Session IV: Micro-environment and Immune Regulation in WM

Abstract 122

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T_H17 pathway and associated pro-inflammatory cytokines in Waldenström's macroglobulinemia (WM). Rao Prabhala, Dheeraj Pileru, Steven P. Treon and Nikhil C. Munshi. Dana Farber Cancer Institute, Boston VA Healthcare System, Harvard Medical School, Boston, MA, USA.

Waldenström's macroglobulinemia (WM) is a low-grade lymphoproliferative disorder with lymphoplasmacytic differentiaon. Similar to myeloma, WM is associated with immune dysfunction. Both T and B cell dysfunctions are reported with suppressed uninvolved immunoglobulin, and inadequate vaccine and T cell responses. Although some mechanisms mediating immune dysregulation in WM have been studied, its molecular and cellular basis is ill defined. IL-6, TGF-β and IL-1β have been implicated in this process in multiple myeloma (MM), but their mechanisms of effects on immune function have not been studied. Together, IL-6 and TGF-β enhance the generation of T_H17 cells, important in the development of immunity and auto-immunity. Additionally, T_H17 cells are differentiated by number of inflammatory cytokines including, IL-21, IL-22, IL-23, and IL-27. Therefore, we evaluated the immune dysfunction and the role of T_H17 cells and associated pro-inflammatory cytokines in WM. We first 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. In addition, we observed modulation of chemokines including, MCP-1, MIP-1, Eotaxin and RANTES in sera from WM patients. Next, we analyzed T helper cell subsets (TH1, TH2, and TH17) in freshly isolated PBMC from WM, and observed that all three cell types were decrease in WM compared with normal donors. Particularly, the IFN-gamma producing TH1+ cells were significantly reduced, while unlike myeloma, IL-17 producing TH17 cells were also reduced (2 folds) in PBMC from WM patients compared to PBMC from normal donors. Furthermore, when we polarized PBMC isolated cells from WM patients to induce TH17 cells in the presence or absence of TGF-beta, WM patients showed lower induction of (3 folds) TH17 cells in CD4 population by flow cytometry. 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.