Psoriasis: Targets and Therapy

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REVIEW

Psoriasis and inflammatory bowel disease: links and risks

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Abstract: Psoriasis and the spectrum of inflammatory bowel diseases (IBD) are chronic, inflammatory, organotropic conditions. The epidemiologic coexistence of these diseases is corroborated by findings at the level of disease, biogeography, and intrafamilial and intrapatient coincidence. The identification of shared susceptibility loci and DNA polymorphisms has confirmed this correlation at a genetic level. The pathogenesis of both diseases implicates the innate and adaptive segments of the immune system. Increased permeability of the epidermal barrier in skin and intestine underlies the augmented interaction of allergens and pathogens with inflammatory receptors of immune cells. The immune response between psoriasis and IBD is similar and comprises phagocytic, dendritic, and natural killer cell, along with a milieu of cytokines and antimicrobial peptides that stimulate T-cells. The interplay between dendritic cells and Th17 cells appears to be the core dysregulated immune pathway in all these conditions. The distinct similarities in the pathogenesis are also reflected in the wide overlapping of their therapeutic approaches. Small-molecule pharmacologic immunomodulators have been applied, and more recently, biologic treatments that target proinflammatory interleukins have been introduced or are currently being evaluated. However, the fact that some treatments are quite selective for either skin or gut conditions also highlights their crucial pathophysiologic differences. In the present review, a comprehensive comparison of risk factors, pathogenesis links, and therapeutic strategies for psoriasis and IBD is presented. Specific emphasis is placed on the role of the immune cell species and inflammatory mediators participating in the pathogenesis of these diseases.

Keywords: psoriasis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, immune cells, inflammation

Introduction

Psoriasis and the group of inflammatory bowel diseases (IBD) are chronic, inflammatory, organotropic conditions. The former affects the skin of 2%–3% of the population, with hyperproliferation of keratinocytes, impaired epidermal barrier function at the sites of skin lesions, and skin infiltration by activated inflammatory cells.[1] Ulcerative colitis (UC) and Crohn's disease (CD) are the two most prevalent representatives of the IBD group. UC usually affects the rectum and may extend to the colon, with restriction of the inflammatory process to the mucosa and submucosa layers, while CD can affect any site of the digestive tract, with segmentary distribution of the lesions and inflammatory infiltration of all intestinal wall layers.[2]

Immune dysregulation, determined by genetic predisposition and environmental assaults, underlies all three conditions. A coincidence of psoriasis and IBD has been

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observed in various clinical settings: they can appear as concomitant disease events in the same patient or as "paradoxical" treatment-related adverse events.[3,4]

Moreover, a wide spectrum of therapeutic modalities is used to treat psoriasis and IBD, a fact that further underscores pathophysiological disease similarities. There are also cases of distinct discrepancies in the effectiveness of certain modalities that highlight differences in the pathophysiology between skin and gastrointestinal (GI) diseases and even within the IBD themselves.

The objectives of this paper were to review the most relevant literature data on the role of microbiota, inflammatory cell species, and humoral inflammation mediators in psoriasis and IBD immunopathogenesis and treatment response. For this purpose, corresponding core review articles were compiled, and a focused literature search was performed for retrieving the updated information. The search was conducted periodically during progressing text editing, employing Medline (PubMed). Two search filters were applied (language "English" and field "Title/abstract"), and the identified material was explored for selecting papers with adequate content. The full text of selected articles was retrieved, each study was individually evaluated, and the resulting material was integrated in this descriptive report.

After a short comparison of the genetic collation, we will survey the role of microbiota and selected innate and adaptive immunity inflammatory cell species and humoral inflammation mediators in the pathogenesis of these diseases. Finally, we discuss similarities and discrepancies in the response of psoriasis and IBD patients to the established pharmacologic therapies of either to additionally highlight the nosologic relationships of these conditions.

Diseases coincidence

Psoriasis and IBD cluster at all genetic levels of human populations, ie, they share the same geographic/ethnic, kindred, and patient niches. These diseases are more frequent in Northern Europe and North America (psoriasis prevalence: ~2%; UC and CD incidences: 19.2–24.3 and 12.7–20.2 per 100,000 person-years, respectively) compared to most regions of Africa, Asia, and the Middle East (psoriasis prevalence: <0.5%; UC and CD incidences: 6.3 and 5.0 per 100,000 person-years, respectively).[5–7]

Both psoriasis and CD present with much higher incidence among family members of patients than in the general population.[8,9] Almost one-third of patients with psoriasis also have a first-degree relative affected with the disease.[9] In contrast, the risk of the siblings of a CD patient to be affected is only ~5%.[8] Moreover, differences in concordance rates between monozygotic and dizygotic twins both in psoriasis (70% vs 23%, respectively) and CD (37% vs 7%) support the important role of genetic background.[10,11]

Psoriasis and CD also coexist in the same patient more often than expected by chance: the prevalence of psoriasis in patients with CD is 9.6% (vs 2.2% in controls).[12] The relative risks of psoriasis are significantly increased in both UC (1.56-fold) and CD (1.52-fold) patients and psoriasis patients are at increased risk to develop IBD (2.49-fold for CD and 1.64-fold for UC).[13,14]

Genetic collation

A shared genetic susceptibility background probably underlies the pathobiological and clinical overlap of psoriasis and IBD. To date, the literature describes 13 psoriasis susceptibility loci (designated *PSORS1-13*), and genome-wide association studies implicate 32 loci in the pathogenesis of CD and 17 in UC (Table 1).[15–17]

The epidemiologic coincidence of the conditions is partly explained by the sharing of disease susceptibility loci: 20q13 corresponds to *PSORS12* and *IBD24*, 19p13 to *PSORS6* and *IBD6*, 6p21 to *PSORS1* and *IBD3*, and 5q31 to *PSORS11* and *IBD5*.[17] However, despite loci concordance, the involved genes are often different. For example, in the 6p21 region, psoriasis seems to be linked to the HLA-Cw*0602 allele, while IBD are mainly linked to polymorphisms in the TNF-α gene promoter.[17]

Of note, a recent meta-analysis of genome-wide association studies that included >4,500 patients and 10,000 controls recognized seven susceptibility loci outside the human leukocyte antigen region (9p24 near *JAK2*, 10q22 at *ZMIZ1*, 11q13 near *PRDX5*, 16p13 near *SOCS1*, 17q21 at *STAT3*, 19p13 near *FUT2*, and 22q11 at *YDJC*) shared by psoriasis and CD and confirmed four already established common psoriasis and CD risk loci (*IL23R, IL12B, REL, and TYK2*).[18] Future functional studies that explore these genetic relationships will contribute to better understanding of the resonance of genetic colocalization to the pathophysiology of the diseases.

