Do defects in T-cell immunity contribute to disease progression in plasma cell disorders?

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An understanding of T-cell and tumor interactions in the immune system of patients with plasma cell disorders has great potential to improve therapeutic options. In myeloma and Waldenstrom's macroglobulinaemia, there are measurable changes in the immune system with abnormalities of T-cells, NK cells and the ability to respond to external antigenic stimuli. In Waldenstrom's macroglobulinaemia, cytotoxic T-cells may play a significant role in tumor surveillance as illustrated by case reports of rapid transformation to large cell lymphoma following the introduction of cladribine or fludarabine, spontaneous remission of transformed lymphoma following their cessation and an increased incidence of transformation in patients treated with fludarabine.

Approximately 50-75% of patients with myeloma and Waldenstrom's macroglobulinaemia have expansions of cytotoxic T-cell clones. In myeloma these clones are associated with an improved prognosis and this suggests that they have an anti-tumor role or a role in tumor surveillance. Such clonal T cells are however in a state of proliferative hypo-responsiveness to T-cell receptor stimulation.

In myeloma T-cell hypo- responsiveness is not the result of *anergy* or *exhaustion*but rather the result of tumor induced immunological *senescence*. The cells exhibited a senescent associated secretory phenotype (SASP): KLRG-1+/CD57+/CD160+/CD28- with normaltelomere lengths for age, suggesting telomere-independent senescence. Such cells are not comparable to the exhausted T-cells seen in chronic viral infections and in such tumors as melanoma. All patients with myeloma who survive more than 10 years have clonal expansion of T-cells and in patients such clones retain or regain their responsiveness to T-cell receptor stimulation.

In Waldenstrom's macroglobulinaemia the relationship between clonal expansion and prognosis is not as clear. This is because these clones are largely eliminated by nucleoside analogue therapy. Gene set enrichment analysis has also identified upregulated pathways associated with anti-proliferation, T cell inactivation, cell cycle arrest and anti-apoptosis. Furthermore such expanded T cell clones in Waldenstrom's macroglobulinaemia do not exhibit *senescence* but rather show phenotypic changes of *exhaustion* which suggests that checkpoint inhibition would play a significant therapeutic role in patients not exposed to nucleoside analogue therapy.

Additional changes such as Treg Th17 imbalance,trogocytosis and the presence of myeloid derived suppressed T-cells are more prominent in myeloma than in Waldenstrom's macroglobulinaemia and further differentiate the immunological reaction of the host to these clonal B cell diseases.