smoking (O.R 0.6) represent independent factors protecting against colectomy in UC patients.[35,42] The question of whether currently available therapies are able to alter natural history of IBD still remains largely unanswered also in the view of the high response to placebo therapy.[43-44] Large cohort prospective studies well balanced for clinical, endoscopic and laboratory parameters are needed to clearly address this important issue. The risk of colorectal cancer is an extremely important but still contradictory issue as far as its extension is concerned. In UC, there is a great variability in cancer reported incidence with hospital studies reporting up to 40% cumulative cancer rates and population based studies reporting only 13.5%.[45-48] However both types of studies agree on the increased risk of cancer in patients with pancolitis. The risk of colorectal cancer in UC patients begins to increase 8 years from diagnosis and high risk groups are patients with extensive colitis, young age at UC onset, familial cancer history and co-existing primary sclerosing cholangiitis.[49-53] In CD the risk of cancer seems to be comparatively smaller that that of UC but rare lymphoma cases as well as cases of malignancies arising from fistula tracts need to be addressed here. Life expectancy of CD patients is slightly lower and most pronounced in women less than 50 years old at diagnosis.[54-55] Life expectancy in UC patients is generally normal except for patients over 50 years of age and with extensive colitis at diagnosis.[52] All information on IBD natural history presented here, although it seems that it has not substantially changed in the last forty years[56-61] with the probable exception of fatal fulminant colitis, has limitations[62], the most important being the lack of large prospective population-based studies and the lack of widely published long-term experience of other than the northern European and the northern American IBD study centers.

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