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The proton channel HVCN1 inhibits leukaemia progression in the CLL mouse model Eμ-TCL1 and regulates sialylation of T antigen in MM

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Background: HVCN1 (hydrogen voltage-gated channel 1) is the only mammalian gene that codes for a voltage-gated proton channel 1. HVCN1 is highly expressed in immune cells. In B cells, HVCN1 modulates B cell receptor (BCR) signaling while supporting ROS production by the NADPH oxidase activity 2. Human HVCN1 expression is increased in a number of mature B cell malignancies such as lymphoma and chronic lymphocytic leukaemia (CLL). CLL cells in particular show an up-regulation of a shorter isoform of HVCN1 and mediate stronger proton currents. Given the increase in HVCN1 expression in CLL cells and their reliance on BCR signaling for survival and proliferation, we hypothesized HVCN1 loss or inhibition would counteract leukaemia progression. As a comparison, we also investigated HVCN1 role in BCR negative B cell tumors such as multiple myeloma.

Methods: We generated a transgenic TCL1/HVCN1-/- mouse by crossing HVCN1 knock-out (KO) mice (HVCN1-/-) with the Em-TCL1, a well-known and extensively studied mouse model of CLL4. We also knocked down HVCN1 in a multiple myeloma cell line (EJM) to study the role HVCN1 in BCR deficient cells.

Results: We monitored a cohort of TCL1/HVCN1 KO (n=15) and TCL1 wild-type mice (n=19) for the development of CLL. Unexpectedly, TCL1/HVCN1 KO mice had significantly shorter survival than controls. Interestingly, we noticed an increase in CD3+ T cells in the spleen of TCL1/HVCN1 KO mice. However, HVCN1 KO leukemic cells showed diminished BCR signaling compared to wild-type controls, as expected. On the other hand, in multiple myeloma cells lines which do not express a BCR, down-regulation of HVCN1 by shRNA showed no significant changes in proliferation, survival and energy metabolism compared to control cells. However, analysis of the cell glycomics profile illustrated a significant difference in the sialylation of the O-glycan core 1 (T antigen) in HVCN1 knock-down cells compared to scrambled control.

Conclusions: The proton channel HVCN1 plays a role in CLL, surprisingly this appears to be inhibiting tumor growth. We are currently extending our mouse studies as well as assessing human CLL cells in order to establish if, contrary to what happens in normal B cells, proton channels support a novel mechanism that results in tumor inhibition in CLL cells. Furthermore, we are investigating the functional consequences of increased T antigen sialylation in multiple myeloma on tumor spreading.

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