Editorial

Psoriatic Disease 10 Years Later

The concept of psoriatic disease was developed and introduced 10 years ago[1]. It originated from a better understanding of molecular mechanisms at the basis of the pathogenesis of psoriasis and the associated musculoskeletal manifestations.

In subjects susceptible through a genetic predisposition, in the presence of active environmental factors, an altered immune response induces the inflammation of both skin and musculoskeletal structures, including joints, entheses, synovial sheaths of tendons, as in dactylitis, and the axial skeleton. Tumor necrosis factor-α (TNF-α) appeared to be the prevalent molecular driver of this inflammation through the activation of epidermal keratinocytes, antigen-presenting dendritic cells, T lymphocytes, endothelial cells, and enthesosynoviocytes. Similar to that of skin and musculoskeletal structures, the microscopic involvement of the bowel described in psoriatic arthritis (PsA) was then included in the concept of psoriatic disease under the same biological propulsion sustained by TNF[2]. This cytokine, by stimulating the production of growth factors, adhesion molecules, and chemotactic polypeptides, contributes to the recruitment of the cellular network, which colonizes the bowel along with the skin, the joints, and the entheses[1]. Later, in patients with psoriasis, several studies showed an increased prevalence of metabolic syndrome with a consequential increased risk of myocardial infarction and cardiovascular mortality[3]. Thus, over time with the development of new lines of research, psoriatic disease increasingly appeared a systemic condition confined not only to the skin and the musculoskeletal system, but involving several different anatomical areas[4,5]. Along with bowel, the eye, the metabolic profile, and bone metabolism are now fields of growing attention.

Regarding genetic aspects, the dominant psoriatic disease susceptibility sequences have been identified in several regions located within the MHC[6]. In particular, HLA-Cw0602 has been shown to be associated with cutaneous manifestations and the HLA-B*27 allele with severe articular phenotypes, mainly with the psoriatic spondyloarthritis subset[7,8].

Other genetic regions have been investigated in the context of multiple and genome-wide association studies. The killer cell Ig-like receptors (KIR), KIR2DS2, expressed on natural killer cells, have been found to be significantly associated to PsA[9].

These advancements have improved the understanding on the link between adaptive and innate immunity existing in psoriatic disease, since its first phases.

In fact, Class I HLA molecules, whose involvement is key for antigen presentation, represent a ligand of KIR acting as an adaptive immunity potential driver of innate immunity responses[10].

Apart from TNF, other cytokines have acquired relevance in the pathogenesis of psoriatic disease. Barnas and Ritchlin have described an interesting model[11]. They supposed 3 steps of molecular involvement: epidermis, dermis, and lymph node. At the level of epidermis, the model describes the activation of keratinocytes by different stimuli (mechanical and/or infections) with the release of DNA and RNA, which are recognized by plasmocytoid dendritic cells delivering in response to interferon (IFN)-α. At the level of dermis, IFN activates dendritic cells, which stimulate draining lymph nodes releasing cytokines influencing T cell differentiation. Interleukin (IL)-23 triggers the proliferation of IL-17–producing T cells while IL-12 promotes development of IFN-producing T lymphocytes, which migrate back to the skin or colonize the entheses and joints. The consequential release at dermis of IL-17 and IL-22 induces the proliferation of keratinocytes with the production of IL-19 and IL-36 and the release of neutrophil chemotactic factors. The accumulation of neutrophils leads to the formation of Munro's abscesses with the formation of psoriatic plaques[11].

We have amplified Barnas and Ritchlin's proposal[11], suggesting a further phase we call the "systemic phase," with the involvement of extracutaneous sites among which we include, along with entheses and joints, the bowel, eye, and adipocytes (Figure 1).

This would better explain the onset of entheso-arthritis, colitis, uveitis, and metabolic syndrome. Our suggestion emphasizes the biological involvement of other cytokines operating with TNF in the development of systemic inflammation, designing a new pathogenetic scenario in which IL-12, IL-17, IL-23, and the axis IL-23/Th17 acquire prominence. Entheso-arthritis is the first extraarticular site of importance. It is the consequence of cytokine involvement of the synovial-entheseal complex, the anatomical entity described by McGonagle, *et al*[12]. TNF, IL-17, and the IL-23/Th17 axis play a fundamental role in explaining the different articular features that characterize PsA, including enthesitis, arthritis, and dactylitis[13]. Bone metabolism is affected, too. Receptor activator of nuclear factor-κB (RANK)/RANK ligand signaling, which regulates activity and differentiation of osteoclasts, has been found altered in PsA synovial tissue. This may occur because the IL-23/17 axis upregulates RANK expression with a possible indirect effect on PsA synovitis[14].