Microbiota

Microbiota play a significant role in the pathogenesis of different diseases.[19] Skin and intestine are the two major niches of prokaryotic and eukaryotic symbiotic microorganism flora in humans.[20,21] The inflammatory diseases evaluated herein primarily affect the structure and function of the corresponding organism–environment interface linings, resulting in distinct sustained alterations in the respective

Table 1 Genetic susceptibility loci associated with psoriasis and IBD

Locus	Candidate implicated genes	Protein	Function	Psoriasis association with relevant SNP	IBD association with relevant SNP	Comment
6p21	*CDKAL1*	Cyclin-dependent kinase 5 regulatory subunit-associated protein 1-like 1	Unknown (shared domain with CDK5 protein inhibitor)	Low levels of protein expression in lesions SNPs (rs6908425) appear as risk factors.[180]	Low levels of protein expression in lesions SNPs (rs11584383) appear as risk factors.[181]	Similar pathophysiology; divergent SNPs
1p31.1	*IL-23R*	Interleukin-23 receptor	Inflammatory mediator	Protective (rs7530511) and predisposing (rs11209026) SNP polymorphisms.[182]	Protective (rs11209026, rs7517847) and predisposing SNP polymorphisms (rs11805303) for Crohn's disease.[17,183]	Existence of risk modifying polymorphisms for psoriasis and Crohn's disease; however, different SNPs and even risk directions for the same SNP (eg, rs11209026).
16q	*NOD2/CARD15*	Nucleotide-binding oligomerization domain-containing protein 2 (also known as caspase recruitment domain-containing protein 15)	Intracellular protein in the proinflammatory NFκB pathway	*NOD2/CARD15* polymorphisms are not connected to psoriasis. However, a psoriasis susceptibility locus on chromosome 16q near marker D16S3110 is identified.[17]	At least three *NOD2/CARD15* gene variants (3020insC, R702W, G908R) have been identified as genetic risk factors for Crohn's disease patients.[17]	No evidence for pathophysiologic connection at gene level. Divergent susceptibility genes within the same locus.
5q33.1	*IL12B*	Interleukin-12 subunit β	Encodes the common IL-12 p40 subunit of IL-12 and IL-23	Strong association with PSORS 11 psoriasis susceptibility locus. Various SNPs (rs7709212, rs10045431, rs3212227, rs6887695) have been identified.[184]	Strong association with IBD19, IBD susceptibility locus. Various SNP recognized as risk factors (rs6887695, rs13361189, rs4958847).[185]	Established susceptibility loci for both diseases; however, divergent polymorphisms.
20q13s	Psoriasis: *RNF114* IBD: *TNFRSF6B*	Ring finger protein 114 Tumor necrosis factor receptor superfamily member 6B	RNF11 participates in Type I IFN production. TNFRSF6B acts as a decoy receptor (DCR3) in preventing FasL-induced cell death.	A single cluster of disease-associated markers, spanning 47 kb on chromosome 20q13. Multiple SNPs (as rs495337) were identified with a putative role in the regulation of immune responses.[186]	A locus at chromosome 20q13 has been associated with IBD. rs2315008T and rs4809330A were present in the tested IBD population with an odds ratio of 0.74.[187]	No evidence for pathophysiologic connection at gene level. Divergent susceptibility genes within the same locus.
19p13	Psoriasis: *BSG* *JunB* *MUC16* IBD: *ICAM1* *C3* *TBXA2* *LTB4H* *TYK2* and *JAK3*	 Basigin JunB Mucin 16 Intercellular adhesion molecule 1 Complement component 3 Thromboxane A2 receptor Leukotriene B4 hydroxylase Janus protein tyrosine kinases TYK2 and JAK3	Basigin possess a fundamental role in intercellular recognition JunB is a transcription factor Glycoprotein, known biomarker Critical molecules in inflammatory pathways, immune responses, and cell activation	A susceptibility factor at chromosome 19p13 had been identified and associated with SNP rs12459358.[188]	A locus on 19p13 confers susceptibility to both Crohn's disease and ulcerative colitis.[189] This is located around microsatellite marker D198247.	No evidence for pathophysiologic connection at gene level. Divergent susceptibility genes within the same locus.

(*Continued*)

Table 1 (*Continued*)

Locus	Candidate implicated genes	Protein	Function	Psoriasis association with relevant SNP	IBD association with relevant SNP	Comment
6p21	*HLA-Cw6*	HLA-CW6	HLA-C belongs to the MHC Class I heavy chain receptors	PSORS1 is the strongest susceptibility locus detectable by family-based linkage studies and accounting for one-third to one-half of the genetic liability to psoriasis.[180] Candidate SNPs include among others rs1050414 and rs697743.	Crohn's disease, ulcerative colitis, and mixed IBD contributed equally to this linkage, suggesting a general role for the chromosome 6 locus in IBD.[190]	Probably not a pathophysiologic connection; a locus of strong genetic linkage between psoriasis and IBD.
5q31	*IL-4*, *IL-5*, *IL-13*	Interleukins 4, 5, and 13	Inflammatory mediators	A SNP in the 3′-untranslated region of the *IL12B* gene on chromosome 5q31-33 has been associated with psoriasis.[182] Two other SNPs offer either protection (rs7709212) or favored disease appearance (rs10045431).	SNP rs6596075 corresponding to a risk haplotype on 5q31 have been associated with Crohn's disease along with rs2188962 on 5q31.[191]	Probably a genetic linkage; divergent SNPs.

Notes: Genetic association studies have discovered various genome areas that are associated with both diseases. Only eight loci are described with well-established associations for both diseases. However, within the same locus, the involved genes and polymorphisms may diverge between the skin and gut diseases.
Abbreviations: SNP, single nucleotide polymorphism; IBD, inflammatory bowel disease; MHC, major histocompatibility complex.

microenvironments of exposed tissue surfaces and, simultaneously, also of the species composition of the microorganism populations (dysbiosis).

Commensal microbes produce numerous biologically active metabolites that impact the physiology and immune response of the underlying epithelia. Notably, members of the phylum Firmicutes, the number of which are decreased in the gut lumen of CD patients, produce short-chain fatty acid metabolites (acetate, butyrate) with anti-inflammatory actions in the normal gut that may fail in IBD patients.[22–24] Aryl hydrocarbon receptor (AhR), the promiscuous receptor that mediates the recognition of xenobiotics and modifies immune responses, may play a distinct role in mediating these pathophysiologic alterations. AhR-deficient mice, a mutant known to develop enhanced Th17-driven inflammatory immune responses, are characterized by a high prevalence of segmented filamentous bacteria in their gut. Interestingly, the administration of antibiotics that target these bacteria results in the reduction of intestinal IL-17 production as well.[24]

Microbiota act both as triggers and inhibitors of inflammation; to date, the balance of these effects have been better studied in IBD compared to psoriasis patients.[19] IBD patients are characterized by a decrease of anaerobic bacteria (*Bacteroides*, *Eubacterium*, *Lactobacillus*).[25] Particularly, CD patients present with a reduction in Firmicutes and *Clostridium leptum* populations, along with a simultaneous increase in Proteobacteria.[26,27] These alterations have been linked to genetic determinants of the immune response (as the *NOD2* gene) or genes that are associated with intracellular degradation of proteins, such as *ATG16L1*.[28] Likewise, Paneth cell function and the *FUT2* genotype (a gene involved in the expression of ABO blood group antigens in the GI mucosa) have been linked to substantial differences in the species composition of the microbial populations that colonize the gut lumen and modify the risk of developing CD.[29,30] Interestingly, similarly to patients with a microbial infection, IBD are characterized by a substantial loss of microorganism species diversity in the gut and by a shift from an innocuous multispecies homeostatic flora to a narrower spectrum of proinflammatory and pathogenic microbial species.[31,32] The impact of antibiotic use in this shift is a matter of debate, yet certain antibacterial agents (such as the 5-aminosalicylic acid) suppress the ability of gut bacteria to build adherent biofilms in patients with IBD, resulting in disease improvement.[33]

