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Comment on "Molecular Basis of the Dual Functions of 2B4 (CD244)"

Dorothy Yuan

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Letters to the Editor

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Comment on "Molecular Basis of the Dual Functions of 2B4 (CD244)"

The article published by Chlewicki et al. in the June 15, 2008 issue of *The JI* (1) presents a series of experiments demonstrating the complexity of activating vs inhibitory signals that can be imparted by the 2B4 (CD244)-CD48 interaction. However, direct correlation of these findings in vivo is still unclear. The authors noted that one possible demonstration of the in vivo inhibitory function of CD244 is demonstrated by EBV infection in that CD48 is up-regulated on EBV-infected B cells and may therefore account for the failure of infected cells to be lysed by activated NK cells. However, there may be additional factors involved that contribute to the insensitivity. In this regard, we wish to remind the authors of a finding published in *The JI* in 2006 (2) showing that nontransformed mouse B cells can stimulate cytokine secretion by IL-2-propagated NK cells and that this interaction is mediated by the interaction between CD244 on NK cells and CD48 on B cells. It is interesting that in contrast to the hypothesis posed by the authors, this interaction occurring in mouse does not result in lysis of B cells.

Dorothy Yuan

Department of Pathology
University of Texas Southwestern Medical Center
Dallas, TX 75390

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2. Gao, N., P. Schwartzberg, J. A. Wilder, B. R. Blazar, and D. Yuan. 2006. B cell induction of IL-13 expression in NK cells: role of CD244 and SLAM-associated protein. *J. Immunol.* 176: 2758–2764.

Response to Comment on "Molecular Basis of the Dual Functions of 2B4 (CD244)"

In a letter to the editor regarding our recent publication in *The JI* (1), Dr. Yuan has suggested that the hypothesis that we proposed in the discussion section may not completely explain the insensitivity of NK cells to lyse EBV-infected B cells expressing increased levels of CD48. We recognize that, and as stated in our discussion, it is difficult to extrapolate our findings to all possible functions of NK cells in vivo. We took a reductionist approach as a starting point of our analysis of NK cells. This was done by design, since eliminating other variables allowed focus on 2B4 and CD48 interactions. This approach revealed for the first time that the surface levels of 2B4 and the availability of adaptor molecules like SAP regulate 2B4 function. Because NK cell function is critically dependent on "fine-tuning" by many receptor/ligand interactions, one must be cautious when using results from simple systems alone for predicting activity of NK cells in vivo. However, our data suggest that factors such as degree of crosslinking and availability of SAP must be taken into account in any system where 2B4-CD48 interactions are involved. In this regard, it would be of interest to know whether a similar regulation of nonlytic NK cell functions occurs when they interact with B cells.

Although we have identified several possible parameters for the regulation of 2B4 function, we are acutely conscious that these factors alone do not determine NK cell function, and additional regulation of 2B4 is most certainly present. Indeed, in ongoing studies we have found that unlike the long isoform of 2B4 used in our article, the short form is always activating regardless of the level of expression and degree of crosslinking. Thus, integration of the signals from the long and short form must also be considered. Other variables to be kept in mind are *cis* interactions between 2B4 and CD48 on NK cells, CD2 and CD48 interactions (both *cis* and *trans*). Our system allows these and other factors to be studied as well, and we are in the process of addressing them.

Lukasz K. Chlewicki

Department of Pathology
University of Chicago
Chicago, IL 60637

References

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