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EDITORIAL

# Interleukin (IL)-1 Gene Cluster in Inflammatory Bowel Disease: Is IL-1RA Implicated in the Disease Onset and Outcome?

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The two major types of IBD are ulcerative colitis (UC) and Crohn's disease (CD), whose etiology involves immunological and environmental factors. CD and UC share some susceptibility loci, but differ at others [1]. In the recent years, the application of genome-wide association studies (GWAS), by successfully defining the genetic architecture of CD and UC, has delivered genuinely novel and important insights into disease pathogenesis.

From a functional point of view, active IBD is immunologically defined as an infiltration of the lamina propria by innate and adaptive immune cells. Increased numbers and activation of these cells in the intestinal mucosa enhance local interleukin (IL) concentrations, affecting the balance of pro- and anti-inflammatory cytokines that is essential for normal gut homeostasis. CD is often described as a T-helper (Th)1-mediated disease since the primary inflammatory mediators are Th1 cytokines, whereas the increased intestinal expression of the Th2-associated cytokines in UC usually defines UC as a Th2-type condition. Classical pro-inflammatory cytokines, such as IL-1α, IL-1β, IL-6, IL-12, IL-17, IL-23, interferon (IFN)-γ, or tumor necrosis factor (TNF)-α, initiate and facilitate progression of IBD [2]. Cytokines with anti-inflammatory or modulatory effects like IL-10 or transforming growth factor (TGF)-β also contribute to the pathogenesis of IBD by decreasing the inflammatory process by down-regulating pro-inflammatory cytokine production.

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IL-1 represents two structurally distinct forms: IL-1α and IL-1β. The naturally occurring antagonist of IL-1, endogenous IL-1 receptor antagonist (IL-1RA), regulates normal immune homeostasis in the gut. The IL-1/IL-1RA parallels colitis activity, remaining constant in the non-affected part of the colon and in non-IBD inflammatory controls. Furthermore, IL-1β promotes Th17 responses from CD4+ T lymphocytes and innate lymphoid cells in the intestine, suggesting synergistic interactions between IL-1β and IL-23 signals that sustain innate and adaptive inflammatory responses in the gut. IL-1β also mediates the regulation of Th17 response in the intestine at steady state by a MyD88-dependent microbial signal. The functions of the majority of the members of the classical IL-1 family (IL-1, IL-1RA, IL-18, and IL-33) differ depending on disease phase, either promoting or maintaining chronic gut inflammation. The different members of IL-1 cluster family, their receptors, and their potential roles in IBD are illustrated in Fig. 1. Accordingly, these cytokines are up-regulated in IBD and potently induce Th2 immune responses, while also amplifying Th1-mediated inflammation. Other members of IL-1 family have also been implicated in epithelial regeneration and mucosal wound healing (such as IL-33), in bowel inflammation and homeostasis (such as IL-36), and for potent anti-inflammatory activity (such as IL-37) with the ability to down-regulate colitis. Polymorphisms of these genes are implicated in intestinal pathology [3–6].

In this issue of *Digestive Diseases and Sciences*, Daryani et al. [7], from the University of Tehran of Medical Sciences, describe the relation of IL-1 genes cluster single nucleotide polymorphism (SNP) with the severity of IBD. Initially, it is remarkable that the authors reported significant associations even with the small number of patients studied. They reported several important results: (a) The