Genes affecting epidermal barrier function and adaptive immune responses with subsequent alterations in

bacterial colonization have been suspected to contribute to the pathogenesis of psoriasis.[34] The interrelationship between microbes and psoriasis pathogenesis is currently under intense investigation. Many studies agree that a certain degree of dysbiosis is a landmark of the skin lesions and that psoriasis may, at least in part, be associated with a substantial alteration in the composition of the cutaneous microflora.[35] The genus most frequently identified in diseased skin areas is *Corynebacterium* as opposed to *Propionibacterium* in healthy controls. In addition, the representation of *Propionibacterium* and *Actinobacteria* species is lower and that of Firmicutes is higher in affected skin.[36,37] Infections also play a central role in the course of psoriasis. Bacteria have been suspected to be an important source of antigens that trigger the immune system activation, which is a characteristic of this condition.[38] Guttate psoriasis flares are usually preceded by streptococcal pharyngitis episodes. Moreover, the distinct differences in the prevalence of psoriasis in different populations have been attributed to the effect of natural selection for gene polymorphisms associated with more vigorous immunity against infectious agents such as invasive streptococci infections or leprosy pandemics in the past.[39,40] T-cell clones primed by streptococcal tonsillitis or pharyngitis are supposed to be reactivated in the skin as a result of their exposure to cross-reactive epitopes expressed there (molecular mimicry).[41]

Microbes seem to further interact with the cells of the innate immune system, resulting in increased expression of antimicrobial peptides, production of cytokines, and subsequently, stimulation of T-cells.[42,43] As in the gut of IBD patients, the absence of AhR enhances skin inflammation both in the skin of patients with psoriasis and in a murine model of psoriasiform skin inflammation.[44] Notably, the potent AhR agonist indirubin, also produced on the surface of the skin by *Malassezia* yeasts, is an ingredient used in topical remedies for psoriasis in traditional Chinese medicine.[45,46]

In conclusion, alterations of the microbial flora in the gut and the skin may not only result from disease-associated tissue perturbations but may also exacerbate and maintain the disease state in a vicious self-perpetuating cycle.

The role of innate immune cells and the IL-23/Th17 axis

Innate and adaptive immune processes are expected to participate in the pathogenesis of both psoriasis and IBD (Figure 1, Table 2). Until recently, the prevailing opinion in the literature favored adaptive immunity as the major player in the pathogenesis of these diseases; however, current evidence

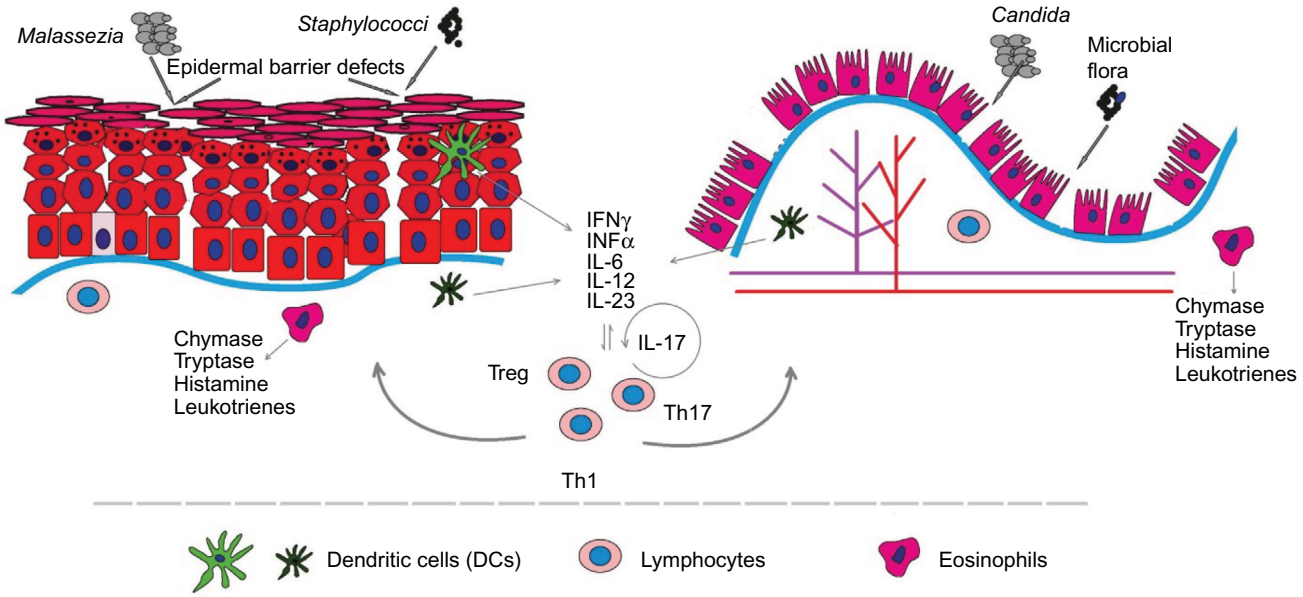

Figure 1 The epithelial barrier in both diseases appears more permeable than normal.

Notes: The increased rate of epithelial cell apoptosis in IBD and the acanthosis/parakeratosis in psoriasis are accompanied by a reduction in the structural complexity of the intercellular junctions. Thus, antigen and pathogen crossing-through is increased, resulting in binding to pattern recognition receptors (PRRs) and immune system activation. The dendritic cells are the main regulators of immune reaction, armored with a wide range of PRRs, including toll-like receptors and nod-like receptors (NLRs). Under inflammation, they produce cytokines, as IL-6 or IL-23, contributing to T helper-17 (Th17) cell formation. Macrophages have a complementary role in eliminating and displaying antigens to T-lymphocytes, besides producing cytokines to recruit other immune cells to the inflammation site. Tissue macrophages are also involved in the generation of T-regulatory cells. The IL-23/Th17 axis interaction with epithelial and synovial cells is one of the main events in the initiation and maintenance of the inflammation in both diseases.

Abbreviation: IBDs, inflammatory bowel diseases.

Table 2 Summary of the role of innate and adaptive immunity cell species in the pathophysiology of psoriasis and inflammatory bowel diseases (IBD)

Cell species	Psoriasis	IBD	Comment
Epithelial cells	Structural alterations in epidermis (increased proliferation, hyperkeratosis, parakeratosis, acanthosis) that lead to increased corneocyte shedding.[192] Reduction of tight junction proteins.[50,54] Alteration of TLR expression patterns.[53,56]	Increased rate of apoptosis or shedding of the intestinal epithelial cells during the disease.[49]	Defective barrier and increased epithelial cell turnover. Leaky barrier function. Immune stimulation tissue state.
Dendritic cells (DCs)	Diminished Langerhans cell numbers. Prominent tissue infiltration by pDCs in early lesions.[63]	$CD103^+$ DCs produce increased quantities of IL-6/IL-23.[59] Increased number of $CD40^+$ DCs.[61]	DCs maintain the proinflammatory tissue state.
Macrophages	Proinflammatory M1 subsets predominate in psoriatic plaques.[72] Anti-inflammatory actions through mediators and Treg generation.	The proinflammatory M1 $CX3CR1^{low/int}$ subpopulation expands and overexpresses antigen receptors and PRRs leading to local immune response exacerbation.[70,72]	Central M1 cell species role in induction and maintenance of tissue inflammation.
Mast cells (MCs)	Increased MC numbers in biopsies from diseased skin and gut areas contribute to tissue inflammation.[79,81,86] MCs mediate the interaction between stress conditions and aggravation of inflammation in skin or intestine.[87,88]		Mediate functional neural–epithelial interactions and augment tissue inflammation.
Natural killer (NK) cells	Proinflammatory $CD56^+CD3^-$ NK cells predominate. NK cells comprise 5%–8% of the inflammatory cell infiltrate releasing IFN-γ, TNF, and IL-22.[94] Decreased number of circulating NK cells.[193]	IFN-γ-producing proinflammatory $NKp46^+$ NK cells considerably outnumber the IL-22-producing $NKp44^+$ NK cells in inflamed mucosa (CD patients).[92,93] Decreased peripheral blood NK cells activity; unaffected cell numbers.[96]	In disease lesions, proinflammatory IFN-γ-producing NK cells predominate. Decreased peripheral blood NK cells activity.
Innate lymphoid cells (ILCs)	ILC3 subpopulation appears increased in both conditions producing IL-22.[101,102,104]		Comparable pattern of alterations in psoriasis and IBD.
Th17 lymphocytes	Promote (IL-17) epidermal hyperplasia and defective keratinocyte maturation. Induce proinflammatory skin state.[114] Alterations in genes related with T-cell development and polarization have been strongly associated with psoriasis and IBD.[111,116] Inhibition of Th17 cytokines improves the inflammation.[113]	Massive gut infiltration by Th17 cells and excess production of Th17-related cytokines are in both CD and UC tissues.[110,112] Inhibition of Th17 cytokines is not effective.[194]	Central role in the pathogenesis of psoriasis and IBD. However, unfavorable outcomes in IBD with the currently available anti-Th17 modalities.
Tregs	Accumulate in the inflamed tissues of skin and intestine. Functional and numerical alteration of the equivalent blood population.[117,122] Foxp3 polymorphisms contribute to the risk of the diseases.[118,119]		Movement of Treg cells from the circulation into the inflamed tissue sites.

