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- This study reveals novel insights into the pathogenesis of lymphatic filarial dysfunction, despite some minor limitations. Since DEC had been administered only to the CP Ag- group and the presence of other parasitic infections not examined, the effect of treatment with DEC as well as the influence of other parasitic infections could not be ascertained in this study.

- We show that circulating levels of LPS, acute phase proteins and certain cytokines are significantly elevated in filarial disease with active infection but not in the other groups indicating that filarial infection induced increased production of these factors correlated with the development of filarial lymphatic pathology.

- These data suggest that while filarial lymphedema is characterized by alterations in certain pro-fibrotic factors such as MMPs/TIMPs, it is not associated with a generic increase in the circulating levels of other factors known to influence tissue fibrosis.

- These data indicate clearly that these particular cytokines are associated with development of overt pathology in actively infected individuals.

- Our examination of filaria-infected individuals also reveals a significantly positive association between MMP-1/TIMP-4 and MMP-8/TIMP-4 ratios (both of which were specifically elevated in CP Ag+) and Type 2 (and pro-fibrotic) cytokines. Our study clearly implicates a tissue-fibrosis promoting role for IL-5 and IL-3 in filaria-induced lymphatic pathology.
We show that altered ratios of the metalloproteinases and their inhibitors as well as elevated levels of pro-fibrotic cytokines characterize filarial infection-induced lymphatic pathology.

Our study examines in depth the CD4⁺ Th2 cell subset repertoire in a chronic parasitic infection and sheds light on the role of these subsets in both the regulation of immune responses in active infection and in the pathogenesis of filarial lymphedema. While we have not performed longitudinal studies to define the development of pathology in filarial infection, our strategy of contrasting immune responses in individuals with early or subclinical disease and those with late or clinical disease yields important information on the role of Th2 subsets in pathogenesis. In addition, while we have demonstrated the presence of Th2 subsets in filarial infections, disease association is not formal proof of function and the elucidation of function needs to be explored in the future. Nevertheless, our study clearly defines and important association of filarial infection with heightened expansion of Th2 cells suggesting that these subsets play an important role in infection.

Th9 cells are a subset of CD4⁺ T cells, shown to be important in allergy, autoimmunity, and antitumor responses; however, their role in human infectious diseases has not been explored in detail. We identified a population of IL-9 and IL-10 coexpressing cells (lacking IL-4 expression) in normal individuals. These cells respond to antigenic and mitogenic stimulation, but are distinct from IL-9⁺ Th2 cells. We also demonstrate that these Th9 cells exhibit Ag-specific expansion in a
chronic helminth infection (lymphatic filariasis). Comparison of Th9 responses reveals that individuals with pathology associated with filarial infection exhibit significantly expanded frequencies of filarial Ag-induced Th9 cells, but not of IL9+Th2 cells in comparison with filarial-infected individuals without associated disease. Moreover, the per cell production of IL-9 is significantly higher in Th9 cells compared with IL9+Th2 cells, indicating that the Th9 cells are the predominant CD4+ T cell subset producing IL-9 in the context of human infection. This expansion was reflected in elevated Ag-stimulated IL-9 cytokine levels in whole blood culture supernatants. Finally, the frequencies of Th9 cells correlated positively with the severity of lymphedema (and presumed inflammation) in filarial-diseased individuals. This expansion of Th9 cells was dependent on IL-4, TGF-β, and IL-1 in vitro.

Our study examines in depth the complex cytokine patterns involved in the pathogenesis of filarial lymphedema. While we have not performed longitudinal studies to define the development of pathology in filarial infection, our strategy of contrasting immune responses in individuals with early or subclinical disease and those with late or clinical disease yields important information on the role of T cell cytokines in pathogenesis. Our data reveal a preponderant Th1 cytokine profile in CP individuals, while INF individuals exhibit a highly polarized Th1 profile. Therefore, our study clearly defines important roles for both Th1 cells in driving the inflammatory pathology. IL-6, TNFR and IL-23 plays the role in regulation in filarial lymphedema.
The role of the recently described Th17 and Th22 cells has not been examined in detail in filarial infection or disease. To explore the role of Th17 and Th22 cells and their subsets, we examined the frequency of these cells in individuals with filarial lymphedema (CP) at baseline and in response to parasite or non-parasite antigens; these frequencies were compared to those in clinically asymptomatic patently-infected (INF) and to uninfected (UN) individuals. At baseline, CP individuals exhibited a significantly higher frequency of Th17 and Th22 cells in comparison to INF and/or UN individuals. Similarly, CP individuals also exhibited significantly increased frequencies of Th17 subsets in comparison to INF and/or UN individuals. This antigen driven expansion of Th17 and Th22 cells was dependent on IL-1, IL-23 and to lesser on extent on TGF-β since blockade of these cytokines resulted in a significantly decreased expansion of Th17 and Th22 cells. Our findings, therefore, implicate an important association for filarial – parasite driven expansion of classical Th17 and Th22 cells with the pathogenesis of filarial lymphedema.

Host immunologic factors that influence the pathogenesis of disease in these individuals are not completely understood. CD4+ and CD8+ T cells are known to play a role in promoting pathogenesis through the secretion of pro-inflammatory cytokines, while IL-10 is known to play an important role in dampening inflammation. IL-10 belongs to a family of cytokines that include IL-19, IL-24 and IL-26, known as the IL-10 superfamily. We investigated whether these cytokines have a function similar to IL-10 in individuals with asymptomatic infection and no clinical pathology and those with overt, clinical pathology. We first identify that CD4+ and CD8+ T cells produce these cytokines. We next identify a significant
association of IL-19 and IL-24 secreting T cells with asymptomatic infection. IL-26 secreting T cells, in contrast, appear to be significantly associated with the presence of lymphatic pathology in filarial infection. Therefore, we have uncovered a potentially new regulatory pathway involving the IL-10 superfamily cytokines in filarial infections.