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Research paper

Inflammatory cells implicated in neoplasia development in idiopathic inflammatory bowel disease

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ABSTRACT

The inflammatory mechanisms that lead to the clinical symptoms that are grouped under the term inflammatory bowel disease have not been fully characterized. Although a specific mechanism has not been identified, inflammatory bowel disease is believed to be related to an inability by the immune system to shut active inflammation within the intestine. Many contributing factors have been implicated in the disease process. Based on population studies, patients with inflammatory bowel disease have an increased risk for neoplastic development. Although no specific immune cell has been implicated in neoplastic development within this patient population, several immune cells have been implicated as possible etiologies in inflammatory bowel disease. In this review, we will review the clinical evidence about the risk for neoplastic development in inflammatory bowel disease and the current clinical guidelines to survey this patient population. We will also review the pathologic assessment of inflammation within this patient population as well the underlying immune cells and cytokines that have been implicated in the etiology of inflammatory bowel disease.

Inflammatory bowel disease (IBD) is a group of chronic inflammatory conditions that affect the gastrointestinal (GI) tract. Clinically, the two major subtypes of IBD are Crohn's disease characterized by affecting the GI tract anywhere between the mouth and the anal verge, and ulcerative colitis characterized by only affecting the colon. The involved areas of the GI tract include neutrophilic inflammation of the epithelium with subsequent loss of the epithelial integrity, chronic inflammation (generally characterized by lymphocytes and plasma cells) and epithelial metaplasia. Until today, the etiology of IBD remains largely unknown [1]. It is currently thought to be related to a complex interaction between environmental triggers that may cause a shift in the microbiome in a genetically susceptible host whose immunologic response fails to downregulate in an otherwise high inflammatory state. Epidemiologic data does suggest that these syndromes do increase the life time risk for neoplastic development within the colon and small intestine [2]. Herein, we will review the clinical studies/characteristics that have been linked to the neoplastic risk of idiopathic inflammatory bowel disease, some of the unique molecular abnormalities that have been described in neoplasia that arises in the GI tract of these patients and review the inflammatory cells commonly implicated in the etiology of inflammatory bowel disease.

1. Clinical characteristics

The symptoms experienced by patients are believed to be related to the amount of inflammation present within the intestine. There are several drug classes that are used to treat IBD including the 1) 5-aminosalicylic acid (5-ASA) drugs which include the mesalamines and sulfasalazine, 2) immunomodulators which include methotrexate and the thiopurines such as azathioprine and 6-mercaptopurine, as well as 3) biologic agents which include either anti-TNF agents, anti-IL-12/IL-23 medications, or anti-integrins. There are also many therapies for different mechanisms of action that are in development/at the clinical trial stage.

Patients with IBD are at an increased risk for the development of colorectal carcinoma as compared to patients who do not have IBD [2]. A large meta-analysis showed that after 20 years of diagnosis, the risk of colon cancer in patients with UC is as high as 8% [3,4]. This rate increased to 18% after 30 years of having ulcerative colitis. Patients with Crohn's disease whose inflammation affects the colon are also at an increased risk for the development of colon cancer. Studies that included both Crohn's disease and ulcerative colitis patients together showed that the rates of cancer where comparable amongst the two disease subtypes [5].

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The pathogenesis behind colon cancer development in IBD patients is not clear but contributing factors include genetic, immune, oxidative stress, shift in the intestinal microbiome, and environmental. There are several factors that contribute to the increased risk of colon cancer amongst IBD patients. Chronic inflammation is one of the important factors [6,7]. This is represented by duration of inflammation and anatomic extent of involvement. The severity of previous inflammation has also been noted to increase the risk of cancer development [8]. Duration of IBD is an important factor increasing the risk of cancer in patients who have had IBD for 8 years and longer [9]. As for the histologic extent of disease, patients who have more extensive disease are at a higher risk than those patients with limited disease. Colon cancer arises in areas that had harbored histologically active disease at some point in time, even if the area shows inactive colitis presently. Areas that have always been spared of inflammation do not carry an increased risk for the development of cancer. Patients who have pseudopolyps tend to be those who have had severe inflammation previously. These patients are at an increased risk for colon cancer development, supporting that history of more severe inflammation may contribute to cancer risk [10].

