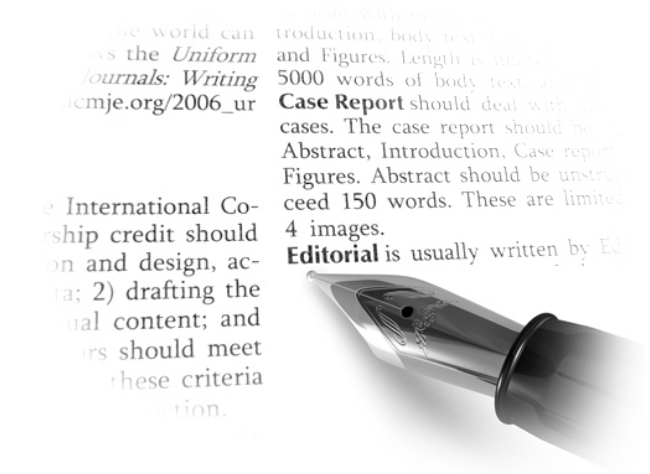

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Editorial

Way to go to exploit NK cells' versatile talents for cancer immunotherapy

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Natural killer (NK) cells are derived from CD34+ hematopoietic progenitor cells. NK cells are lymphocytes of the innate immune system that function as both cytotoxic effectors and immunoregulatory cells secreting cytokines and chemokines. However, considerable experimental evidence suggests that NK cells, like T and B cells, have a certain feature of the adaptive immune system, i.e., memory.

It has been reported that NK cells can directly kill target cells via the perforin−granzyme pathway, death receptor ligand-induced apoptosis, and antibody-dependent cellular cytotoxicity (ADCC). Owing to these abilities, NK cells have been examined clinically in several immunotherapeutic strategies for cancer. Two general approaches for NK cell-based immunotherapy for cancer have been developed. The first approach involves *in vivo* activation and expansion of NK cells in patients with cancer by administering cytokines such as interleukin (IL)-2. The second approach involves the infusion of *ex vivo* manipulated NK cells (autologous or allogeneic NK cells, purified or expanded NK cells) into patients with cancer. Recently, in addition to these approaches, administration of a tumor antigen (TA)-specific monoclonal antibody (mAb) (e.g. rituximab) into patients with TA-expressing cancers has been performed, whereby the Fc portion of the antibody can bind to CD16 expressed on NK cells, thus initiating ADCC [1].

To enable successful adoptive cell therapy, several methods for generating a large number of activated NK cells have been introduced. Although several groups tried to expand NK cells using OKT-3 anti-CD3 antibody without feeder cells, remarkable NK cell-expansion rates (30–31,747-fold within 7–21 d) were achieved when feeder cells were used. Commonly used feeder cell lines for successful NK cell expansion were RPMI8866, Wilms tumor cell line (HFWT), Epstein-Barr lymphoblastoid cell line (EBV-LCL), Jurkat (designated as KL-1 from Korean Cell Line Bank), K562, and genetically engineered K562 cells (i.e., K562-mb15-41BBL and K562-cl9-mIL21) [2-5]. In addition to these cancer cell lines, allogeneic peripheral blood mononuclear cells (PBMCs) can also be used to activate and expand NK cells. So far, however, the comparison of the feeder activities between feeder cells and the mechanism of the feeder cells have not been well studied.

In the current issue of **Blood Research**, Bae *et al.* report the development of NK cell expansion methods by using K562 feeder cells [6]. They compared feeder activities of three different cells−PBMCs, Jurkat, and K562. The results showed that K562 feeder cells expanded NK cells by nearly 20-fold. They also showed that K562-NK cells had powerful cytotoxic activity against cancer cells expressed the NK cell activating receptors (NKG2D and DNAM-1), and produced more perforin and granzyme B than did naïve NK cells and Jurkat-NK cells [6]. Although this study extends the previous finding that K562 feeder cells enhanced proliferation and cytotoxic activity of human NK cells and suggests that K562 is one of the best feeder cell lines for

expansion of human NK cells *ex vivo*, the expansion rate is not satisfactory. Further investigations are required to enhance expansion rate of NK cells, to expand a specialized NK cells like cytokine-induced "memory-like" NK cells, and to expand a NK cell subset with strong ADCC in the target monoclonal antibodies era by developing a new genetically engineered K562 cells.

Another paper on NK cells is published in the current issue of **Blood Research**. Kim *et al.* explored the influence of NK cell count on the survival of patients with diffuse large B-cell lymphoma (DLBCL) when treated with rituximab, cyclophosphamide, vincristine, adriamycin, and prednisone (R-CHOP) [7]. They previously reported that a low absolute lymphocyte count (ALC) can influence outcomes in patients with non-germinal center (non-GC) subtype DLBCL receiving R-CHOP therapy, and suggested that a low ALC in patients with non-GC subtype DLBCL counteracted the beneficial effect of rituximab on survival [8]. This time, they further investigated the impact of NK cells among the lymphocytes on clinical outcomes and concluded that a low NK cell count at diagnosis is associated with poor clinical outcomes only in patients with non-GC subtype DLBCL, but not in patients with GC subtype DLBCL.

Besides the GC subtype in DLBCL, several studies about an association between FCGR3A/2A genotypes and clinical outcomes in patients treated with mAb therapy have shown that NK cell-mediated ADCC is not efficacious against tumor targets. Although *FCGR3A* gene polymorphisms correlated with response to frontline R-CHOP therapy for DLBCL, the *FCGR3A/2A* genotypes did not show any correlation in breast cancer patients treated with trastuzumab [9]. Therefore, another strategy may be required to improve the clinical efficacy of NK cell-mediated ADCC in the targeted mAb era. One approach would be administration of immunomodulatory cytokines to enhance the *in vivo* ADCC of NK cells. It has been reported that co-administration of IL-12 can enhance the effects of anti-tumor mAbs via the activation of NK cells *in vitro* and in the context of a phase I trial of IL-12 and trastuzumab [10]. Another approach might be to combine mAb therapy with the adoptive transfer of *ex vivo*-expanded NK cells with strong ADCC activity.

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