What's New in Laboratory Research?

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ABSTRACT. Psoriasis is a multigenic disease with a number of susceptibility loci on different chromosomes predisposing to the disease, which is in turn triggered by environmental factors. The pathogenesis of psoriasis is characterized by 2 main components, the dysfunctions of the immune system and the alteration of keratinocyte homeostasis. While the Th1 T cell response has long been considered the sole immune agent in the pathomechanisms of psoriasis, recently, the role of IL–23-driven Th17 has been shown to be predominant. Subsequently, only effector memory T cells expressing α1β1 integrin migrate into the epidermis, and psoriasis development is inhibited by blocking this integrin. Psoriatic epidermis contains high amounts of antimicrobial peptides, which have been shown to be a key mediator of plasmocytoid dendritic cell activation in psoriasis. The keratinocyte component has recently regained the central stage, as the abrogation of JunB/activator protein 1 in mouse keratinocytes induces development of psoriasiform lesions in T cell deficient mice. Moreover, inhibition of nerve growth factor and its receptor in keratinocytes strikingly improves psoriatic lesions. (J Rheumatol 2009;36 suppl 83:17-18; doi:10.3899/jrheum.090213)

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In recent years tremendous progress has been made in the pathophysiology of psoriasis; this has led to a generally accepted model where different stimuli, such as trauma, medication, microbes, etc., trigger, in a genetically predisposed individual (reviewed in[1]), an inflammatory cascade made of many cell types and cytokines. This network in turn generates a number of events ultimately resulting in the formation of the psoriatic plaque. Although an antigen has not yet been identified, a large body of evidence supports the role for the immune system in the pathogenesis of psoriasis, involving mainly the cytokine mediated response by the Th1 type T cell[2]. The "cytokine storm" triggered by Th1 type immune reaction through the release of interleukin 12 (IL–12) and interferon–γ has dominated the scene in the immune mechanisms of psoriasis until recently: a number of studies point to a key role for IL–23 in the maintenance of the inflammatory reaction. IL–23 promotes the development of an IL–17 and IL–22 producing T cell subset (Th17) through activation of the transcription factor STAT3[3]. IL–23 is overproduced in psoriasis[4], while IL–22 mediates IL–23 induced acanthosis and typical dermal inflammatory histologic features of psoriatic skin through the activation of STAT3 in vivo[5]. The injection of IL–23 in mouse skin results in erythema, mixed dermal infiltration, and epidermal hyperplasia that characterize the psoriatic plaque[6]. Taken together, these data support a critical role for IL–23 in the pathogenesis of psoriasis, whereas the pathogenic role of the Th1 mediated response is now questioned. While future studies will dissect the function of Th1 versus Th17 in the mechanisms underlying the development of psoriasis, a monoclonal antibody against the p40 subunit shared by IL–12 and IL–23 has recently been developed and successfully used in the treatment of psoriasis[7]. The efficacy of this drug would appear to reconcile the role of Th1 and Th17 in this disease. This is also supported by the recent large scale association study demonstrating that individuals homozygous for both the IL12B and the IL23R predisposing haplotypes have an increased risk of psoriasis[8].

The concept of psoriasis as an immune mediated disease, with a cellular infiltrate mainly composed of T lymphocytes releasing a wide array of cytokines, is widely accepted. On the other hand, the lesion develops in the epidermis when keratinocytes overproliferate and are resistant to apoptosis, thus contributing to the alteration of epidermal homeostasis. Therefore, some kind of interaction between T cells and the epidermis is conceivable. In psoriatic lesions, while CD4+ T cells are mostly localized in the upper dermis, CD8+ memory effector T cells are predominantly found in the epidermis. Moreover, it has recently been demonstrated that only T cells expressing α1β1 integrin (very late antigen, VLA 1), an adhesion receptor that binds to type IV collagen, can travel through the basement membrane into the epidermis. Antibodies to α1β1 integrin block emigration of T cells into the epidermis, aborting formation of psoriasis lesions[9]. These data indicate that migration of T cells expressing α1β1 integrin into the epidermis is essential for the development of psoriasis[10].

In addition to T cell involvement, innate immunity also plays a prominent role in psoriasis. Among the major constituents of innate immunity, antimicrobial peptides such as defensins and cathelicidins have recently been

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shown to be overproduced in psoriasis[11], which also accounts for low propensity to infection of psoriatic plaques. Recently, Lande and co-workers uncovered a fundamental role of an endogenous antimicrobial peptide, by demonstrating that cathelicidin LL37 is the key mediator of plasmacytoid dendritic cell (pDC) activation in psoriasis. LL37 converts inert self DNA into a potent trigger of interferon production by dendritic cells, providing the first link between an antimicrobial defense system and the pathogenesis of psoriasis[12].

While for over 30 years the role of the keratinocyte component in the pathogenesis of psoriasis has been considered secondary, psoriatic keratinocytes recently gained wide attention in an article that was featured in *Nature*[13]. Psoriatic keratinocytes have decreased expression of JunB, and deletion of JunB and its functional companion c-Jun in the basal layer of adult mouse skin results in a phenotype resembling the histological and molecular hallmarks of psoriasis and psoriatic arthritis. In particular, abrogation of JunB/activator protein 1 (AP–1) in keratinocytes triggers chemokine/cytokine expression, which recruits neutrophils and macrophages to the epidermis, thereby contributing to the phenotypic changes observed in psoriasis, also without the contribution of T and B cells (Rag2–/– mice). On the other hand, the development of arthritis requires T and B cells and signaling through tumor necrosis factor receptor 1 (TNFR1)[13]. These data provide genetic evidence that the skin disease in mice can develop independently of T cells and that the PsA is primarily mediated by TNF signaling.

Neurotrophins (NT) are a family of growth factors that control the development and survival of neurons; they also fulfill multiple regulatory functions at the skin level[14]. NT exert their effects through binding to 2 classes of receptors: the low affinity receptor p75NTR and the high affinity receptor Trk. While the latter mediates keratinocyte proliferation and survival, p75NTR seems to mediate apoptosis. In psoriasis lesions, Trk receptors are overexpressed[15], whereas p75NTR is absent (personal observation), pointing to an important role of NT receptors in the alteration of epidermal homeostasis in psoriasis. Moreover, keratinocytes in lesional and non-lesional psoriatic tissues express high levels of the NT nerve growth factor (NGF), compared to controls[16]. The critical involvement of the NGF/Trk system in psoriasis is confirmed by the efficacy of K252, which, by inhibiting Trk function, can reduce the thickness of psoriatic plaques transplanted onto the skin of immunodeficient mice in 2 weeks[17]. These data suggest that NGF is involved at least in part in the pathophysiology of psoriasis, and that inhibition of Trk signaling may be beneficial in psoriasis treatment. Against this background, a new molecule is under development for the topical treatment of psoriasis.

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