Abbreviations: TLR, toll-like receptors; PRR, pattern recognition receptors; TNF, tumor necrosis factor; IFN, interferon; CD, Crohn's disease; UC, ulcerative colitis; pDCs, plasmacytoid DCs.

highlights a more decisive role of the innate immunological mechanisms.

The innate immune system includes the host's primary response mechanisms against foreign agents: protective physical barriers, inflammation-related proteins like the complement system and C-reactive protein, antimicrobial peptides, such as defensins and cathelicidins, and pattern recognition receptors (PRRs), cytokines, phagocytic cells, dendritic cells (DCs), and natural killer (NK) cells.[22,43]

The intestinal epithelial barrier is a physical defense line that encompasses intestinal epithelial cells, tight junctions, and a layer of mucous. The resident microbiota can activate specific PRRs in the epithelial cells,[47] effecting downstream signaling that leads to proinflammatory protein synthesis and in the case of IBD to a more susceptible and permeable epithelial barrier.[48,49] The anatomical and functional integrity of the barrier is further compromised by proinflammatory cytokines (such as TNF-α), which disturb the integrity of intercellular tight junctions by affecting the synthesis of occludins and other related proteins in the gut epithelium.[50] In addition, mucous production is either up- or downregulated in IBD patients, further contributing to disease processes.[51]

Compared to healthy individuals, intestinal epithelial cells of IBD patients express an altered pattern of Toll-like receptors (TLRs): increased TLR4 expression in UC patients and decreased TLR4 and TLR3 expression in CD patients.[52] An overexpression of TLR4 and TLR2 in intestinal wall macrophages during inflammation also contributes to a state of gut hyperresponsiveness to xenobiotics in these patients.[53] Based on the aforementioned observations, in IBD patients, the defective epithelial barrier function facilitates intestinal

antigens to reach and bind to PRRs, activate the immune system, and ultimately herald inflammation.

Likewise, defects in the structure and function of the epidermal barrier seem to play an important role in the pathogenesis of psoriasis. Similar to the aforementioned IBD findings, the expression of structural proteins such as claudin and zonula occludens-1 is reduced in the epidermis of psoriatic lesions, which results in alterations in the structure of epidermal tight junctions.[54] The overall pathophysiologic consequence is a partially compromised epidermal barrier capacity that enables enhanced invasion of microorganisms, their products, and other foreign molecules, ultimately leading to the stimulation of inflammatory skin processes.[55]

On the other hand, the expression of TLRs is also modified in psoriasis.[56] TLR 2 is constitutively expressed in the suprabasal layers of normal skin, but it is limited to the basal cell layers of the epidermis in diseased skin. There is also a characteristic tissue shift in epidermal TLR 4 expression, with an inversion of the spatial expression gradient from a basal to superficial pattern in the normal skin to a more pronounced expression in more superficial layers in psoriasis lesions. These shifts are associated with the disturbed skin barrier, and are interpreted as an adaptation of the tissue to meet the need for enhanced immune surveillance and avoidance of overstimulation due to pathophysiological inflammation cascades in diseased skin.[56]

Dendritic cells (DCs) are the main regulators of immunity since they are able to provoke inflammatory responses or impose immune tolerance.[22] They are equipped with a wide range of PRRs, including TLRs and Nod-like receptors (NLRs), allowing them to distinguish between microbiota and pathogens. So far DCs have not been stimulated by immunological insults their state corresponds to an "immature" phenotype that maintains the T-lymphocytes inactive.

In the intestine, submucosal DCs reach the intestinal lumen by projecting their dendrites through the tight junctions boundaries between epithelial cells.[57] In IBD, gut inflammation and the defective mucous membrane barrier allow an increased amount of intestinal lumen antigens to reach the DCs, resulting in their maturation and activation, thus enhancing immune responses.[58] The population of mucosal DCs and the number of $CD40^+$ DCs is significantly increased in UC and CD, when compared to controls.[59] Among intestinal DCs, the $CD103^+$ cell subpopulation seems to be essential for maintaining the homeostasis of the mucosa and for regulation of the balance between effector and regulatory T-lymphocytes.[60] During an IBD disease flare, DC subsets expressing E-cadherin (a CD103 receptor) in the intestine and the draining mesenteric lymph nodes and provide proinflammatory cytokines, such as IL-6 and IL-23, which are suggested to contribute toward Th17 cell maturation and colon damage in at least a subset of IBD patients.[61,62]

Also in psoriasis the cellular composition of cutaneous DC subsets is modified compared to healthy skin: Langerhans cells (LCs) are markedly reduced, whereas plasmacytoid DCs (pDCs) are increased in human psoriasis lesions and in the animal skin of a murine psoriasis model (DKO* mice).[63] Particularly, the depletion of LCs in the latter model aggravated the disease, while depletion of pDCs (before disease onset) resulted in an overall milder phenotype. The proposed mechanisms included IL-10 and IL-23 decrease. The modulating role of LCs in psoriasis is further highlighted by the fact that after treatment with adalimumab, the density of epidermal LCs increases rapidly (with a concomitant normalization of their spatial localization within the epidermis).[64]

pDCs predominate among the immune cells of the dermis of lesions and uninvolved skin of psoriasis patients.[65] In healthy skin, pDCs are almost absent, but they are abundant in the skin of psoriatic plaques, particularly in early lesions, where they become activated and produce interferon-α (INF-α), an inflammatory mediator essential for the development of psoriasis lesions.[65] A less distinct role for pDCs is presumed for the chronic-stationary state of psoriasis lesions;[66] other dermal DC subsets appear to be more important for the stabilization of disease state and the persistence of these lesions.[67]

Macrophages participate in innate and adaptive immune processes at the epithelium, acting as an environmental barrier through phagocytosis and antigen presentation.[68] Two major subtypes of macrophages and further cellular subsets are distinguished: inflammatory (M1) and anti-inflammatory (M2a, M2b, M2c), reflecting the vast cellular diversity and functional plasticity of this cell species in the skin and intestine.[69]

In healthy individuals, the main intestinal population of macrophages bears the $CX3CR1^{high}$ phenotype and, although, nonresponsive to inflammatory stimuli, these cells preserve phagocytic capacity. Under the proinflammatory circumstances of the gut tissues in IBD, another subpopulation of $CX3CR1^{low/int}$ macrophages expands there due to the emigration and differentiation of precursor monocytes.[70] This M1 macrophage subset that overexpresses antigen receptors and PRRs augments the environmental signaling for the synthesis of proinflammatory cytokines (TNF, IL-1, IL-6) and contributes to local immune response exacerbations.[71]