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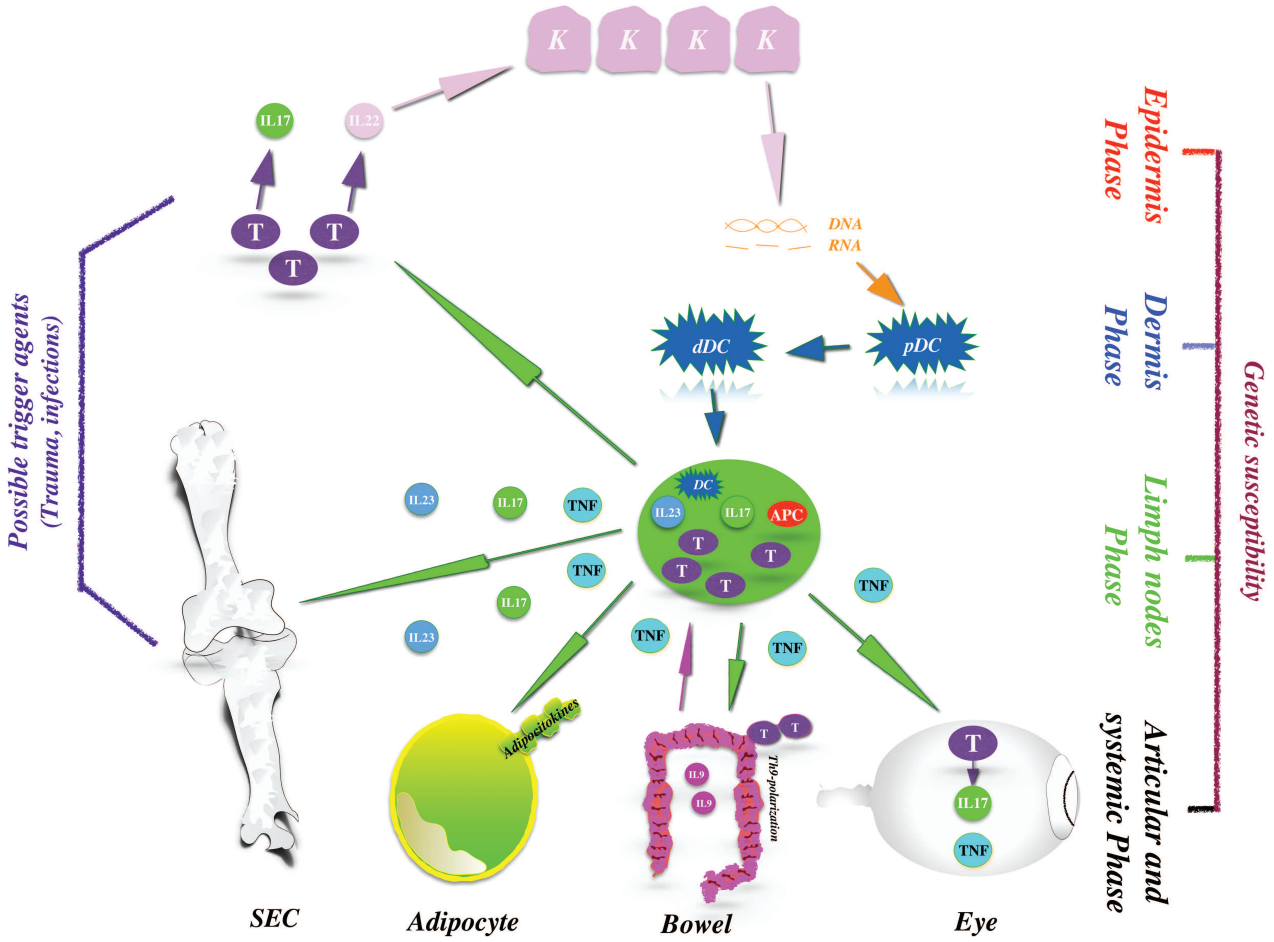

Figure 1. A speculative scheme representing physiopathological mechanisms and clinical manifestations of psoriatic disease. Possible trauma or infective agents trigger at different sites innate and adaptive immune mechanisms in genetically predisposed subjects. In the epidermis phase, T lymphocytes, by IL-17 and IL-22, start the dermis phase with activation of pDC to dDC. Lymph node phase includes APC involvement and activation of T lymphocytes with increased release of proinflammatory cytokines, mainly TNF-α, IL-17, and IL-23. These are keys in determining the heterogeneous spectrum of the psoriatic disease, involving eye (uveitis), bowel (colitis), adipocyte (metabolic syndrome), and SEC and the skin itself. A possible link between intestinal and synovial inflammation through IL-9 overexpression and Th9 polarization that occur in synovitis and in the peripheral blood of patients with psoriatic arthritis suggests a potential existence of a bowel-joint migratory axis. Adapted from: Barnas JL, Ritchlin CT. Etiology and pathogenesis of psoriatic arthritis. Rheum Dis Clin North Am 2015;41:643-63. IL: interleukin; pDC: plasmacytoid dendritic cells; dDC: dermal dendritic cells; APC: antigen presenting cells; TNF-α: tumor necrosis factor-α; SEC: synovial-entheseal complex; K: keratinocytes.