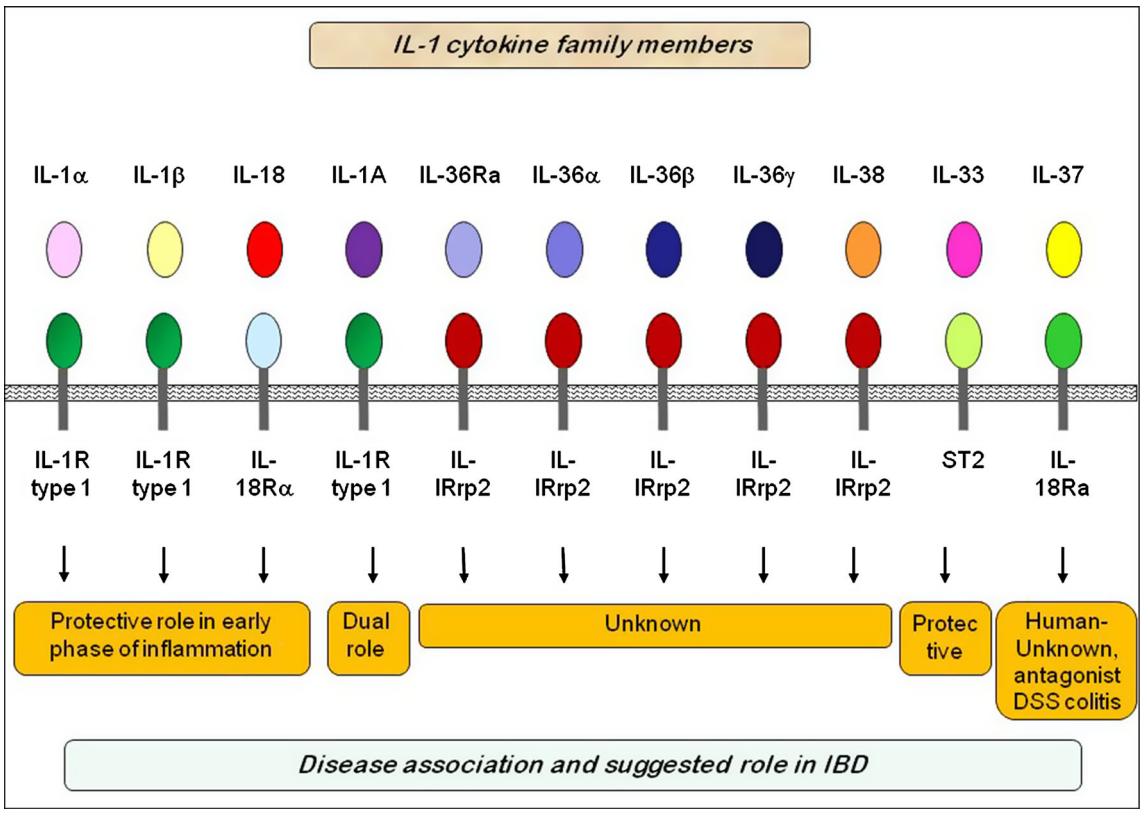


**Fig. 1** Members of IL-1 cluster family, their receptors, and their potential roles in IBD. *IL* interleukin, *IBD* inflammatory bowel disease, *DSS* dextran sulfate sodium

IL-1β −511CC genotype was significantly less frequent in UC compared to controls (implicating a potential protective function of the IL-1β −511 genotype from UC in Iranian populations). This finding has been reported in other populations such as in Mexican Mestizo patients [8], in whom the IL-1RA Mspa-I11100 CC SNP was significantly associated with CD and UC. (b) The IL-1α −889 TT genotype was more frequently associated with extra-intestinal manifestations. (c) A significant association was also observed between IL-1β +3962 TT genotype and disease activity in IBD, paralleling other reports of an association between the IL-1β +3962C allele and higher serum IL-1β concentrations and a lower response to infliximab treatment in CD patients [4]. (d) IL-1RA Mspa-I11100 CC was significantly less frequent in CD patients who require immunosuppressive therapy; the CT genotype was associated with earlier age of onset of IBD, whereas the TT genotype was associated with higher age of onset in IBD.

Although these results could enhance the understanding of the development and the clinical behavior of patients, other recent and similar studies have not reported any relationship between IL-1 gene cluster polymorphisms and IBD in populations of different ethnic origin [5, 6, 9].

The present study has some important limitations, such as the low number of studied patients, and should therefore be replicated in an independent patient cohort. Further functional studies are also necessary to determine the biological significance of the reported findings. Furthermore, the patients were not evaluated for potential disease triggers, especially their stress status. The patients should also have been better characterized for the presence of other CD and UC-related diseases, such as chronic fatigue syndrome, fibromyalgia, mastocytosis, and bladder pain syndrome/interstitial cystitis which may contribute their own pathological characteristics.

Another important limitation is that other IBD-associated IL-1β gene polymorphisms, including IL-1β −31, +3953, +3954, and +5887 [10], were not studied by the authors. The IL1β +3954 genotype was associated with altered IL-1β serum concentrations, similar to the increased concentration of IL-1β associated with the CC genotype in UC. Indeed, the IL1β +5887 polymorphism alters IL-1β production following lipopolysaccharide stimulation in vitro.

Finally, the authors do not analyze gene polymorphisms of other important IBD-implicated cytokines from the IL-1 family such as IL-18, IL-33, IL-36, IL-37, IL-38, or their corresponding receptors (or co-receptor molecules, as IL-

1RAcP), including their interrelationships. With respect to the IL-1RA polymorphism, it would be interesting to combine the results from this article with other published data describing the polymorphisms of IL-1RA in IBD, such as VNTR.

## Summary and Future Directions

In summary, IL-1 SNPs are probably associated with IBD, likely affecting disease onset and severity. The recent successes in this area suggest that a detailed description of the genetic basis of IBD is a realistic and achievable goal, unearthing a plethora of attractive targets for the development of future therapeutics. Insights into the natural history of these complex diseases may enable in the near-future appropriate patient selection for early aggressive therapy aimed at modifying the course of the disease.

RNA interference (RNAi) holds great promise for the specific and selective silencing of aberrantly expressed genes, such as pro-inflammatory cytokines TNF-α, IL-18, or IL-1 gene family in IBD [11, 12]. This interesting approach could be implemented for other inflammatory cytokines or their receptors, such as IL-1RA.

Moreover, further large-scale and functional studies of cytokine genes and polymorphisms are required in order to determine specific associated variations within the loci responsible for the gene dysfunction that confers IBD risk and to identify gene variants that may alter the response to the treatment with important translational implications for disease prevention and outcome modification.

Finally, meta-analyses should be carried out to determine the specific contribution of every member of the IL-1 family in the modulation of chronic bowel inflammation in humans. Studies like the one authored by Daryani et al. remind us, more than anything else, of the need for perseverance in this field of research.

## Key Messages

- How IL-1 cytokine SNPs affect IBD predisposition remains controversial.
- SNPs affect the transcription activity of the IL-1 family members and their serum concentrations.
- SNPs belonging to the IL-1 gene family, primarily the IL-1RA polymorphism, could be associated with IBD severity.
- The differential treatment response could also be modulated by immunogenetic markers of this interesting family.
- Thorough characterization of the associations between the Il-1 gene family and disease activity, manifestations, onset, and severity may have profound future therapeutic and prognostic implications.

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**Conflict of interest** None.

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