Chronic lymphocytic leukaemia is driven by antigen-independent cell-autonomous signaling. Minden et al. *Nature*. 2012;489:309–312.

It has long been known that, during early B-cell development, the immature B-cell receptor (BCR) provides an antigen independent signal that prevents cell death. In this paper, Jumaa and co-authors show that in CLL, but not other B-cell malignancies, the BCR behaves in the same way. This developmental throwback represents a novel mechanism of leukaemogenesis and explains a number of the hitherto unexplained features of CLL.

The study revolves around a "triple knock-out" (TKO) murine pre B-cell line that is deficient for the RAG2, SLP65 and lambda-5 genes and cannot make pre- or mature immunoglobulin (Ig) or mobilise intracellular calcium in response to BCR pathway activation. The authors then reconstituted these cells with BCRs derived from CLL and a range of other B-cell neoplasms and a Tamoxifen responsive SLP65 construct. Induction of SLP65 resulted in a spontaneous Ca^{2+} flux in each of 17 cases of CLL but none of the other B-cell tumours, suggesting that constitutive activation is a property specific to CLL BCRs. Interestingly, spontaneous Ca^{2+} release was observed in CLL BCRs with both mutated and unmutated Ig variable heavy chain genes (IgHV). The phenomenon was also observed in CLL-like clones emerging in the TCL1 transgenic mouse model but not in BCRs cloned from normal human donors or hapten-specific murine B-cells.

Since CLL BCRs show biased CDR3 usage, the authors replaced this domain in a non-autonomous murine BCR with those from cases of CLL and in each case reconstituted the spontaneous Ca^{2+} response. Analysis of peptides previously shown to bind to CLL BCRs revealed homology to the FR2 region of the immunoglobulin sequence. The authors therefore postulated that an epitope within this region might bind to the CDR3 of the CLL BCRs and went on to perform site directed mutagenesis of the FR2 region identifying a valine residue required for the autonomous Ca^{2+} signal in CLL. Although the CLL specific constitutive Ca^{2+} signalling could be due to binding of the BCR to a self antigen, the finding that most did not show polyreactivity and that a Ca^{2+} flux was observed in single isolated tumour cells suggests that this is not the case.

Finally, since the BCR induced Ca^{2+} signal is Syk dependent, the authors performed studies in normal and CLL B-cells in the presence and absence of the Syk inhibitor R406. These revealed that both bulk and single isolated CLL B-cells had a higher background intracellular Ca^{2+} level than their normal counterparts and that treatment with the Syk inhibitor reduced both the background levels and anti-IgM induced Ca^{2+} signals in both CLL and normal controls.

These findings go some way to explaining some of the puzzling features of CLL. Despite a lack of mutations in the relevant pathways, CLL cells generally show constitutive activation of Syk, Akt and Erk as well as the NFAT and NFkB transcription factors and presumably intrinsic BCR activation is the reason for this. What is less clear however is how the reported differences in signalling capacity of CLL cases with mutated and unmutated IgHV genes arise. As the authors point out, the present findings do not exclude the possibility that other antigen(s) might also play a role in BCR activation in CLL and perhaps the unmutated cases retain the ability to recognize and respond to these. Finally, although CLL cells are chronically activated, they do not spontaneously proliferate and require additional signals from the microenvironment for this to occur. It will be of great interest to determine how the phenomenon described in this paper influences and modifies these interactions.

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