

## **BR3 and TACI Differentially Mediate NF- $\kappa$ B Pathway Activation**

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BLyS and APRIL influence the survival and differentiation of peripheral B cells. Evidence suggests that the BLyS family of receptors, BCMA, TACI, and BR3, possibly in conjunction with BCR derived signals, regulate B cell positive selection and homeostasis. BLyS can activate both classical and non-classical NF- $\kappa$ B pathways, but since most primary B cells express both TACI and BR3, their respective roles in driving these two pathways remain unclear. Accordingly, we have generated retroviral constructs containing either BR3 or TACI, enabling exclusive expression and interrogation of each receptor in NIH 3T3 cells. Our results indicate that BR3 activates only the non-classical pathway following BLyS ligation, as evidenced by p100 processing. In contrast, TACI induces I $\kappa$ B $\alpha$  degradation but not p100 processing following stimulation with its native ligands, BLyS or APRIL. In agreement with these findings, *ex vivo* stimulated CD23<sup>+</sup> cells process p100 when stimulated with BLyS but not APRIL. Finally, A/WySnJ CD23<sup>+</sup> cells do not process p100 following *in vitro* culture with either BLyS or APRIL. We also analyzed the capacity for TACI signaling to promote survival by measuring cell viability via TOPRO-3 exclusion. We find that APRIL promotes survival in both resting and activated B cells, albeit not as effectively as BLyS. Together, these observations indicate that BR3 and TACI directly activate distinct NF- $\kappa$ B pathways, but both can initiate survival related programs.