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High P-glycoprotein expression and increased IL-12 and IL-23 levels are responsible for the transition of Th17 cells to pathogenic IFN- γ producing Th17 cells in Refractory Nephrotic Syndrome

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Objectives: Th17 cells are critical effectors mediating autoimmunity in nephrotic syndrome (NS). Elevated IFN-γ has also been involved in NS; however, it remains unclear to what extent Th1 cells contribute to glucocorticoid resistance in NS. P-glycoprotein (P-gp) effluxes glucocorticoids outside the cells and is selectively expressed differentially on T cell subtypes. In this study, we investigated the role of P-gp and the cellular source of IFN-γ and assessed its contribution to glucocorticoid resistance in NS.

Methods: We analyzed the frequency of pathogenic IL-17A+IFN-γ+ Th17/1 lymphocytes and P-gp expression on their surface by flow cytometry in SSNS (n = 32; mean age: 9.06 ± 5.84) and SRNS (n = 28; mean age: 11.29 ± 3.73) patients. All patients were recruited as per the criteria of ISKDC. We also included 15 age- and sex-matched healthy controls. All patients were of biopsy-proven minimal change disease and all patients were treated with steroids.

Results: We found a significant IL-17A+IFN-γ+ Th17/1 population ($P < 0.001$) in steroid-resistant NS (SRNS) as compared to steroid-sensitive NS (SSNS) patients. IL-12 and IL-23 are significantly higher in SRNS as compared to SSNS patients which are required for the transition of pathogenic Th17 cells to IFN-γ producers. Of the IL-17A+IFN-γ+ Th17/1 population, 95.8% of cells expressed P-gp on their surface in SRNS; however, only 30.1% of cells expressed P-gp in the SSNS group. (Figure 1) We also observed that P-gp expression correlate positively with the IL-17A+IFN-γ+ Th17/1 population ($r= 0.739$, $p< 0.001$) significantly.

Conclusions: The above findings clearly show that higher expression of P-gp on IL-17A+IFN-γ+ Th17/1 cells is associated with steroid resistance in nephrotic syndrome through both IL-17A and IFN-γ.

Figure 1