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Editorial

CD25 and IFN-γ expression in the diagnosis of primary immunodeficiencies

Susan McClory[a] and Jianhua Yu[b,*]
[a]*The Medical Scientist Training Program, The Ohio State University, Columbus, OH, USA*
[b]*Division of Hematology, The Ohio State University, Columbus, OH, USA*

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Primary Immunodeficiency Diseases (PID) are a group of rare genetic disorders characterized by a severe deficiency in immune function. These deficiencies result from abnormal differentiation, maturation, or activation of specific immune cells, and can involve humoral, cellular or complement-mediated immunity [1]. Typical presentation involves recurrent and persistent infections, autoimmune-type reactions, and in some cases malignancy [2]. To date, more than 95 disorders are classified as PID [1]. Early detection of PID is paramount, as infections in childhood can cause debilitating organ failure or even death [3].

Flow cytometry provides an ideal method for analyzing the populations present in peripheral blood, allowing for quick and cost-effective assessments of immune function. In the case of PID, flow cytometry has been used to help with initial diagnosis by characterizing the absence of specific cellular subsets or to enhance an established diagnosis by examining specific markers of immune cell function [4]. Throughout the past two decades we have seen rapid advances in the level of complexity and the usefulness of clinical cytometry with regard to PID. Indeed, as flow cytometry itself becomes more advanced, we should constantly strive to apply this technology to improving diagnoses and outcomes of our patients.

*Correspondence: Jianhua Yu, Ph.D., Biomedical Research Tower Room 882, The Ohio State University, 460 West 12th Avenue, Columbus, OH 43210, USA. Tel.: +1 614 292 4158; Fax: +1 614 292 4158; E-mail: jianhua.yu@osumc.edu.

In this issue of the *Journal of Pediatric Biochemistry*, Almeida et al. demonstrate that the measurement of T cell activation by flow cytometry can be used to distinguish the cellular immune responses of children with PID from those of healthy children in the same age group [5]. Specifically, the authors discovered that by exposing whole blood to phytohemaglutinin (PHA) for 18 hours, the intracellular levels of interferon-gamma (IFN-γ) produced by activated T cells was statistically lower in pediatric patients with PID than those without. Similarly, expression of CD25 on activated T cells was decreased in patients with PID when compared to children without immune-deficiency after whole blood exposure to candidin for 72 hours [5].

In addition to highlighting flow cytometry-based assays that may be useful in diagnosing and assessing PID, this work by Almeida et al. also emphasizes the importance of using relevant clinical controls when assessing immune function in children [5]. A positive correlation between age and CD25 or IFN-γ expression in the T cells of healthy donors was demonstrated using several different stimuli [5], emphasizing that T cell-mediated immunity is altered with age even in the absence of disease. Indeed, the authors report several conditions where the measured immune response of both PID patients and healthy children was statistically lower than that of healthy adults, but in these same conditions there were no statistical differences between patients with PID and normal donors when age was considered [5]. This underlines the importance of using

the appropriate age-matched controls when assessing immune function in individuals with PID.

However, several questions remain with regards to utilizing IFN-γ and CD25 expression by T cells as a biological marker for PID. While the authors were able to tentatively suggest cutoffs in IFN-γ and CD25 expression that could be used to distinguish children with PID from normal pediatric donors, only 9 PID patients were analyzed in this study. Furthermore, PID is not a single diagnosis, but is instead a conglomerate of specific disorders characterized by immune deficiency. The specific disorders which fall under the umbrella of PID result from individual etiologies, and each can exhibit deficiency in either humoral, cellular, and complement- mediated immunity or a combination of all three [1,2]. Thus, without considering the specific nature of the deficiencies seen in the PID cohort studied by Almeida et al., it is difficult to conclude with certainty how the measured differences in T cell immune function can be applied to the broad spectrum of individuals with PID. Furthermore, it seems logical that CD25 and IFN-γ expression by activated T cells would be more useful in assessing PID in patients with a primary T cell-mediated dysfunction than those with a non-T cell based PID. However, this was not addressed in this study.

In conclusion, the study by Almeida et al. establishes specific *in vitro* assays for assessing T cell function in patients with PID using flow cytometry, and suggests that expression of CD25 and IFN-γ may be important diagnostic markers for PID. Future studies should corroborate these findings in a larger cohort of patients with PID, and should further explore whether these two biological markers can be utilized only in T-cell mediated PID or more generally in a spectrum of different PID subtypes.

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