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The immunoglobulin tail tyrosine of membrane-bound IgG and IgE provides antigen receptor-intrinsic costimulation to class-switched memory B cells

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Improved antibody responses by class-switched memory B cells require enhanced signaling from their antigen receptor (BCR) in a coreceptor-independent manner. However, all BCR classes on newly generated and antigenexperienced B cells utilize the canonical Igα/Igβ subunit for signaling via the immunoreceptor tyrosine-based activation motif (ITAM) in their cytoplasmic domains. We have now identified the signal amplification mechanism of the activated IgG- and IgE-BCR on class-switched B cells. An evolutionary conserved tyrosine residue in the cytoplasmic segments of membrane-bound IgG and IgE heavy chains, named Immunoglobulin Tail Tyrosine (ITT), becomes phosphorylated and recruits the adaptor protein Grb2 in order to prolong activation of protein kinases and sustain the generation of second messengers. Exchange of the ITT for phenylalanine phenocopies the reduced signaling profile of the IgM-BCR expressed on naïve B cells. Hence membrane-bound IgG and IgE not only recognize antigen but also exert BCR-intrinsic costimulation to render memory B cells less dependent on T cell help for activation. Moreover, our finding of a signaling competent phospho-ITT confutes the paradigm of BCR tyrosine phosphorylation being confined to ITAMcontaining subunits.