The M1 macrophages subset is also closely linked to the proinflammatory situation of the psoriatic plaques.[72]

A variety of exogenous pathogen-associated molecular patterns and endogenous ligands, recognized through PRRs, are implicated in the molecular pathways by which macrophage activation is induced after the skin barrier is breached.[73] Thepen et al[74] showed that local elimination of macrophages led to resolution of focuses of cutaneous inflammation. A number of endogenous anti-inflammatory mediators produced by macrophages have also been identified, including IL-10, TGF-β, lipoxins, and prostaglandins.[75] In addition, tissue macrophages have been involved in the generation of T-regulatory cells.[76] Taken together, macrophage subsets in psoriatic skin may delineate both pro- and anti-inflammatory roles in the pathogenesis of psoriasis. Given the central role of macrophages in maintaining tissue inflammation, better understanding of their pathophysiological role is predicted to contribute innovative macrophage-targeting therapeutic modalities for psoriasis and IBD in the future.

Mast cells (MCs) are another cell species with a recognizable role in the pathogenesis of IBD and psoriasis. There are two subsets of MCs, mucosal and connective tissue MCs. The human mucosal MCs are a functionally T-cell-dependent population mainly found in the lungs and the intestine. Connective tissue MCs are not as much T-cell dependent and are found in the skin and the intestinal submucosa.[77]

The largest number of MC progenitors are found in the intestine. These cells continue to differentiate, mature, and establish residence there.[78] Increased number of MCs are found in biopsies from UC- or CD-affected gut areas.[79,80] Under conditions of tissue inflammation, intestinal MCs degranulate and release substances such as tryptase-β and chymase-1[81] leading to increased tissue levels of histamine, prostaglandin D_2, and leukotrienes.[82] In the intestine, MCs also play an important homeostatic role by regulating the baseline permeability of the gut epithelium[83] and by modulating epithelial–neuromuscular interactions in the gut. Thus, they participate in the pathogenesis of altered motility patterns seen in functional GI disorders, postoperative ileus, food allergy, and also IBD.[84]

In the human skin, connective tissue MCs play an essential role in diverse physiological and pathological processes such as the mediation of type I hypersensitivity reactions and allergic diseases. Upon activation, they produce large amounts of TNF-α, IFN-γ, IL-8, IL-33, and multiple other mediators, such as VEGF, contributing to the creation of a tissue microenvironment essential for the recruitment of neutrophils and lymphocytes during innate and T-cell-mediated inflammatory processes.[85] The increased number of MC that are found in psoriasis skin, underscore the important role of these cells in the pathophysiology of this disease.[85,86]

In particular, a postulated interaction between stress and inflammatory processes in both the skin and the intestine is suggested to be mediated via the function of MCs.[87,88] MC–neuronal interactions are thought to be involved in translating stress insults into psoriasis flares.[89]

The natural killer (NK) cells are a specialized subset of $CD56^+CD16^+$ cells that can recognize injured cells and promote their death through a non-MHC-dependent manner.[90] They also produce cytokines, particularly IFN-γ, TNF-α, and TGF-β but also IL-2, IL-15, and IL-23, and affect the maturation of DCs.[91]

In IBD, NK cells are characterized by increased IL-21R expression, which amplifies the effect of IL-21 and the downstream proinflammatory cytokine cascade.[92] In the intestinal mucosa of CD patients, there are alterations in the ratio of NKp44- and NKp46-expressing NK cells.[93] Increased numbers of IFN-γ-producing $NKp46^+$ cells are found in CD-affected mucosa sections, whereas IL-22-producing $NKp44^+$ cells are significantly decreased compared to UC patients and healthy controls.

In the acute state of psoriatic plaques, ~5%–8% of the inflammatory cellular infiltrate consists of NK cells expressing the $CD56^+CD3^-$ phenotype and the activation antigen CD69. Compared to the uninvolved skin of psoriasis patients or healthy controls, NK cells in the lesional psoriasis skin produce large quantities of IFN-γ and express higher levels of perforin, a pore-forming protein found in the cytotoxic granules of NK cells and a key mediator of NK cells cytotoxicity.[94,95]

Finally, decreased number of circulating NK cells is found in patients with long-standing psoriasis. Decreased NK cell activity was also observed in the peripheral blood of IBD patients, but this could not be attributed to decreased NK cell number.[96]

Another leukocyte species involved in IBD pathogenesis is the innate lymphoid cell (ILCs).[22] ILCs are abundant at barrier surfaces of the body such as the skin and the intestine.[97] These cells play a key role in tissue remodeling and controlling microbe tissue load, lymphoid tissue development, and tissue homeostasis.[98,99] ILCs are divided into subtypes based on the patterns of synthesized cytokines and on the expression of specific transcription factors.[99,100]

Besides their important role in gut homeostasis, these cells are probably also involved in the pathogenesis of IBD, where increased numbers are found compared to controls.[101] In a proinflammatory environment, these cells produce IL-22; a pathophysiologic adaptation that limits apoptosis,

preserves intestinal barrier, and protects the gut during inflammation.[101–103]

Blood and lesional skin biopsies of patients with psoriasis showed enrichment of NCR^+ ILC3; however, similar frequencies of $CD161^+$ ILC1 and $CRTH2^+$ ILC2 compared to controls.[104] ILC3 is an innate source of IL-22 and IL-17 in the psoriatic skin, and an increased skin concentration of $NKp44^+$ ILC3 cells has been associated with disease severity.[105] It is worth noting that treatment of psoriasis patients with adalimumab reversed the number of these cells in parallel with clinical disease improvement.[106]

Regarding the role of the adaptive immunity, the latest pathophysiologic hypotheses consider an interaction of Th17, T-regulatory lymphocytes (Tregs), and Th1 cells crucial for the pathogenesis of both psoriasis and IBD.[107]

Th17 cells comprise a subpopulation of T-helper cells that produce mainly IL-17 and IL-21.[108] They comprise a T-lymphocyte subset evolutionarily distinct from the Th1 and Th2 lymphocyte subpopulations, with a key role in chronic organotropic inflammatory processes such as psoriasis and CD.[109] Some Th17 subtypes also produce IL-22, which is associated with disease aggravations in psoriasis; however, it has a protective function in IBD. Inflammatory foci of the GI mucosa in IBD patients display a massive infiltration of Th17 cells, and Th17-related cytokines are produced in excess in both CD- and UC-affected tissues.[110] Genome-wide association studies have revealed increased frequencies of certain Th17-related gene polymorphisms (such as *STAT3* or *IL-23R*) in IBD patients, thus supporting the involvement of the Th17 pathway in IBD pathogenesis.[111] Despite earlier findings, to date, targeting Th17 cells,[112] either by blocking their proliferation and differentiation or by inhibiting and neutralizing their specific cytokines, is a highly disputed, rather ineffective therapeutic pathway for IBD (see "Comparison of pharmacologic treatment modalities" section).