Presence of concomitant primary sclerosing cholangitis (PSC) further increases the risk of colon cancer by 4.8-fold compared to other ulcerative colitis patients and these patients with PSC should have yearly surveillance colonoscopies due to their increased risk for cancer [11]. Family history of colon cancer in a first degree relative also contributes to an increased colon cancer risk [12]. The best marker of colorectal cancer risk amongst IBD patients is the presence of dysplasia. Dysplasia, however, does not always precede colon cancer in IBD patients. Similarly, IBD patients may progress from low grade dysplasia to cancer without a detectable high grade dysplasia phase.

Due to this increased risk of colon cancer compared to the general population, there have been surveillance guidelines for the early detection of dysplasia and neoplasia amongst IBD patients. In conjunction with the American Gastroenterology Association (AGA), the American Society of Gastrointestinal Endoscopy (ASGE) group published the SCENIC guidelines [13]. Table 1 summarizes these recommendations. The American College of Gastroenterology (ACG) recommends that after at least 8 years of ulcerative colitis, annual or biannual surveillance colonoscopy should be performed [14].

There have been several drugs investigated for their possible chemopreventive role against the development of dysplasia/neoplasia, and the use of all of these remains controversial. Such medications include ursodeoxycholic acid, 5-ASA medications, and folic acid, amongst others.

2. Histologic evaluation

Although there have been several proposed grading schemes for inflammation within inflammatory bowel disease, only two have been recently clinically validated and only for ulcerative colitis – Nancy Score and Robart's Histopathology Index [15–17]. The scoring systems are present in Tables 2 and 3 [16,17]. The above two classification schemes do not take into account basal lymphoplasmacytosis or eosinophils within their evaluation. Over twenty different histologic schemes have been proposed to evaluate the inflammation in IBD. Perhaps one of the most widely used in research studies, the Geboes index is extensive in evaluating each inflammatory component within a given piece of tissue [18]. The Geboes index is illustrated in Table 4 [18]. An individual assessment of each inflammatory cell component is summated in this scoring system. However, for routine cases, this scoring schema does represent some difficulty in achieving widespread adoption even among expert gastrointestinal pathologists and so it has largely been used in research studies. The routine pathology description for inflammatory bowel disease will generally provide a description of activity (neutrophil tissue infiltration) and chronicity (architectural changes and lymphocytic/plasma cell infiltrate). These two components are the principle unifying theme within each of the patterns that we describe as inflammatory bowel disease.

Table 2
Nancy Score [16].

	Grade	Description
Chronic inflammatory infiltrate	0	No increase
	1	Mild but unequivocal increase
	2	Moderate increase
	3	Marked increase
Neutrophils in the epithelium	0	None
	1	< 50% of crypts involved
	2	> 50% of crypts involved
Ulceration	0	Absent
	1	Present
Acute inflammatory cell infiltrate	0	None
	1	Mild
	2	Moderate
	3	Severe
Mucin depletion	0	None
	1	Mild
	2	Moderate
	3	Severe
Neutrophils in lamina propria	0	None
	1	Mild
	2	Moderate
	3	Severe
Basal plasmacytosis	0	None
	1	Mild
	2	Moderate
	3	Severe
Serrated architectural abnormalities	0	None
	1	< 5% crypts involved
	2	< 50% crypts involved
	3	> 50% crypts involved

Table 1
SCENIC Recommendations for surveillance of dysplasia in patients with IBD [13].

