

## MS10 Protein-carbohydrate interactions

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Glycan-mediated activation of B cells in chronic lymphocytic leukaemia subsets

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### Abstract

Chronic lymphocytic leukaemia (CLL) is the most common form of adult blood cancer, characterized by the clonal expansion of neoplastic B cells that ultimately invade the circulation and secondary lymphoid organs. The importance of B-cell receptor (BCR)-mediated signalling is highlighted by several findings. CLL displays very heterogeneous clinical courses, ranging from indolent to highly aggressive, but patients expressing highly homologous BCRs can be grouped into subsets with homogenous clinico-biological characteristics [1]. Moreover, inhibition of specific kinases along of the BCR signalling cascade is effective, albeit resistance develops upon prolonged treatment of patients. The self-antigen(s) so far characterized that select the leukemic B-cells are quite heterogeneous, but a shared, unifying feature of CLL B-cells is their apparent ability to proliferate in absence of added exogenous antigens through a mechanism of cell-autonomous signalling [2]. Three CLL-derived BCRs have been previously shown to activate signalling through protein-protein homotypic interactions [3,4]. Here, we show that two BCRs from CLL subsets that differ in heavy and light chain usage bind via their combining sites to N-linked glycans of glycoproteins. Crystal structures demonstrated that in both cases the  $\alpha$ -1-3 arm of hybrid or complex glycans is recognized via specific interactions with the CDR3 loops of both heavy and light chains of the BCR. However, the modes of interactions are distinct, thus showing that autoreactive BCRs directed towards a common, ubiquitous self-ligand can originate through different genetic rearrangements. The binding of glycans to the two BCRs activates intracellular signalling in a B lymphocyte model cell line, and thus pinpoints the molecular basis of the hallmark cell-autonomous signalling of CLL in these subsets. These findings suggest that a strategy based on antagonists of the glycan-BCR interaction may be highly effective in a personalized approach to CLL treatment.

### References

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### Glycan binding to a CLL-derived BCR

