

# Secreted IgM versus BLyS in germinal center formation

NICOLE BAUMGARTH

Center for Comparative Medicine, University of California, Davis, CA 95616, USA ([nbaumgarth@ucdavis.edu](mailto:nbaumgarth@ucdavis.edu)).

I would like to bring to your attention a major weakness that I see with one of the studies you published. The study is that by Yan *et al.* "Identification of a receptor for BLyS demonstrates a crucial role in humoral immunity"<sup>1</sup>. My criticism is as follows.

The authors identify an orphan TNF receptor homolog as the receptor for the cytokine

BLyS and demonstrate that blockade of receptor-BLyS interaction will inhibit the production of IgM and IgG1 secretion *in vivo* following antigen administration. The authors conclude from these data that BLyS "is essential for formation of splenic germinal centers" (last paragraph, page 37).

In my opinion the data shown in this manuscript are too preliminary to allow such conclusion to be drawn. A number of studies on mice deficient in secreted IgM have clearly demonstrated that secretion of IgM is essential for optimal induction of germinal center reactions and IgG production after antigen encounter<sup>2-4</sup>. Furthermore, it has been demonstrated that

the lack of secreted IgM causes inefficient germinal center formation<sup>2</sup>. Therefore an alternative interpretation of the data generated by Yan *et al.*, and one which is consistent with these previous reports, is that BLyS does not affect germinal center formation and affinity maturation. Instead, BLyS simply inhibits B cell activation and IgM secretion. The subsequent events, lack of germinal center formation and affinity maturation might be simply a consequence of the lack of secreted IgM. The finding that inhibition of the BLyS-receptor interaction affects IgM secretion much more than IgG secretion (see Fig. 5 in Yan *et al.*) supports such alternative interpretation.

1. Yan, M. *et al.* *Nature Immunol.* **1**, 37–41 (2000).
2. Boes, M. *et al.* *J. Immunol.* **160**, 4776–4787 (1998).
3. Ehrenstein, M. R., O'Keefe, T. L., Davies, S. L. & Neuberger, M. S. *Proc. Natl Acad. Sci. USA* **95**, 10089–10093.
4. Baumgarth, N. *et al.* *J. Exp. Med.* **192**, 271–280 (2000).

## Response

AVI ASHKENAZI<sup>1</sup>, IQBAL S. GREWAL<sup>2</sup> AND VISHVA M. DIXIT<sup>1</sup>

Departments of <sup>1</sup>Molecular Oncology and <sup>2</sup>Immunology, Genentech Inc., 1 DNA Way, South San Francisco, CA 94080, USA ([aa@gene.com](mailto:aa@gene.com) and [dixit@gene.com](mailto:dixit@gene.com)).

The alternative interpretation proposed by Dr Baumgarth, namely that the effect of BLyS inhibition on germinal center formation occurs indirectly, through inhibition of IgM secretion, was noted in our discussion (see page 40, bottom left)<sup>1</sup>: "... TACI-Fc-treated mice showed a marked deficit in both IgM and IgG production. Thus, it is possible that BLyS and TACI operate early on in B cell activation, and blocking their

function impairs all phases of the humoral response." Notwithstanding, TACI-Fc inhibits interactions that are crucial for germinal center formation regardless of the underlying mechanism.

The studies that Dr Baumgarth refers to show that a complete lack of IgM secretion attenuates or delays germinal center formation in mice after immunization with a suboptimal dose of antigen<sup>2,3</sup>; however, absence of secreted IgM clearly did not abolish this event, as properly organized splenic germinal centers with peanut-agglutinin-staining B cells were readily detectable. Moreover, mice deficient in secreted IgM showed no defect

in germinal center formation in response to a higher dose of antigen, as compared to heterozygous controls<sup>2</sup>. Hence, IgM secretion is not essential for germinal center formation, although it may augment this process. On the other hand, we found that TACI-Fc treatment after immunization (with an even higher dose of antigen) prevented germinal center formation completely, despite inhibiting IgM secretion only partially<sup>1</sup>. On the basis of these observations, it is likely that TACI-Fc prevents germinal center formation independently of its inhibitory effect on IgM secretion.

1. Yan, M. *et al.* *Nature Immunol.* **1**, 37–41 (2000).
2. Boes, M. *et al.* *J. Immunol.* **160**, 4776–4787 (1998).
3. Ehrenstein, M. R., O'Keefe, T. L., Davies, S. L. & Neuberger, M. S. *Proc. Natl Acad. Sci. USA* **95**, 10089–10093.