When performing surveillance with white-light colonoscopy, high definition is recommended rather than standard definition	Strong recommendation, low-quality evidence
When performing surveillance with standard-definition colonoscopy, chromoendoscopy is recommended rather than white-light colonoscopy	Strong recommendation, moderate-quality evidence
When performing surveillance with high-definition colonoscopy, chromoendoscopy is suggested rather than white-light colonoscopy	Conditional recommendation, low-quality evidence
When performing surveillance with standard-definition colonoscopy, narrow-band imaging is not suggested in place of white-light colonoscopy	Conditional recommendation, low-quality evidence
When performing surveillance with high-definition colonoscopy, narrow-band imaging is not suggested in place of white-light colonoscopy	Conditional recommendation, moderate-quality evidence
When performing surveillance with image-enhanced high-definition colonoscopy, narrow-band imaging is not suggested in place of chromoendoscopy	Conditional recommendation, moderate-quality evidence

Table 3
Robart's Histopathologic Index [17].

Component	Scoring	Multiplier
Chronic inflammatory infiltrate	0 = No increase 1 = Mild but unequivocal increase 2 = Moderate increase 3 = Marked Increase	1 X score result
Lamina propria neutrophils	0 = None 1 = Mild but unequivocal increase 2 = Moderate increase 3 = Marked increase	2 X score result
Neutrophils in epithelium	0 = None 1 ≤ 5% crypts involved 2 ≤ 50% crypts involved 3 ≥ 50% crypts involved	3 X score result
Erosion or ulceration	0 = No erosion, ulceration or granulation tissue 1 = Recovering epithelium + adjacent inflammation 1 = Probable erosion – focally stripped 2 = Unequivocal erosion 3 = Ulcer or granulation tissue	5 X score result
		Summation of the above scores (Range 0 (no disease activity) up to 33 (severe disease activity)

Table 4
Geboes Histologic Index [18].

	Subgrade	Description
Structural (Architectural change)	0.0	No Abnormality
	0.1	Mild Abnormality
	0.2	Mild or Moderate or multifocal abnormalities
	0.3	Severe diffuse or multifocal abnormalities
Chronic inflammatory infiltrate	1.0	No increase
	1.1	Mild but unequivocal increase
	1.2	Moderate increase
	1.3	Marked increase
Eosinophils (lamina propria)	2A.0	No increase
	2A.1	Mild but unequivocal increase
	2A.2	Moderate increase
	2A.3	Marked increase
Neutrophils (lamina propria)	2B.0	No increase
	2B.1	Mild but unequivocal increase
	2B.2	Moderate increase
	2B.3	Marked increase
Neutrophils in epithelium	3.0	None
	3.1	< 5% crypts involved
	3.2	< 50% crypts involved
	3.3	> 50% crypts involved
Crypt destruction	4.0	None
	4.1	Probable – local excess in part of crypts
	4.2	Probable – marked attenuation
	4.3	Unequivocal crypt destruction
Erosion or Ulceration	5.0	None
	5.1	Recovering epithelium + adjacent inflammation
	5.2	Probable erosion – focally stripped
	5.3	Unequivocal erosion
	5.4	Ulcer or granulation tissue

3. Recurrent molecular abnormalities within carcinomas arising in IBD patients

Several authors have studied carcinomas that arise in IBD in order to understand whether there are unique molecular signatures within this patient group. Many of these studies are limited due to the small number of cases and how to define IBD-associated carcinoma. This second issue specifically refers to the question whether IBD itself has a carcinogenic effect or simply potentiates a background risk for neoplastic development. The lack of a clear etiology for IBD adds to the difficulty of defining the patient population. We have identified mutations in isocitrate dehydrogenase (IDH1) in a subset of IBD associated adenocarcinomas from the colon and small bowel [19]. This mutation affects the alpha ketoglutarate metabolism pathway leading to a so-called oncometabolite, 2-hydroxyglutarate. Our findings have been confirmed by a second group [20]. This group also found that there was an increased association of c-MYC amplification within IBD associated adenocarcinoma when compared to sporadic adenocarcinoma. Additionally, whole exome sequencing has been performed on a group of IBD associated adenocarcinoma [21]. In this study, besides two cases with a hypermutation profile, the IBD associated adenocarcinoma was associated with an average of 71 somatic mutations [21]. This somatic mutation rate was similar to those reported for non-hypermutated and microsatellite stable cases [21]. Additionally, the authors report a specific pattern of base changes at amino acid dinucleotides (base change from C:G to T:A) similar to those described in esophageal and gastric carcinomas (cancers which have been associated with chronic inflammation) [21]. Additionally, each of these studies have found a lower rate of Kras mutation rate than sporadic intestinal adenocarcinoma [19–21]. Several proteins have been associated with neoplastic development in inflammatory bowel disease. Mutations in p53 seem to be widely present within IBD associated dysplasia/neoplasia [21]. Additionally, programmed cell death 4 (PDCD4) and atonal homolog 1 (Atoh1) have been associated with neoplastic development (specifically mucinous adenocarcinoma for the latter protein) [22,23]. Although these abnormalities do not account for every case of IBD associated adenocarcinoma, it does suggest that there are different molecular abnormalities that characterize IBD associated adenocarcinomas.

