Introduction

Patients with idiopathic inflammatory bowel disease (IBD) have traditionally been characterized as having either Crohn's disease (CD) or ulcerative colitis (UC). Such strict dichotomization, though not based on pathogenic mechanisms of disease, is clinically useful in order to: (1) describe specific patterns of disease, (2) predict outcome, (3) help guide medical and surgical treatment strategies [1]. Following the original descriptions of CD and UC, many variations in the clinical presentations and clinical courses of these diseases have been appreciated [2-4]. Thus, what has been classically termed 'Crohn's disease' and 'ulcerative colitis' each actually represents diverse, heterogeneous groups of diseases (i.e. 'Crohn's diseases' and 'ulcerative colitis') manifesting with some similar features [5-10]. Furthermore, rather than regarding CD and UC as two distinct, mutually exclusive disease entities, mounting evidence suggests that IBD may represent multiple overlapping subgroups of inflammatory intestinal disorders located along a continuum of IBD with CD and UC representing the extremes of this spectrum (Fig. 1). Newly described serologic and genetic markers in combination with more specifically defined disease characteristics have been used to identify and delineate specific subgroups of patients within each of the broader categories of CD and UC that are more homogeneous in clinical presentation and natural history.

Serum immune marker expression in IBD permits stratification at the mucosal, clinical, immunologic, and genetic levels, and has been associated with distinct disease subgroups. Recent evidence suggests that the pattern of expression of certain serum immune markers actually represents genetically mediated immunologic traits that may be related to disease susceptibility and phenotypic disease expression [10-16]. The value and potential role of serum immune and genetic markers in the evaluation of patients with IBD has been increasingly appreciated and can potentially be applied at several levels including: diagnosis (initial delineation of IBD from non-IBD), differentiation of UC from CD, stratification into phenotypic subgroups with specific patterns of disease distribution and behaviors, and to characterize potential therapeutic subgroups.

This chapter focuses on the utilization of serologic, genetic, and cytokine markers, as well as immune responses to bacterial antigens, in the context of identifying and further defining more homogeneous subgroups of IBD. As more markers and their associations are defined, their diagnostic and predictive value may be enhanced as they are used in combination, versus being utilized as isolated tests. This approach will hopefully enable clinicians not only to accurately diagnose IBD, but also prospectively determine disease patterns and prognosis and individualize therapeutic regimens.

ANCA Overview

Serum antineutrophil cytoplasmic antibodies (ANCA) are autoantibodies directed against intracellular components of neutrophils. Three subtypes of serum ANCA expression have been described in patients with IBD based on the pattern of staining of neutrophils upon indirect immunofluorescent (IIF) microscopy. The three staining patterns are illustrated in Fig. 2. ANCA exhibiting predominant perinuclear highlighting are termed pANCA; those with cytoplasmic highlighting, cANCA. The third is a new ANCA subtype characterized by a diffuse 'speckled' staining pattern over the entire neutrophil (sANCA).
New diagnostic approaches in inflammatory bowel disease

Traditional Clinical Parameters: [Diagram]

Genetic, Serologic, and Biochemical Profiles: [Diagram]
- Genetic Markers
- Serum Immune Markers
- Cytokine Profile
- Enzyme Activity
- Metabolite Levels

Individualized "Reagent Grade" Intervention

"Crohn's Diseases" & "Ulcerative Colitides":

Figure 1. 'Reagent-grade' therapeutic intervention. In the near future it is foreseeable that when patients present to the clinician their traditional clinical parameters will be combined with their specific genetic (i.e. HLA, TNF microsatellite, TPMT genotype), serologic (i.e. immune markers), and biochemical (i.e. TPMT activity, drug metabolite) profiles. Based on the composite profile, the specific subtype of CD and UC could be determined and the most appropriate individualized treatment intervention selected (Modified from ref. 97).

Figure 2. Immunofluorescence staining patterns of sera from patients with IBD. Three subtypes of serum ANCA expression have been characterized in patients with IBD based on the predominant immunofluorescent (IIF) microscopy staining patterns of neutrophils. A: The characteristic perinuclear highlighting of pANCA. B: Cytoplasmic highlighting of cANCA. C: The newly-described diffuse 'speckled' staining pattern over the entire neutrophil of sANCA.