Commentary

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Treating Bullous Pemphigoid Today: Urgent Need for Biomarkers

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Description

Bullous Pemphigoid (BP) is a heterogenous chronic bullous autoimmune skin disease, characterized by different phenotypes, with distinct types of inflammatory process. BP is considered a mediated by Th1/Th2 cells associated with BP180/ BP230 autoantibodies. In most of the cases, the principal pathophysiological pathway appears to be Th2 dependent eosinophilic inflammation. It seems that another pathway is the non Th2 type, mediated by Th1 and especially Th17 lymphocytes, responsible for neutrophilic infiltration. Accumulating evidence suggests that aberrant IL-17 production is a key determinant at least in some of severe phenotype of BP [1,2].

In a recent review, several cytokines and chemokines were founded to be elevated in both serum and BP blister fluid, including IL-5, IL-6, and TSLP, and CXCL8. IL-17, IL-21, IL-36, APRIL BAFF, and TWEAK were elevated only in the serum, while increased levels of IL-1α and TNF-αonly in BP blister fluid [3]. For BP where mainly type 2 and in a questionable way type 1 inflammation may play an important role, further studies can address whether biomarkers such as elevated serum IgE, IL-17, IL-23, TNF-α andeosinophilia, can predict grated beneficial response to drug therapies targeting this pathway [3].

Type 2 inflammation involves a complex milieu of leukocytes and secreted proteins. The principal effectors include Th2 CD4+ T cells and group 2 innate lymphoid cells that produce type 2 cytokine IL-4, IL-5, and IL-13, B cells that secrete IgE and granulocytes such as eosinophils, mast cells, and basophils. Several lines of evidence point to a predominant type 2 inflammatory response in BP, which include important roles of Th2 cytokines and chemokines, eosinophils, and IgE. While anti-BP180 and anti-BP-230 IgG antibodies are well-established drivers of BP pathogenesis, IgE antibodies against these epitopes have also been shown to play an important role [4]. IgE production depends on IL-4 and IL-13 induced B cell class switching [5].

A possible ideal therapy might focusonTh1 molecule, on Th2 molecule, or on molecules that link type 1 and type 2 inflammation. Although, altered levels of type 1 cytokines, such as IL-17 and IL-23, have been shown in skin lesions, serum, or blister fluid of BP patients, some contradictory observations have so far been reported. Understanding the biology of IL-17 in the context of allergic inflammation may be informative in the development of novel approaches to the diagnosis and treatment of BP. Increased levels of IL-17 in blister fluids of BP patients could be in line with findings indicating the contribution of IL-17-producing cells in BP disease, which may confirm that BP regulation is beyond the Th1/Th2 paradigm [2]. It is also possible that IL-23 impacts the progression of autoimmune inflammation through both its effects on myeloid cells activation, as well as by driving downstream Th17 responses [1].

It is notable that the balance between Th1/Th2 cytokines remains under discussion and it might contribute to predicting the BP outcome directly or indirectly, by influencing the cell skin infiltration. Both neutrophils and eosinophils have the capacity to form DNA traps in BP lesional skin. The study of Giusti et al. [6] showed that IL-23 favors DNA extracellular traps released by neutrophils (NETs) formation, whereas the effects of interleukin 17A (IL-17A) are environment dependent. Specifically, IL-17A displays a protective effect on NET formation when associated with interleukin 23 (IL-23), showing for the first-time differential effects of these two cytokines in BP. Since the Th17/IL23 pathway plays a significant role in tissue immunosurveillance and autoimmunity mechanisms, it has recently been under intensive research. Given the importance of IL-17/IL-23 in BP, inconsistent data have been so far reported. Gene variations in the Th17/IL23 axis may influence its function, and therefore may cause dysregulation of this pathway in BP [7]. In a recent study, the data indicate an association between IL-23R rs7530511 and rs2201841 SNPs and BP susceptibility. The C-allele of IL-23R rs7530511 was found to be more frequent in the patients, while the G-allele distribution of IL-23R rs2201841 is significantly recognized in the control individuals [7]. Finding possible susceptible and protective impacts of IL-23R polymorphisms on autoimmune disease could provide additional information and supports in the direction of developing potential therapeutic approaches in patients with BP.

Case reports and other descriptive research into off-label usage of biologics provide useful information that helps guide treatment decisions for patients who have otherwise exhausted therapeutic options [8-10]. This approach in especially intriguing in dermatology, where there is a set of diseases that individually may have low prevalence but share common immunological mechanisms.

Conclusion

BP management can be challenging as treatment modalities vary greatly and no single standard of care exists. While autoantibody-induced infiltration of inflammatory cells in BP is a prerequisite for initiating the inflammatory processes involving in blister formation, several cytokines play a significant role and therefore, their alteration may influence the predisposition to BP disease. We support the theory in which, according with BPDAI and biomarkers, the future therapeutic agents target a specific molecule.

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