4. Inflammatory cells implicated in IBD

As previously mentioned, the underlying etiology for IBD is unknown but is believed to be due to a complex interaction between environmental triggers in a genetically susceptible host that leads to an immune response that does not resolve spontaneously. There are several mouse models that have been used to study IBD – the two most common being the DSS mouse model and the TNBS mouse model. The following section will describe some of the research that has been done in connection between a specific inflammatory cells/cytokines and the risk for neoplasia in both humans and mouse models.

4.1. Neutrophils

As mentioned previously, neutrophils constitute one of the key the diagnostic features in IBD. In fact, the presence of neutrophils has been utilized to develop a non-invasive test to assess for disease activity – fecal calprotectin levels [24]. The measurement of fecal calprotectin has been shown to correlate with disease activity in IBD [24]. Although it has not been extensively studied, fecal calprotectin does not appear to be predictive of colorectal carcinoma in a primary care patient population [25]. In a mouse model of colitis, vaccination against MUC1 led to a decrease in the presence of neutrophils within the colon and a decreased development of neoplasia [26]. Kvedaraite et al. have identified interleukin 23 expressing neutrophils in IBD patients [27]. These findings support the implication that interleukin 23 may play a role in initiating or promoting IBD [28]. The important role of neutrophils in

proper intestinal maintenance can be seen in patients with chronic granulomatous disease where there is a defect in NADPH oxidase activity [29]. The many functional aspects of neutrophils within the intestinal epithelium have been previously reviewed [30].

4.2. Eosinophils

Eosinophilia within the peripheral blood and within colonic tissues has been associated with a more severe phenotype for IBD [31]. The role of eosinophils within tissue remains of uncertain clinical significance. One study of a HuR small molecule inhibitor, MS-444, found a decrease in decrease in tumor associated eosinophils within an AOM/DSS mouse model for colitis associated colon cancer [32].

4.3. Chronic inflammation

4.3.1. T lymphocytes

Regulatory T-cells are defined as a subpopulation of T cells with the expression of CD4, CD25, forkhead box P3 (Foxp3), Tr1, Th3 and CD8. These cells have a role in suppressing the immune system and self-tolerance. In a mouse model for chemically induced tumors, CD4 + CD25 + cells were necessary for tumor acceleration in an immunization acceleration of tumor induction [33]. When the CD4 + CD25 + cells were transferred to a naïve mouse model, tumor acceleration was still observed despite the lack of immunization [33].

4.3.2. B cells/plasma cells

Plasma cells have historically been ignored in the etiology of inflammatory bowel disease although the presence of basal lymphoplasmacytosis is a histologic feature for chronic IBD. The humoral immunity of the gastrointestinal tract has been suggested to be altered in inflammatory bowel disease by several studies [34–39]. The accumulated plasma cells can act as a source of IgG and monomeric IgA [35]. Recent work has attempted to specifically target B-cell receptors in order to more selectively target the plasma cells that may be active within IBD [40]. In the future, selective targeting of plasma cells may prove to be helpful in reducing activity and therefore the dysplastic risk in patients with IBD. Lombardi et al. investigated whether changes within the genome of circulating lymphocytes could be predictive of either sporadic colorectal cancer or colitis-associated carcinoma and found that the presence of γH2AX was a marker of double stranded breaks in DNA and the presence of micronuclei both correlated with genomic instability [41].

