Psoriasis and Inflammatory Bowel Diseases: Epidemiological, Genetic and Pathogenetic Correlations: A Review of Literature

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Introduction
Crohn’s disease (CD) and ulcerative colitis (UC) are chronic relapsing inflammatory disorders of the gastrointestinal tract and of the skin. The relationship between IBDs and psoriasis has been observed only through epidemiological studies, however starting from 1990s genetic and immunological aspects have been studied in detail. Both conditions share a strong genetic correlation that involves the chromosomal loci 6p22, 16q, 1p31 and 5q33. Polymorphisms of these susceptibility loci are related to the alteration of immune mechanisms in both psoriasis and IBD. Cytokines such as IL-17A, IL-22, TGFβ, IL-6, IL-21 and IL-23 influence the activity of T-Helper 17 Cells (Th17) and T-Regulatory Cells (T-Regs), playing a key role into the inflammatory process and tissue damage. The comparable common course of psoriasis and IBD explains systemic implication seen in both conditions and legitimizes similar therapeutical approach. The aim of this article is to explore the nature of the relationship between inflammatory disease and psoriasis in terms of epidemiology, genetics and pathogenesis.

Epidemiological correlations
The prevalence of psoriasis in the Caucasian population is about 2.3%, almost one-third of patients with psoriasis have a first-degree relative affected by the same disease [4]. The prevalence of CD in the general population is around 7 per 100,000 in the United States [5] with a risk of 3%-5% for the siblings of an affected patient to have the same disease [6]. An increased incidence of IBD among patients with established psoriasis was described in a recent study on 12,502 psoriatic patients and 24,287 controls, that demonstrated that the prevalence of UC was significantly higher in patients with psoriasis compared to those of the control group, respectively 0.5% and 0.3%, with =0.002. Also the prevalence of CD was higher in patients with psoriasis compared to those of the control group, respectively 0.5% and 0.2%, with =0.001. In the same study, multivariate analysis confirmed that psoriasis is associated with CD (OR: 2.49, 95% CI: 1.71 to 3.62) and UC (OR: 1.64, 95% CI: 1.15 to 2.33, and =0.006) [7]. This data shown that psoriasis is strongly associated with CD than UC.

Genetic correlation
Genome wide association (GWA) studies have proven a correlation between psoriasis and IBD, identifying 13 psoriasis susceptibility loci (called PSORS1-13) and 28 IBD susceptibility loci (called IBD1-28). The stronger correlations involve the chromosomal loci 6p22, 16q, 1p31, and 5q33 that will be further analyzed.

A single nucleotide polymorphism (SNP: rs6908425) in locus 6p22 was related to CD in WTCCC study in 2007 [8]; later in 2008 Walf found an association of 6p22 with psoriasis compared with healthy controls (OR: 1.26, 95%CI: 1.12 to 1.42 and =0.00015) [9].

Locus 16q corresponds to PSORS8 and IBD3. NOD2/CARD is a gene located on chromosome 16; three polymorphisms (G2722C; C2104T; 3020insC) of this gene are strongly related to CD but not to psoriasis [10]. A 2012 meta-analysis by Zhu of nine studies, confirmed the absence of association between psoriasis, psoriatic arthritis, and common polymorphisms of NOD2/CARD15; however the authors emphasized the importance of the protein encoded by this gene in the pathogenesis of psoriasis and psoriatic arthritis and the presence of conflicting results among the studies analyzed [11].

The IL-23R has a fundamental pathogenetic role both in IBD (IBD17) and in psoriasis (PSORS7). This important gene is located on locus 1p31.1. More studies shown a correlation between two SNPs (rs7530511 [L310P] and rs11209026 [R381Q]) of IL-23R and psoriasis [12,13]. In IBD risk variants different from psoriasis have been identified (rs7517847 and rs11805303). So, while IBD and psoriasis share the same protective polymorphism, rs11209026 (R381Q), the risk variants, rs7517847 and rs11805303, were different.
The association of psoriasis (PSORS11) and IBD (IBD19) with locus 5q33.1 is widely documented, especially with the polymorphisms of IL12B gene (i.e., IL-23B, or p40). In IBDs the risk alleles identified were rs6556416 and rs6887695 that were found in psoriasis too [14,15].

Moreover, locus 6p21 and locus 5q31 appear to be more important in IBD and psoriasis pathogenesis but these correlations should be evaluated by further research.

**Pathogenetic correlation**

Pathogenetic mechanisms of psoriasis and IBDs have been individually investigated but there's lack of studies on patients who suffer concurrently from both these diseases. Based on current knowledge, psoriasis and IBDs pathogenesis have two different moments, the first related to the innate immunity triggered by unknown stimuli, the second as a consequence of the adaptive immunity caused by the cytokines released from innate immune cells (mainly dendritic ones).

Cytokines influence the activity of T-Helper 17 Cells (Th17) and T-Regulatory Cells (T-Reg) that play a key role into the inflammatory processes and tissue damage in both Psoriasis and IBDs. Th17 are a sub-population of T-helper cells related to chronic conditions such as psoriasis, juvenile diabetes, celiac disease, rheumatoid arthritis and Crohn's disease [16-18]. The main cytokines that stimulate the Th17 differentiation from T-helper naïve cells are TGFβ, IL-6, IL-21 and IL-23 (the last one produced by dendritic cells). Th17, in turn, produce IL-17 and IL-21 [19,20]. The IL-17 promotes the chemotaxis of neutrophils and monocytes and the migration and activation of T lymphocytes and neoangiogenesis. Furthermore it also induces other cytokines such as IL-6, GMCSF, IL-1β, TGF and TNFα and chemokines (e.g. IL-8, GRO-α, MCP-1) and prostaglandins (e.g. PGE2) by different cells. Augmented levels of IL-23 and IL-17 in the inflamed mucosa of patients suffering of IBDs suggest an alteration of Th17. Likewise, biopsies of psoriatic patients show a high number of Th17 and high levels of TGFβ1, IL-6, IL-15, IL-22 and IL-23 [21,22]. In skin diseases Th17 promotes acanthosis, hyperkeratosis and parakeratosis due to the synthesis of inflammatory molecules within dermis and epidermis [23,24].

T-Reg also called T-suppressor are a sub-population of T-Cells specialized in suppressing of abnormal activation of the immune system in different organs including intestine and skin [25]. Abnormalities in the number and function of these cells have been found in psoriasis and other several autoimmune diseases [26,27]. In patients with CD and UC the number of T-Reg in peripheral blood and in inflamed intestinal mucosa is reduced if compared to controls [28,29]. Similarly, functional and numerical abnormalities of T-Reg have been described in patients with psoriasis, both in peripheral blood and superficial dermis [30].

The relationship between Th17 and T-Reg have been postulated and defined through the discovery of TGFβ. This cytokine is responsible of the induction of both lymphocytes subtypes. Recent evidences show that TGFβ participates in the induction of T-Reg but in the presence of IL-6 contributes to the induction of Th17 [31].

**Conclusion**

Skin and bowel represent barrier and connection between inner and outer sides of the body. In these organs immune system has a fundamental role in maintaining homeostasis. Therefore the alteration of immune processes is related to development of both psoriasis and IBDs, and explains their relationship in terms of epidemiology, genetic subset and pathogenetic mechanisms.

**References**