Recent advances in understanding the psoriasis pathogenesis indicate to an interaction of the IL-23/Th17 cells axis with keratinocytes and synovial cells as one of the main pathophysiologic events in the initiation and maintenance of tissue inflammation in this disease.[113] IL-17-producing Th17 lymphocytes promote the synthesis of inflammatory molecules and induce acanthosis, hyperkeratosis, and parakeratosis.[114,115] As in the case of IBD, polymorphisms of genes have been observed in psoriasis that relate to development and functional polarization of Th17 lymphocytes. For example, polymorphisms in the aforementioned genes *STAT3* and *IL23* are strongly associated with the psoriasis phenotype.[116] The key role of IL-17 in psoriasis is further underlined by the distinct effectiveness of treatment modalities (contrary to IBD) that either target the IL-17 cytokine directly (secukinumab, bimekizumab, ixelkizumab) or block the IL-17 receptor (IL-17R: brodalumab).[113]

Another lymphocyte subpopulation with increasing importance in IBD and psoriasis research is the Tregs. In various organs, including intestine and skin, these cells counteract the abnormal activation of the immune system, preventing excessive stimulation and contributing to self-tolerance.[117]

Compared to controls, Tregs are reduced in peripheral blood in the active phase of both CD and UC; however, they normalize during disease remissions. This observation suggests that during the course of IBD, Tregs migrate from peripheral blood to the inflamed intestinal mucosal sites, the lamina propria, and mesenteric lymph nodes.[118,119] It is worth noting that at the level of the intestine, the tissue concentration of Tregs is higher in IBD irrespective of the activity state of the disease, when compared to healthy controls.[120,121]

Tregs were significantly increased in the dermis and epidermis of psoriatic skin too, as compared to normal skin.[122] Functional and numerical abnormalities of Tregs have also been documented in the peripheral blood of psoriasis and IBD patients.[123] However, although *Foxp3* polymorphisms appear to contribute to the risk of developing psoriasis (at least in certain patient subpopulations), a similar association could not be verified in IBD patients.[124,125]

Comorbidities

Chronic inflammatory conditions such as psoriasis and IBD also share a series of important comorbidities. Most of these connections have been attributed to the systemic action of sustainably increased tissue levels of inflammatory mediators, shared genetic risk factors, and, in some cases, predictable adverse effects of the employed treatments.[126] Patients with severe psoriasis are at increased risk of premature death from most leading mortality causes in the population, including cardiovascular (CV) disease, malignancies, chronic lower respiratory disease, diabetes, dementia, infection, and kidney disease.[127] Moreover, in psoriasis, besides the characteristic arthropathy and the concordance with IBD, variable evidence for a higher prevalence has been observed for CV disease, obesity, diabetes, hypertension, dyslipidemia, metabolic syndrome, nonalcoholic fatty liver disease, cancer, and anxiety/depression.[128] On the other hand, apart from psoriasis, usual comorbidities of IBD include arthritis, asthma, pericarditis, certain malignancies, and also psychiatric conditions. Notably, among IBD, patients with UC (but not with CD) are additionally at increased risk of developing chronic renal

failure and multiple sclerosis.[129] It is worth noting that overall mortality rates are also slightly increased in IBD patients at a rate comparable to that observed in the case of severe psoriasis.[130] Table 3 compares the evidence for selected major comorbidities in patients with psoriasis and IBD. Corresponding data concerning three selected major comorbidities (cancer, obesity, and CV diseases) will be briefly discussed.

Besides epidemiologic evidence, the rationale for the search for possible connections of psoriasis and IBD, on one hand, and malignancies, on the other, is the bidirectional relationship between chronic inflammation and cancer. Chronic inflammatory conditions are frequently associated with the induction $CD8^+$ cytotoxic T-lymphocytes and increased NK cell activities. Moreover, INF-γ and TNF-α produced by the

Table 3 Psoriasis and IBD share a series of important comorbidities.

Comorbidity	Psoriasis	IBD	Comment
Arthritis	Psoriatic arthritis (PsA) typically affects the large joints, especially those of the lower extremities, distal joints of the fingers, and toes, and more rarely the back and sacroiliac joints. The frequency for PsA within psoriasis has been reported to range from 7% to 42%.[195]	Musculoskeletal symptoms are the most frequent extraintestinal manifestation of IBD affecting 6%–46% of patients. The IBD-related arthropathy includes peripheral arthritis, enthesitis and dactylitis, axial arthropathy, isolated sacroiliitis, and ankylosing spondylitis.[196]	IBD-related arthropathy as well as psoriatic arthritis belong to the group of seronegative spondyloarthropathies. TNF-α participates in the pathogenesis of both the diseases and the related arthropathies. Anti-TNF-α treatments are highly effective.[197,198]
Cardiovascular (CV)	Overall inconclusive and questioned epidemiologic evidence: a 10-year 6.2% additional absolute risk of major CV events compared to the general population; however, no corresponding evidence in short-to-medium term (over 3–5 years).[146]	IBD in the absence of traditional risk factors is not associated with an increased risk of premature/excess CV disease events.[150]	More data are needed to support a relationship. The role of treatments awaits further evaluation.
	Postulated mechanism: skin and intestine inflammation promote vascular inflammation leading to atherosclerosis and thrombosis.[146,149,151,152]		
	Pathophysiologically evidenced approved treatment modalities may have deleterious effects on CV morbidity (eg, escalation of severe heart failure with TNF-α-blocking modalities, in spite of markedly increased TNF-α blood levels in these conditions). In total, anti-TNF-α agents may reduce CV events in psoriatic patients but increase the incidence in IBD patients.[199,200]		
	Certain medications for CV diseases, as β-blockers exacerbate psoriasis.[201]	Although certain drugs have been related to IBD onset or worsening, CV medications are not included.[202]	
Obesity	Twofold increased risk compared to general population.[138]	Relatively low (15%–20%), but rising prevalence of obesity in IBD patients.[143]	Abdominal pain and diarrhea, weight loss, and malnutrition affect the majority of IBD patients. However, an increasing prevalence of obesity in patients with IBD has been described recently.
	Common mechanism of obesity induction: obesity as a chronic, low-grade inflammatory condition.[136,142]		
	Obesity may induce psoriasis.[138]	No evidence that obesity may induce IBD.	
Hepatobilliary	Increased NAFLD risk compared to controls (odds ratio =2.15).[203,204]	Markedly increased prevalence of IBD, mainly UC, among patients with PSC (21%–80%).[205]	Divergent comorbidity
	Therapy often includes hepatotoxic drugs as methotrexate[206]		
Psychiatric	Anxiety and depression are more common (approximately twofold) in patients vs controls.[207] Stressful events are risk factor for disease exacerbations.[208,209]		Shared comorbidity
Cancer	NMSC is the most common malignancy arising in psoriatic patients. The risk in severe psoriasis approaches that of patients with solid organ transplantation (relative risk =2.12).	Overall, NMSC incidence is increased in patients with IBD, most probably as a consequence of the wide use of azathioprine to treat these conditions.[210–212]	Share probably treatment – associated increased NMSC risk.[135]
	The adjusted hazard ratios for any incident cancer excluding NMSC were 1.06. Hazard ratios were increased for NMSC, lymphoma, and lung cancer.[194]	Overall cancer incidence rates are increased in CD, with a spectrum similar to that in the general population.[210] UC patients have increased risk of colorectal carcinoma, liver–biliary cancer, and leukemia.[213,214]	Differences probably reflect pathophysiologic differences or divergent treatment preferences.

Notes: Most of these connections have been attributed to the systemic action of sustainably increased levels of inflammatory mediators, shared genetic risk factors, and employed treatments.

