Do checkpoint inhibitors offer a novel therapeutic strategy in WM?

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The tumor microenvironment plays an important role in regulating malignant cell growth and mechanisms to enhance anti-tumor immune function have been shown to improve patient outcome. Interactions between programmed death 1 (PD-1) and its ligands (PD-L1 and PD-L2) have been shown to be an important checkpoint in immune regulation. While it is well known that PD-1 is expressed on normal T cells and signaling through PD-1 inhibits T cell function, PD-1 is also expressed on a subset of B-cells but little is known about PD-1 signaling in B-cells. Furthermore, the role of PD-1/PD-1 ligand interactions in Waldenstrom macroglobulinemia (WM) is not really known.

In recent work, our group hasfound thatWM cell lines (MWCL-1, BCWM.1 and RPCI)express PD-1 on their cell surface. Using flow cytometry and immunohistochemistry to examine bone marrow specimens from WM patients, we confirmed PD-1 expression on CD19+ CD138+ malignant B-cells. Furthermore, positive staining for the ligands, PD-L1 and PD-L2, was found in bone marrow of WM patients when compared to normal bone marrow specimens and this was shown by RT-PCR. PD-L1 and PD-L2 expression was increased in both the CD19+CD138+ and the CD19-CD138- fractions from WM samples. When WM cell lines are co-cultured with stromal cells that overexpress PD-L1 or PD-L2, there was an increase in cell viability compared to controls. When malignant B cells from WM patients were co-cultured with stromal cells expressing the ligands, viability was unchanged but there was an increase in cell proliferation, most noticeably when co-cultured with cells expressing PD-L2. To determine potential mechanisms that account for upregulation of PD-1 on malignant B-cells, we tested whether cytokines including IL-6, IL-21 and BAFF that promote WM cell growth and survival, increased PD-1 expression. We found that WM cell lines and CD19+CD138+ B-cells from patients with WM when incubated with IL-21 demonstrated an increase in PD-1 expression.

We conclude that that signaling through PD-1 may promote WM cell growth and survival. Blocking PD-1/PD ligand interactions may therefore be a potential therapeutic strategy in patients with WM and clinical trials of anti-PD-1 antibodies are currently in progress.