## Probing the B-cell receptor in Waldenstrom's macroglobulinemia

Surinder S. Sahota,[1] Stéphanie Poulain,[2] Nicky Weston-Bell,[1] Gavin Babbage,[1] Xavier Leleu[3] & Pierre Morel[4]

[1]Tumour Immunogenetics Group, Cancer Sciences Division, University of Southampton School of Medicine, UK; [2]Service d'Hématologie-Immunologie-Cytogénétique, Centre Hospitalier de Valenciennes, Valenciennes, France ; [3]Service des Maladies du Sang, Centre Hospitalier Régional Universitaire, Lille, France / U837, INSERM ; [4]Service d'Hématologie Clinique, Centre Hospitalier Schaffner, Lens, France

In normal B-cells, a functional surface B-cell receptor (BCR) is essential for survival, enabling response to cognate antigen and tonic stimuli. The role of the BCR in sustaining survival and growth of malignant B-cells is less well understood. In Waldenstrom's macroglobulinemia (WM), neoplastic B-cells invariably express sIgM, often with sIgD as respective components of the BCR complex. To date however, the functional capacity of the BCR in WM remains undefined. It is evident however, from the analysis of immunoglobulin (Ig) variable (V) region genes in WM that the antigen-binding domain of the sIg molecule is potentially functional. WM-derived $V_H$ genes also reveal other distinctive features, of relevance to understanding tumor origins and clonal history. WM displays two disease subsets, the major subset characterized by somatic hypermutation (SHM) in V genes (M-WM), indicative of prior antigen contact by the cell of origin, although as yet it is not known whether this occurs via T-cell help or in a T-cell independent manner. In the minor subset displaying unmutated V genes (U-WM), a role for antigen in disease origins is less clear. In M-WM, the BCR also undergoes a low degree of continual diversification, as a very low level of on-going SHM can be observed in $V_H$ genes. Here, we investigate BCR functionality at the cellular level in unselected WM cases. Using anti-sIgM/D stimuli, we observed two patterns of BCR-mediated $Ca^{2+}$ flux in M-WM, and activation of key downstream molecules. Strikingly, cross-linking BCR with anti-IgM promoted tumor cell survival, apparent as reduced apoptosis. These findings reveal that WM tumor cells retain a functional BCR, which does not appear to be anergic and can potentially transduce survival signals *in-vivo*. This has relevance for targeting therapy in WM to signalling cascades regulated by the BCR.