Effect of CD3/CD28 Bead-Activated T Cells on Leukemic B Cells in Chronic Lymphocytic Leukemia

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APC-Independent NK Cell Activation

Last year, The Journal of Immunology published Kerstin N. Schmidt’s work titled "APC-Independent Activation of NK Cells by the Toll-Like Receptor 3 Agonist Double-Stranded RNA" (1). In this paper there is an unclear issue about NK cell cytotoxicity assay. The effector cells were human purified CD56+/H11001 NK cells, but the target cells were YAC-1 cells, an NK cell-sensitive murine-derived cell line. We think the appropriate target is human K562 cell line.

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Reference

The Authors Respond
We reported that human NK cells express TLR3, and that stimulation with TLR-3 agonist poly(I:C) induces APC-independent NK cell activation (1). Specifically, we found that poly(I:C) stimulation leads to up-regulation of CD69, activation of NF-kB, production of proinflammatory cytokines, and augmentation of NK-cell mediated cytotoxicity. The latter was demonstrated with two different target cell lines, human Daudi cells and mouse YAC-1 cells.

Dr. Zhongjun Dong suggests that K562 would be the appropriate target cell line to use. We appreciate Dr. Dong’s comment and his interest in analyzing the lysis of other human cell lines, like K562, in addition to Daudi cells.

In alignment with our data in Daudi and YAC-1 cells, our unpublished results show that poly(I:C) stimulation of NK cells significantly enhances lysis of K562 cells (see Fig. 1). The increase in cell lysis is comparable to that reported for other NK cell activators, IFN-γ (2), IL-2, and IL-12 (3) using K562 as a target cell line.

Furthermore, our findings have been confirmed and extended by A. Moretta’s group, which reported up-regulation of cytolytic activity against tumor cell lines K562 and FO-1, and immature dendritic cells after stimulation with double-stranded RNA (4).

In conclusion, all data available, including lysis of K562 cells, support direct induction of NK cell activation after stimulation of NK cells with a TLR3 agonist.

References

Human Acidic Mammalian Chitinase Erroneously Known as Eosinophil Chemotactic Cytokine Is Not the Ortholog of Mouse Ym1

Recently, Raes et al. (1) responded in a letter to the editor to a paper of Scotton et al. (2) dealing with the effects of IL-13 on the transcriptional profile of human monocytes and those of IL-4 on murine macrophages (3, 4). The discussion dealt with the differences that were observed in these separate studies with regard to the expression of YM1 and arginase I, which are both up-regulated in mouse macrophages but not in human monocytes (1). The point that Raes et al. make is that the differences observed could also be ascribed to differences between human and mouse macrophages rather...
than differences in the effects of IL-4 and IL-13 as proposed by Scotton et al.

To support their proposal, Raes et al. show that IL-4 combined with IL-13 does not induce arginase-1 or eosinophil chemoattractant cytokine (CHIA) in human macrophages contrasting to the situation in mouse cells, indicating that murine and human alternatively activated myeloid cells exhibit differences (1).

We would like to point out that human CHIA is not the orthologue of mouse YM1. CHIA is an alternative name for human acidic mammalian chitinase (AMCase). It erroneously received this name due to its sequence identity to YM1, also known as eosinophil chemoattractant factor, the closest homologue at that time. More recently we demonstrated that the true orthologue of human AMCase is mouse AMCase (both active chitinases) and not YM1 (5). Moreover close examination of the mouse and human genome suggests that there is no human orthologue of YM1. It seems that the mammalian members of the chitinase family have arisen from several separate duplication events in these different species.

Therefore we feel that the comparison between mouse YM1 and human AMCase is not valid as an argument for the alternative explanation of Raes et al. However, it is interesting to note that Zhu et al. recently described that an IL-13-dependent mechanism was responsible for the induced AMCase expression in alveolar macrophages and lung epithelial cells in a mouse Aeroallergen asthma model (6). Since Raes et al. did not observe any induction of AMCase by IL-4/IL-13 in human macrophages, this seems to support their hypothesis that important differences exist between human and mouse alternatively activated macrophages.

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We read with interest the paper by Bonyhadi et al. (1) published February 15, 2005, and also the interesting letter by Patten et al. (2). We have also studied the effect of activated T cells on cocultured chronic lymphocytic leukemia (CLL) lymphocytes and our results agree with those reported by Patten et al.

The use of a ratiometric flow cytometry method for the enumeration of cells (3) clearly demonstrated that T cells activated with anti-CD3- and anti-CD28-coated microbeads can sustain the viability of autologous leukemic B cells even over long culture times (16 days). When only percentages are studied, a marked reduction in the percentage of B-CLL cells is observed, but this decrease is apparent, not real. This is shown in Fig. 1, where our cell enumeration experiment clearly demonstrates that coculture with activated T lymphocytes maintains the number of viable B-CLL cells in culture. We conclude that, under certain experimental conditions, CD3/CD28 bead-activated T cells can prolong the survival of cocultured CLL cells.

As reported by Patten et al., our experiments were performed without washing the microbeads. However, we believe that Bonyhadi’s argument that these beads can “provide a physical barrier that could inhibit the interaction of T cells with CLL

Figure 1. CD3/CD28 bead-activated T cells prolong the in vitro survival of B-CLL cells. PBMCs of B-CLL patients were cultured for 7, 11, or 16 days with (○) or without (●) anti-CD3- and anti-CD28-coated microbeads (TCE). A, the percentage of leukemia B cells. B, the number of leukemia B cells per microliter over the kinetics of the culture. Data of one representative experiment of three are shown.

Figure 1.
“cells” may not hold since we have also shown that uncoated or CD3/CD28 beads neither induce nor inhibit B-CLL lysis, but CD23/CD28 microbeads even stimulate the specific lysis of autologous B cells by T cells (Fig. 2).

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