In the bowel involvement, TNF represents the principal promoter of inflammatory changes. However, several studies have opened new perspectives on the understanding of inflammatory bowel diseases (IBD). In particular, today it is recognized that Th17 cells drive colitis pathogenesis. IL-23 sustains Th17 cell responses and gut inflammation[15]. The introduction of the anti-IL-12/23p40 antibody ustekinumab for the treatment of Crohn disease (CD), approved also for PsA and psoriasis, has contributed to the elucidation of a shared pathway between these pathologies based on the IL-23–driven process[16].

However, the dual involvement of Th17-related IL-17 cytokines, with protective rather than negative effects in the gut, can be a discriminatory element for differentiating colitis of IBD from PsA colitis[15]. Peculiar balances of intestinal microflora could be involved in the differentiation of these conditions as one of the effects of the different combination of these cytokines produced by Th17[17]. Further, subclinical gut inflammation in patients with PsA has been reported as characterized by a specific histologic and immunologic signature represented by pronounced Paneth cell hyperplasia and Th17 and Th9 responses. Th9 responses have been reported to be a specific PsA signature when compared with ankylosing spondylitis and CD[18]. A possible link has also been hypothesized between intestinal and synovial inflammation through IL-9 overexpression and Th9 polarization that

occur in synovitis and in the peripheral blood of patients with PsA. This could suggest a potential existence of a bowel-joint migratory axis[18].

TNF is a major factor sustaining uveitis[19], and initial data on the possible involvement of the IL-17 are emerging[20]. In several experimental models, different researchers have shown an increased production of IL-17 during uveitis[21,22].

The improvement of noninfectious uveitis reported with use of secukinumab could support a role for IL-17A in its pathogenesis in the course of psoriatic disease, but further studies are required[23].

Finally, we should consider the metabolic syndrome, which develops under the inflammatory propulsion of psoriatic disease. Adipose tissue secretes several adipokines that produce inflammation and metabolic dysfunction[24,25,26]. The rationale sustaining the connection between pathogenetic aspects and systemic involvement is reinforced by studies conducted by the University of Toronto group. In particular, they have highlighted how adipocytokines, metabolic syndrome, and inflammatory severity are correlated in patients with PsA[27].

TNF is the most important adipokine, inducing adipocytes apoptosis, insulin resistance, increased plasma levels of triglycerides, and stimulating lipolysis[28,29]. In obese subjects, TNF levels appear increased in the plasma and in adipose tissue[27]. The therapeutic block of TNF has demonstrated the improvement of metabolic syndrome[25,26], with positive effects on all its different components. The actual scenario is made even more complex by the new components deserving growing attention. The involvement of intracellular enzymes, such as phosphodiesterase 4 (PDE4), and molecules, such as Janus kinase (JAK), playing a key role in cellular signaling, has been characterized in PsA[30,31,32].

The development of therapeutic agents targeting intracellular molecular pathways is a promising opportunity for PsA[33]. Among them we mention the emerging treatments targeting PDE4 (apremilast) and JAK (tofacitinib)[34].

The underlying heterogeneity inherent to the systemic expression of psoriatic disease needs to be investigated in depth. This heterogeneity is not fully understood at present, but needs to be considered to optimize the therapeutic approach. Indeed, pathogenetic mechanisms can contribute to differentiated tissue involvements that, in turn, might require a best-targeted approach to the management of the disease[35].

Because of the heterogeneous molecular background underlying psoriatic disease, the availability of multiple therapeutic approaches would guarantee in the future the possibility of a personalized therapy[33].

The complexity of the PsA pathogenetic aspects involving multiple cytokines and molecules encourages the continuous collaborative effort of investigation, ranging from molecular research to clinical studies.

After 10 years, the concept of psoriatic disease has gained relevance and may further direct this collaborative effort.

RAFFAELE SCARPA, MD,
Associate Professor,
FRANCESCO CASO, MD, PhD,
Assistant Professor,
LUISA COSTA, MD, PhD,
Assistant Professor,
ROSARIO PELUSO, MD, PhD,
Assistant Professor,
ANTONIO DEL PUENTE, MD,
Assistant Professor,
Rheumatology Unit,
Department of Clinical Medicine and Surgery,
University Federico II,
Naples, Italy;
IGNAZIO OLIVIERI, MD,
Rheumatology Institute of Lucania (IRel),
and Rheumatology Department of Lucania,
San Carlo Hospital of Potenza
and Madonna delle Grazie Hospital of Matera,
and Basilicata Ricerca Biomedica (BRB) Foundation,
Potenza, Italy.

Address correspondence to Dr. R. Scarpa, Rheumatology Unit, Department of Clinical Medicine and Surgery, University Federico II, Via S. Pansini 5, 80131 Naples, Italy. E-mail: rscarpa@unina.it

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