The role of T_H17 pathway in Waldenstrom's macroglobulinemia

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Waldenstrom's macroglobulinemia (WM), a low-grade lymphoproliferative disorder, is associated with immune dysfunction. Similar to multiple myeloma (MM), some mechanisms mediating immune dysregulation in WM have been studied, its molecular and cellular basis is ill defined. Number of inflammatory cytokines and chemokines has been implicated in this process, but their mechanisms on immune function have not been well characterized. Recently, a new CD4 cell population, the T_H17 cells, has been identified based on the presence of certain inflammatory cytokines. These cells are important in the development of anti-tumor immunity and auto-immunity. Therefore, we evaluated the immune dysfunction and the role of T_H17 cells and associated pro-inflammatory cytokines in WM. We first analyzed T helper cell subsets (TH1, TH2, and TH17) in freshly isolated PBMC from WM, and observed that all three cell types were decreased in WM compared to normal donors. Particularly, the IFN-γ producing TH1 cells from WM patients were significantly reduced compared to normal donors (11±2% vs 30±3% respectively). While unlike myeloma, IL-17 producing TH17 cells were also reduced in PBMC from WM patients compared to PBMC from normal donors. Furthermore, ability to polarize naïve CD4 cells from WM patients to TH17 cells, unlike myeloma patients, was also significantly lower. Next, we evaluated the serum levels of cytokines and chemokines in sera from patients with WM in comparison with normal donors. The sera from WM patients showed significantly elevated levels of IL-2 (5 folds), IL-15 (2 folds) and GM-CSF (2 folds) among 19 cytokines, compared with sera from normal donors. When we evaluated T_H17 cell-associated cytokines, both IL-1-beta (3 folds) and IL-17 (2 folds) were significantly elevated in sera from WM patients compared with sera from normal donors. Finally, when we culture WM cell-line in the presence or absence of IL-17 with or without stromal cells, we observed that WM cells proliferation was significantly increased by IL-17 and an anti-IL17 antibody inhibited cell-proliferation. These data shows that similar to myeloma there is immune dysfunction in WM; however, the differences in the cytokine milieu, and T_H17 cell population which is increased in MM, signifies the different cellular events affecting immune function in these two diseases.