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Evidence for independent fate competition within B lymphocytes: CD40 signal strength regulates the rate of B cell differentiation to plasmablasts by altering their time to divide only

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During the adaptive immune response, T and B lymphocytes receive and integrate signals from different sources that determine the strength and type of response they follow. Here we asked how reducing stimulation strength through the CD40 receptor could lead to an accelerated division-linked B cell differentiation, as noted in an earlier study [Hawkins *et al.*, Nat Comms 2014]. We observed using flow cytometry that reducing CD40 stimulation strength had two effects on B cell fates in vitro: it slowed down B cell division, and produced a greater proportion of differentiated plasmablasts in each subsequent generation. We studied this system with direct time-lapse imaging to observe division, death, and differentiation to Blimp-1+ plasmablasts, after 3-4 days in culture. We found that strength of stimulation by CD40 affected division times, as predicted, whereas times to die and times to differentiate to plasmablasts were unaffected. We could also show, by fitting mathematical models, that simple fate competition between division and differentiation could explain the accelerated differentiation by slowing division alone. Thus, our data suggest that weakly CD40 stimulated B cells divide slowly, and as a consequence, have more time to undergo differentiation before their next mitotic event. By understanding how different components of the B cell response are controlled and affected by regulatory signals, we aim to build up models of complex signal integration by cells that can predict net immune outcome. Successful models built in this way have many potential applications such as rational immunotherapy design.

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