7. Summary

Engagement of the antigen receptor on murine immature B lymphocytes leads to growth arrest followed by apoptosis. Concomitant signalling through CD40 rescues the cells from apoptosis and sustains proliferation. It is shown here, that in primary murine B cells crosslinking of CD40 stimulates the expression of A1, an anti-apoptotic member of the Bcl-2 family. CD40 dependent stimulation of A1 was confirmed in WEHI 231 cells, an immature B cell lymphoma line.

WEHI 231 cells were transduced with A1 and a chimeric selection marker comprising the enhanced yellow fluorescent protein and the zeocin resistance protein via recombinant replicationdefective retroviruses. Expression of A1 and marker proteins was coupled through an internal ribosomal entry site.

A1 transduced WEHI 231 cells showed a significantly enhanced survival rate after engagement of the antigen receptor whereas constitutive expression of A1 did not abrogate c-myc downregulation and activity-loss of a NFκB-dependent luciferase reporter, both of which were induced by BCR-crosslinking.

Expression of inducible cMyc-ER in A1 transduced cells did not restore proliferation in these populations. In contrast, upon induction cMyc-ER itself caused growth arrest and apoptosis of these cells despite the presence of A1.

Studies of functional properties of A1 revealed that it was able to suppress BCR-induced degradation of the caspase substrate PARP as well as activation of Caspase 7. The generation of reactive oxigen species, a further consequence of BCR signalling, was also significantly reduced by A1.

Taken together these result suggest that upstream of A1 the CD40 signal is divided into two major components, one of which is responsible for the upkeep of proliferation whereas the other secures cell survival. It seems that for the latter A1 is of major importance.