Abbreviations: NAFLD, nonalcocholic fatty liver disease; PSC, primary sclerosing cholangitis; NMSC, nonmelanoma skin cancer; CD, Crohn's disease; UC, ulcerative colitis; PsA, psoriatic arthritis; IBD, inflammatory bowel disease.

activated CD4+ Th1 cells in inflammatory conditions may cause tumor cell senescence and tumor control. In addition, Th1 immunity may induce antiangiogenic chemokines that in certain circumstances could counteract cancer growth.[131] On the contrary, other studies indicate that inflammation contributes directly to tumorigenesis.[132] Chronic inflammation can initiate tumors directly by causing DNA alterations or by making cells more susceptible to mutagens. In addition, inflammation can also act as a tumor promoter since inflammatory mediators such as cytokines (TNF-α, IL-1, IL-6), growth factors, chemokines, and proteases produced by tumor-associated lymphocytes, and macrophages can enhance tumor cell growth and metastasis.[133,134] However, taking available data together, there is no evidence of increased cancer incidence among patients with psoriasis and IBD, with the exception of the association of UC with certain GI malignancies. Probably these opposing mechanisms generally balance themselves in the case of the present chronic inflammatory conditions, resulting in overall unaffected cancer risks. Nonmelanoma skin cancer represents an exception among malignancies for both conditions; however, their increased incidence is most likely secondary to the application of therapeutic modalities with recognized tumor-promoting risks (ie, ultraviolet radiation and azathioprine in psoriasis and IBD, respectively).[135]

From a pathophysiologic point of view, obesity is an interesting comorbidity that potentially highlights the shared pathogenesis mechanisms of psoriasis and IBD. Obesity is currently considered a chronic, low-grade inflammatory condition;[136] proinflammatory adipose tissue macrophages stimulate the secretion of proinflammatory mediators, such as TNF-α, IL-6, and leptin, which establish and maintain an inflammatory tissue state.[137] With a doubled odds ratio compared to controls, obesity is a recognized serious health risk factor in patients with psoriasis.[138] In addition a role for obesity in the pathogenesis of psoriasis is speculated.[139] More specific, significantly increased blood levels of leptin are found in patients with psoriasis, a mediator that might have participated to psoriasis induction by promoting Type 1 cytokines synthesis.[140] On the other hand, due to the nature of IBD (with abdominal pain and diarrhea, weight loss, and some degree of malnutrition affecting the majority of the patients), obesity was not predicted to be an important comorbidity of IBD patients.[141] However, it is surprising that a recent study finds an increasing prevalence of obesity in patients with IBD (15%–20%), with a further 40% of patients being overweight.[142] Chronic inflammation, the type of intestinal microbiota, the medication for controlling IBD, and the lack of physical activity are all discussed as putative factors that favor overweight and obesity in the IBD patients.[143–145] Future studies should also clarify to what extent the improved efficacy of IBD treatment modalities might per se have contributed to increased obesity prevalence among these patients.

Finally, there is currently increasing interest in the literature concerning the interrelationship between psoriasis and CV morbidity, with particular emphasis in the role of the antipsoriatic therapeutic interventions. Most studies indicate an increased CV risk of patients with psoriasis that is mediated by endothelial dysfunction and is manifested by higher incidences of stroke, atherosclerosis, coronary artery disease, and myocardial infarction.[146] Interestingly, psoriasis and atherosclerosis share a common pattern of Th1 and Th17 cytokine upregulation, T-cell activation, local and systemic expression of adhesion molecules, and endothelins.[147] Moreover, increased amounts of vascular endothelial growth factor produced by proliferating keratinocytes and the hyperhomocysteinemia (a common finding in patients with psoriasis) provide additional possible mechanisms for increased atherosclerosis risk in these patients.[148,149] On the other hand, CV is still a common cause of mortality among IBD patients although they have no different CV risk compared to the general population.[150–152] And this is in spite of the increased prevalence of a series of risk factors in patients with IBD, known to promote CV risk (prothrombotic state, subclinical atherosclerosis).[153–156] This controversy is still increasing when the role of therapeutic interventions is considered. Besides reports of decreased frequency and severity of CV events both in psoriasis and IBD patients under treatment with methotrexate and probably also TNF-α inhibitors, other studies found exactly the opposite, ie, increased myocardial infarction risks, with the same modalities.[157–159]

Taken together, probably with the exception of psychiatric comorbidities and increased nonmelanoma skin cancer risk, there is no conclusive evidence definitively linking both psoriasis and IBD with a certain pattern of comorbid conditions.

Comparison of pharmacologic treatment modalities

The wide overlap of approved modalities employed to treat psoriasis and IBD, particularly the more targeted newer biologics, underscore the pathophysiologic proximity of the mechanisms that underlie the pathogenesis of these conditions. However, distinct differences also exist that obviate core differences in the pathophysiology of these conditions, and the knowledge of these differences is significant for the understanding of core pathomechanistic peculiarities of each condition. Table 4 depicts and compares the use of currently approved pharmacologic modalities for the systematic treatment of psoriasis and IBD.

Although a number of different small molecules are used to treat both psoriasis and IBD, we focus on the comparison

Table 4 Comparison of the use of pharmacological treatment modalities for psoriasis and inflammatory bowel diseases (IBD)

Drug pharmacodynamics	Disease			Comment
	Psoriasis	IBD		
		Crohn's disease (CD)	Ulcerative colitis (UC)	
Biologics				
Infliximab (and biosimilars) Chimeric monoclonal antibody that neutralizes TNF-α	Approved Moderate-to-severe psoriasis High efficiency in multiple trials[160]	Approved Moderate-to-severe disease that relapsed or is steroid refractory[215]	Approved Superior to placebo in both remission induction and maintenance[216]	TNF-α inhibitors (1) have been implicated in de novo development of psoriasis (frequent) and CD (seldom)[217,166] and (2) they concordantly show comparable efficacy for psoriasis and IBD.
Etanercept[a] Fusion protein that binds to TNF-α receptor	Approved Moderate-to-severe psoriasis[218]	Tested, not approved Inadequate effectiveness and increased adverse events risk[219]	Tested, not approved Inadequate effectiveness[220]	
Adalimumab[a] Fully human monoclonal antibody that neutralizes TNF-α	Approved Moderate-to-severe psoriasis[221]	Approved Adalimumab is effective for maintaining long-term clinical remission[222]	Approved Inferior to infliximab as remission induction; comparable as maintenance therapy[223]	Exception: Etanercept is not effective in IBD.
Certolizumab pegol Humanized TNF inhibitor monoclonal antibody	Approved Only for psoriatic arthritis[224]	Approved More effective in patients without prior primary nonresponse to adalimumab[225]	Under investigation[226]	
Ustekinumab Human monoclonal antibody binding p40 subunit of IL-12/IL-23	Approved To date probably the most effective treatment (meta-analyses)[227]	Under investigation Phase III clinical trials[228]	No trials availiable[229]	Probably effective in at least some IBD.
Secukinumab[a] Anti-human IL-17 monoclonal antibody	Approved First line treatment for moderate-to-severe disease. High efficacy[230]	Tested, not approved No benefit outcome vs placebo[231]	Not tested	Not effective in IBD.
Natalizumab and vedolizumab[b] Humanized monoclonal antibodies against integrins α4/α4β7 (anti-integrin therapies)	Not tested	Approved Better for induction and maintenance of remission vs placebo	Approved Efficacy has been proven only for vedolimumab	The approval of efalizumab for moderate-to-severe psoriasis has been withdrawn due to postmarketing serious adverse events.[232]
Small molecules				
Glucocorticosteroids Cell membrane fluidity alterations and steroid receptor hormone activation	Approved only for topical use (first-line topical treatment). Not indicated for systemic treatment (unfavorable benefit-to-risk relationship).[233]	Approved First-line modality for the induction of initial remission and remission in recurrences. If applicable, topically acting glucocorticosteroids (budesonide, beclomethasone) are preferred.[234]		Highly effective in psoriasis and IBD.
Methotrexate Folic acid antimetabolite	Approved All forms of psoriasis and psoriatic arthritis.[235]	Approved (also as monotherapy) Probably prevents immunization when associated with anti-TNF modalities.[236]	Under investigation[237]	Effective in psoriasis and probably most IBD.
Fumaric acid esters[a] Incompletely understood mechanism of action: antioxidant (increase cellular glutathione levels.); immunomodulation	Approved Evidence suggests that fumaric acid esters are superior to placebo and possibly similar in efficacy to methotrexate for psoriasis. However, the quality of evidence that support the use of fumaric acid esters can be improved[238]	Not tested. Experimental model show that dimethyl fumarate reduces inflammatory response[239]		Approved only for psoriasis