5. Epithelial cells

Given there is a defect at the gut-lumen interface in IBD, epithelial cells may be critical factors in IBD or in dysplastic/neoplastic development. They may be either passive or active participants in the process. Myosin light chain kinase (MLCK) protein expression associated with tight junction formation in epithelial cells has been implicated in neoplastic development within a colitis mouse model [42,43]. An abundance of TNF-alpha leads to overexpression of this protein and subsequent disruption of tight junction formation. Disruption of the tight junction formation leads to a “leaky” epithelial layer so that luminal contents can access the lamina propria propagating the inflammatory state [42]. MUC2 deficient mice spontaneously develop chronic colitis and so epithelial goblet cells may play a role in the etiology of IBD [44]. Vaccination against MUC1 has been reported in a mouse model to modulate chronic inflammatory response and prevent the progression to neoplasia [26]. Paneth cells have been implicated in an etiologic role based on genetic studies of patients with IBD [43]. Specifically, NOD2 polymorphisms have been associated with less alpha-defensin production from Paneth cells [45]. Additionally, polymorphisms in ATG16L1 have been associated with defects in the formation of intracellular granules [46,47]. Activated Cdc42 kinase1 (ACK1) is increased in expression in both inflamed epithelial cells and within colorectal dysplasia [48]. The abnormal expression of Caspases 4 and 5 in epithelial cells have been suggested as biomarkers for inflammation as their expression has been observed in inflamed epithelium [49]. Additionally increased expression of these enzymes in the peritumoral stroma has also been observed [49]. Alpha6beta4 integrin receptor defects lead to hemidesmosome disruption which subsequently leads to inflammatory lesions and progression to neoplasia in mouse models [50]. Given the dynamic relationship between the lumen, the epithelial cells and inflammatory system, determining the role and function of each component in IBD will certainly represent a complex task.

6. Microbiota

Intestinal microbiota has been investigated as a contributor to IBD and as a surrogate of disease activity. This field is currently an active area of development and rapid advances are likely to arise from this field of study. Gut microbiota have recently been shown to be able to predict the presence of IBD in pediatric patients [51]. In fact, several studies have proposed modulation of the intestinal microbiota as a chemopreventive therapy in IBD patients [52–54]. The manipulation of the intestinal microbiota will be dependent on further clarifying the mechanism and developing better and more widely available techniques for studying and characterizing the microbiota.

7. Cytokines

Several studies have attempted to assess the role cytokines play in the development of IBD and a role in the subsequent development of neoplasia. Although understanding the role of cytokines is helpful in understanding the disease process, cytokines are difficult to study in vivo or in tissue removed at the time of biopsy. The study of cytokines has clearly shown that they can contribute to the development of effective therapies within IBD. The role of cytokines in IBD and colitis-associated cancer have been reviewed by others [55]. Briefly, tumor necrosis factor (TNF), interleukin-6, interleukin-1, interleukin 17, interleukin 23 and interleukin 22 have been implicated as having a role in the inflammation that arises in IBD [55,56]. Theoretically, by reducing the amount of inflammation within IBD patients, the risk for neoplastic development should be modulated. Some authors have suggested that regulation of the “inflammasome” can modulate the inflammatory disease in IBD [57]. Although it may be helpful to understand from which cell (epithelial vs inflammatory) these cytokines are being released in order to understand the mechanism of IBD, clinical inhibition with effective therapeutic treatment of the disease is more important.

8. Conclusion

Inflammatory bowel disease is characterized by both a neutrophilic infiltration and chronic inflammatory infiltrate. Although the mechanism for these histologic features is not currently known, inflammatory bowel disease is considered a risk factor for the development of subsequent neoplasia within the intestines. Several components of the immune system have been studied to characterize their role in the etiology of IBD, however, no clear cell type has been associated with disease activity or neoplastic risk. As we learn more about which component of the immune system is driving this disease, the component should be evaluated for its contribution to the risk for neoplastic development.

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