Perhaps the most remarkable aspect of in vivo erythroblastic islands is their productiveness, producing more than 2 million new reticulocytes every second in adult humans. 10 Although we can replicate erythroid maturation with erythroid cells alone, a better understanding of macrophage–erythroblast interactions may help us recapitulate the island’s efficiency making the ex vivo production of units of blood that contain trillions of RBCs a practical reality.

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Can Treg elimination enhance NK cell therapy for AML?

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In this issue of Blood, Bachanova et al describe how modulation of the inhibitory tumor environment may enhance natural killer (NK) cell clinical activity and produce encouraging results in the treatment of refractory acute myeloid leukemia (AML). 1 NK cells are highly proliferative, early responders of the innate immune response that in preclinical models can exert potent activity against a wide range of malignancies, including AML, and across HLA barriers. Considerable efforts have been made to exploit this activity in clinical trials but with only modest success.

NK cells are activated by inflammatory cytokines, usually produced in response to pathogens. Following activation, NK cells upregulate activating and inhibitory receptors including killer immunoglobulin-like receptors (KIRs) that recognize HLA class I molecules. The highly polymorphic nature of both HLA and KIR molecules determines whether the NK cell subsequently ignores a target cell or kills it and proliferates. Because KIR receptors are inhibited by autologous HLA class C molecules, many clinical investigators have chosen to infuse allogeneic NK cells to ensure that they can kill recipient tumor cells. 2-4 Several clinical trials have revealed the potential of NK cells as an immunotherapy, but barriers to their wider efficacy have included both their tolerance to self-major histocompatibility complex molecules and their susceptibility to immunosuppressive elements that are present at the sites of many tumors. These elements include inhibitory cytokines, myeloid-derived suppressor cells, and T-regulatory cells (Tregs). Although the range of immunosuppressive elements within tumors is daunting, most converge on and inhibit signaling pathways that are also targets of activating ligands, so that shifting the balance in favor of...
NK-cell activation may require the elimination of only one or a few inhibitory components. In a prior clinical trial, Miller et al treated 19 patients with high-risk AML using enriched NK cells that had been activated by overnight culture with high concentrations of interleukin (IL)-2 and infused after lymphodepleting chemotherapy. The NK cells were HLA haploidentical to the recipient so that half of them were KIR ligand mismatched, potentially overcoming self-tolerance. Following infusion of the NK cells, the investigators administered recombinant (r)IL-2 for 14 days to induce in vivo expansion and sustain persistence. They obtained complete responses (CR) in 5 patients (26%). Although these results were encouraging, there was a concern that the infused rIL-2 had also expanded endogenous Tregs, thereby reducing overall benefit. Like activated NK cells, Tregs express a high affinity IL-2 receptor and therefore may expand concomitantly with the NK cells. In the current trial, the group therefore first treated 15 patients with the short-acting IL-2 diphtheria toxin fusion protein (IL-2DT, Ontak) to deplete Tregs prior to NK-cell infusion and rIL-2 treatment. In 2 historical cohorts without Treg depletion, 21% (9/42) of patients achieved CR with a median duration of 2.7 months (range, 1.8-15 months). By contrast, 53% (8/15) of Treg-depleted patients achieved CR with a median duration of 11.2 months (range, 1.1-32 months). The 6-month disease-free survival with Treg depletion was 33% vs 5% for patients without Treg depletion. Hence, the elimination of Tregs appears to increase the rate of complete response. Although this therapy alone was not curative, the increased CR rate may have allowed more patients to become eligible for potentially curative therapies such as stem cell transplantation. Indeed 4 of the Treg-depleted patients were alive after allogeneic HSCT at the time of writing.

The results from Bachanova et al also highlight the necessity of using multiple early time points for postfusion monitoring so that the kinetics of NK-cell expansion and persistence could be established. At day 14 after infusion (the originally planned end point for measuring NK-cell expansion), there was no evident connection between tumor responses and either NK-cell expansion or Treg depletion. Of the 5 patients with detectable NK cells at day 14, only 3 had CRs: conversely, the 6 remaining patients who achieved CR had no detectable NK cells. Similarly, the median Treg frequency in patients who achieved CR was greater than observed in patients with progressive disease. Furthermore, patients with detectable NK cells had a shorter survival (0.9-2.6 months) compared with those without detectable NK cells (median, 9.7 months; range, 0.4 to >12 months). However, when NK cells and Treg were analyzed on day 7, a different picture emerged. At this time, 10 of the 15 patients had both detectable NK cells and low numbers of Tregs, and of these patients, 7 (70%) attained CR compared with only 1 of the 5 patients (20%) without NK cells.

The importance of studying early time points was further emphasized by the kinetics of endogenous IL-15 production. This homeostatic cytokine accumulates after lymphodepletion and becomes available for the expansion of adoptively transferred lymphocytes, including NK cells. Critically, it does not promote Treg expansion and can render effector lymphocytes resistant to Tregs. Increased IL-15 was detected 2 days after the end of lymphodepletion, on the day of NK-cell infusion, but was no longer detectable by day 7. NK cells expanded only in patients with elevated IL-15.

These studies suggest that NK cells exert a potent antitumor effect in AML but that the desired effects occur soon after infusion and that lack of persistence limits the duration of this benefit. Strategies that prolong NK-cell persistence are therefore likely to correspondingly augment the antitumor effects of NK cells. One possibility suggested by Bachanova et al is to replace administration of rIL-2 with rIL-15, and combinations with other immune modulators such as checkpoint inhibitors may also be beneficial, allowing prolonged disease control in a higher proportion of patients.

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