Drug pharmacodynamics	Disease			Comment
	Psoriasis	IBD		
		Crohn's disease (CD)	Ulcerative colitis (UC)	
Cyclosporine-A[a] and tacrolimus (calcineurin inhibitors) impair/interfere with T-lymphocyte proliferation/activation	Approved (cyclosporine) Cyclosporine: highest short-term efficacy among all nonbiologic systemic therapies.[240]	Not approved Fail to maintain disease remission.[241] Topical tacrolimus and cyclosporine are effective in extraintestinal CD disease.	Tacrolimus: under investigation (appears safe and effective; further trials are needed).[242] Cyclosporine: not approved (fail to maintain disease remission).[243]	To date, clinically adequate effectiveness proved only for psoriasis.
Sulfasalazine (SASP) and mesalamine (5-ASA)[b] Topical antimicrobials. Activation of peroxisome proliferator-activated receptor (PPAR)-γ (hypothetical)	Not tested Anecdotal reports of favorable treatment outcomes.[244]	Approved Established therapy; however, the efficacy is questioned by recent meta-analyses[245]	Approved 5-ASA superior to placebo as maintenance therapy but inferior to SASP[246]	To date, clinically adequate effectiveness proved only for IBD. Effectiveness in psoriasis not defined yet.
Azathioprine and 6-mercaptopurine[b] Purine analogs: reduce the proliferation of T- and B-lymphocytes	Not tested Few reports suggest beneficial outcomes.[247] Randomized trials for azathioprine have not been executed.	Approved (azathioprine) More effective than placebo for induction and maintenance of remission.[248]	Approved (azathioprine) Adequate short- and long-term safety and effectiveness.[249]	To date, clinically adequate effectiveness proved only for IBD.
Apremilast Selective phosphodiesterase 4 (PDE4) inhibitor	Approved Second-line modality for moderate-to-severe disease.[250]	Not tested. Apremilast inhibits lamina propria mononuclear cell TNF-α and MMP-3 production in patients with IBD.[251]		A similar PDE4 inhibitor (tetomilast) is being tested for IBD.

Notes: [a]modality approved only for psoriasis; [b]modality approved only for IBD.
Abbreviations: IBD, inflammatory bowel disease; TNF, tumor necrosis factor; MMP, matrix metalloproteinase.

of the effectiveness of the mechanistically more predictable targeted biologic modalities.

Generally, TNF-α-targeting biologics are effective in both psoriasis and IBD with a vast differentiation: etanercept, which is approved for the treatment of psoriasis, is not effective in IBD.[160,161] Paradoxically, treatment with anti-TNF-α modalities has been implicated in de novo development of psoriasis and, less frequently, of IBD.[162–165] The incidence of anti-TNF-α-associated psoriasis-like manifestations has been estimated at one case per 1,000 patient-years or 3%–10% of the treated patients.[107,166,167]

More recently, monoclonal antibodies against IL-17 (sekukinumab, brodalimumab, ixekizumab) have been developed for the treatment of moderate-to-severe psoriasis, exhibiting exceptional efficacy.[168] Secukinumab and brodalimumab have also been evaluated in randomized trials for moderate-to-severe CD, but neither reached significant effectiveness compared to placebo.[169] The conflicting results provided by IL-17 inhibition verify the complex biology of this immune mechanism in CD as well as indicate the crucial differences with the role of Th-17 cells in the pathogenesis of psoriasis and IBD.[170,171]

Discussion

The concurrent existence of psoriasis and IBD in an increasing number of patients poses a new diagnostic and therapeutic challenge. Health professionals should be aware of the similarities and discrepancies in the pathogenesis and epidemiology of these diseases to successfully distinguish between their random coexistence, their causative concurrence, or their occurrence as a "paradoxical" side effect. IBD patients should be examined for skin lesions, as extraintestinal manifestations markedly increase the overall morbidity of these diseases.[172–174]

In this report, we also compared the role of immune cells in the pathophysiology of psoriasis and IBD. The anatomical and functional integrity of the tissue–environmental barriers is compromised in the skin and intestinal lumen of patients with psoriasis and IBD, respectively, allowing the invasion of allergens and immunomodulatory metabolites from an altered microflora. An increased number of DCs infiltrate the skin in psoriasis and the intestine in IBD. These cells are exposed there to a proinflammatory milieu that mainly favors a Th1 response. Through the interaction of M1 subset of macrophages with tissue MCs in both conditions, increased amounts of substances are released in the tissue environment that promotes the recruitment of neutrophils and lymphocytes. Recently, interest has focused on the role of IL-23/Th17 effector axis, as its interaction with keratinocytes and intestinal mucosa cells appears to be a central pathway for the pathogenesis of psoriasis and IBD and a promising target for treatment modalities.

The aforementioned immune similarities also form the basis for the wide overlap of treatment regimens that are

used to treat psoriasis and IBD. However, there are also remarkable differences in the effectiveness of certain agents that highlight discrepancies in the pathophysiology of these conditions. Etanercept, for example, was not effective in IBD, and this has been attributed to a diminished ability of etanercept to induce T-cell apoptosis in the intestinal mucosa.[175] Correspondingly, the ineffectiveness of secukinumab in the treatment of CD has been related to the importance of mycobiome in the pathogenesis of this disease.[176] Given the high concordance of psoriasis and CD, it is legitimate to take into consideration the significant risk of CD flare inductions in patients receiving secukinumab, particularly as first-line treatment, for moderate-to-severe psoriasis.

It is similarly worth noting that the use of anti-TNF-α biologics to treat IBD, especially CD, has probably increased the prevalence of noninfectious dermatoses in these patients.[177] Next to xerosis and atopic eczema exacerbations, psoriasis is the third most common skin manifestation provoked by the treatment with anti-TNF-α agents in these patients.[177] The vast majority of the cases (76%) developed psoriasis while on infliximab, and the rest (24%) after switching to adalimumab or certolizumab, indicating that this phenomenon is not drug specific, but rather a pharmacological group effect.[107] Cases of psoriasis induced by etanercept have been also reported.[178] Regarding the management of paradoxical psoriasis, no specific guidelines are currently available. It has been hypothesized that individuals with newly developed psoriasis under treatment, whose cutaneous disease persists or recurs despite removal of the suspected agents, probably have an underlying previously unrecognized predisposition to psoriasis. However, those whose skin findings resolve completely after treatment modification are more likely to have suffered a true drug-induced psoriasis episode against the background of low genetic psoriasis preponderance.[179]

Conclusion

Available data support a high degree of overlapping epidemiologic profiles, genetic substrate, disease risk factors, inflammatory pathogenesis cascades, and also therapeutic procedures between psoriasis and IBD, particularly CD. Further studies may unravel the common mechanism that underlies these common chronic inflammatory diseases of skin and gut and may provide valuable insights for the development of innovative interventions for both conditions.

Disclosure

The authors report no conflicts of interest in this work.

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