What role do CD137L and CD4 T-cells have in B-cell lymphoma immuno-surveillance?



During <u>B-cell</u> development within the germinal centre, B-cells can go through multiple rounds of both proliferation and mutation. Some of the mutations these B-cells accumulate are taken to possibly contribute to malignant transformation. Over expression of BCL-6, one of the key promoters responsible for GC development has actually been linked to the process of pathogenesis of diseases like diffuse large B cell lymphoma (DLBCL).

Since CD4 <u>T-cells</u> do have a role to play in <u>anti-tumor</u> <u>immunity</u>, the authors sought to find out what role CD4 T-cells play when it comes to aiding the tumour-suppressing function of CD8 T-cells, and possibly unpack the exact mechanisms that can account for the <u>immunosurveillance</u> observed from CD4 Tcells.

One aspect that was looked at was the role of CD137L, that has been proposed to function as a lymphoma suppressor via regulating GC B-cell responses. This was done using a wellestablished B-cell lymphoma mouse model, the $I\mu$ - $Bcl6^{Tg/+}$ strain. To shorten the time of lymphomagenesis, they crossed $I\mu$ - $Bcl6^{Tg/+}$ and the Cd8^{-/-} mice ($I\mu$ -Bcl6Tg/+Cd8-/-), since CD8 T-cells are important for the immuno-surveillance of B lymphoma cells in the $I\mu$ -Bcl6^{Tg/+} strain.

As seen in Figure 1c, blocking CD137L significantly increased activated fraction of cells with the an В cell in the Iµ-Bcl6Tq/+Cd8-/- mice. Purified B cells phenotype from 12-week-old WT or disease-free $I\mu$ -Bcl6^{Tg/+} mice were cultured in vitro in the presence of anti-CD40 an antibody, IL-4, and IL-21 to induce a GC phenotype. In figure 1d and 1e, we see that crosslinking CD137L by the addition of recombinant CD137 protein to the culture increased the differentiation of Iu-Bcl6*Tq*/+ B cells into GC-like Based on this data, the authors suggest that cells. CD137/CD137L-mediated signalling in $I\mu$ -Bcl6^{Tg/+} B cells promotes activated B cells to differentiate into GC cells.



Figure 1: CD137-CD137L interactions promote the differentiation of CD86hiIgD lo premalignant cells into GC cells in Iµ-Bcl6Tg/+Cd8-/- mice. "(a) Iµ-Bcl6Tg/+Cd8-/-

or Cd8-/- mice were immunised with 100 µg NP-KLH in alum on day 0 (n = 4 for each group).On day 1 and 3, mice were given 200 µg anti-CD137L blocking antibody or vehicle *i.p.* before spleens were harvested on day 7. (b) Representative gating strategy for NP+ naive, activated, and GC B cells among CD19+CD138- B cells. (c) Ouantification of percentages of NP+ activated and GC B cells among CD19+CD138-B cells of all groups. An unpaired t-test was used. (d) Representative gating for strategy IqDlowFAShi GC-like B cells after 3.5 days culture in plates coated with or without recombinant mouse CD137 protein. (e) *Ouantification* of IqDlowFAShi GC-like B cells among total CD19+CD138- B cells as d after gated in culture.

In their next set of experiments, they were able to determine that blocking CD137L *in vivo* promoted B-cell lymphoproliferative disease in their mouse model. Based on this development and the fact that CD137 is primarily expressed on activated T cells, the authors raised a hypothesis of CD 4 T-cells possibly preventing the onset of Bcell <u>malignancies</u> via a CD137-CD137L axis.

In figure 2, RNA sequencing of 12 lymphomas derived from T cell-sufficient mice (Iµ-Bcl6^{Tg/+)} and 11 from T cell-deficient $(I\mu-Bcl6^{Tg/+}Cd3e^{-/-})$ showed that B lymphoma mice cells that absence of T cells developed in the expressed higher T-cell costimulatory amounts of mRNA corresponding to molecules including CD137L and CD70 than lymphoma cells derived from T-cell sufficient $I\mu$ -Bcl6^{Tg/+} mice.



costimulatory molecules including CD137L is upregulated in B lymphoma cells from Ιμ-Bcl6Tg/+Cd3e-/mice compared to that in В lymphoma cells T-cell from sufficient Iμ-Bcl6Tg/+ mice. "Heatmap of gene expression of Tcell costimulatory or coinhibitory molecules in B lymphoma cells from Iµ-Bcl6Tq/+ and Iμ-Bcl6Tq/+Cd3e-/mice".

From the total workup of results, the authors had this to say about their work; "Here we show that the CD137/CD137L costimulatory pathway, also acting in the cognate interactions between premalignant B cells and CD4 Tcells. mediates the further differentiation of **BCI 6**driven premalignant B cells facilitated by CD4 Т cells and this results in the prevention of malignancy at an early activated B cell stage".

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