

Generalized Pustular Psoriasis: a New Emerging Concept Relating to Autoinflammatory Disease

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Generalized Acute Psoriasis (GPP) is a rare systemic inflammatory disease characterized by widespread, superficial sterile pustules over the trunk, which often rapidly develop into erythroderma. Pustular psoriasis is divided into generalized and localized, and the former type includes Zumbusch type, Impetigo Herpetiformis (acute GPP of pregnancy), annular and circinate form, juvenile and infantile pustular psoriasis, and generalized form of acrodermatitis continua (Hallopeau). Annular pustular psoriasis is usually localized, but rarely develops generally with systemic manifestation such as high fever, chills, and systemic inflammation. Histologically, GPP demonstrates subcorneal pustules, abscess, acanthosis, and cellular infiltrates in the papillary dermis. Neutrophils are supposed to be attracted by some chemotactic factors into the epidermis, such as Interleukin-8 (IL-8), Growth-Related Oncogene- α (GRO- α), CXCL2/Macrophage

Inflammatory Protein-2 (MIP-2), Leukotriene B₄ (LTB₄), Platelet Activating Factor (PAF), and C5a. Serum levels of IL-1, tumor necrosis factor- α (TNF- α), IL-6, IL-8, GRO- α , and soluble Fas are increased in patients with GPP, some of which correlate with clinical severities.

GPP may be included in idiopathic febrile syndromes of autoinflammatory diseases, while GPP is definitely an autoinflammatory syndrome is still uncertain. Systemic inflammatory diseases characterized by fever, systemic symptoms (i.e. anemia, arthralgia, liver dysfunction, lymphadenopathy), and increased levels of acute-phase protein are suggestive of autoinflammatory diseases, in which innate immunity is mainly involved. A growing body of evidence has shown that activated T lymphocytes play an important role, via an array of proinflammatory cytokines, in the pathogenesis of psoriasis. Although psoriasis was considered to be a Th1-dominant disease, recent progress has shown that psoriasis is mediated by Th1/Th17 subset, including IL-17, TNF- α and IL-22. IL-23 functions as a key differentiation and growth factor for Th17 cells, and thus the IL-23/Th17 axis is currently suggested to play a crucial role in psoriasis. Furthermore,

recent studies have shown that IL-36 is the upstream and master regulator of IL-23/IL-17/IL-22 pathway [1].

IL-1 β is a key mediator of acute inflammation, innate immunity, and adaptive immune response. In addition, recently, IL-1 family proteins such as IL-33 and IL-36, are also important in autoinflammatory disorders. IL-36 (α -, β -, γ -) are novel members of IL1 family, which bind to the IL-36 receptor and lead to the activation of Nuclear Factor- κ B (NF- κ B) and Mitogen-Activated Protein Kinase (MAPK) pathways. IL-36 Receptor Antagonist (IL-36RN) antagonizes the activity of IL-36. Recent studies have shown a significant role of IL-36 in psoriasis [1]. In particular, genetic analysis has revealed the mutations of IL-36RN in familial and also sporadic occurrence of GPP [2-6], and a deficiency of IL-36RN lead to the overproduction of IL-8 in keratinocytes. GPP has been proposed a Deficiency of Interleukin Thirty-six-Receptor Antagonist (DITRA). In many autoinflammatory diseases, the responsible mutated genes lead to excessive production of IL-1 β . Successful treatment by IL-1 receptor antagonist, Anakinra, has also been reported in a patient with GPP [7].

The trigger of GPP is supposed to be viral or bacterial infection and Toll-Like Receptors (TLRs) are activated, leading to pro-IL-1 β and pro-IL-18 synthesis via activation of NF- κ B signaling pathway. Subsequently, inflammasomes, multiprotein cytoplasmic complexes that activate inflammatory caspases, are activated. Activation of TLR induces enhanced production of IL-1 β , IL-6, IL-18 and IFN- α by peripheral blood mononuclear cells. On the other hand, extracellular stimuli also activate NALP3 inflammasome, which convert pro-IL-1 β and pro-IL-18 to IL-1 β and IL-18 by

proteolytic cleavage and maturation. The recently emerging theories can provide new insights into the pathogenesis of GPP, and also aiming at targeting or controlling of IL-36-mediated cellular events may lead to the novel therapies for GPP.

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