

A Brief Note on Cytokine-Induced Killer Cells

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ABSTRACT

Cytokine-Induced killer (CIK) cells are raising growing interest in cellular antitumor therapy, as they can be easily expanded with a straightforward and inexpensive protocol, and are safe requiring only GMP-grade cytokines to obtain very high amounts of cytotoxic cells. CIK cells do not need antigen-specific stimuli to be activated and proliferate, as they recognize and destroy tumor cells in an HLA-independent fashion through the engagement of NKG2D. In several preclinical studies and clinical trials, CIK cells showed reduced allo reactivity compared to conventional T cells, even when challenged across HLA-barriers.

Keywords: Febrile neutropenia; CTAS; ED; Quality of care; Timeliness of ED care; The Canadian triage and acuity Scale; Emergency triage; Oncological emergencies

INTRODUCTION

Adoptive cell therapy (ACT) aims at restoring cancer recognition by the immune system, leading to effective tumor cell killing. ACT is based on the administration of antitumor immune cells, which have been stimulated and expanded *ex vivo* to obtain highly active tumor-specific effectors to be finally transferred back to the patients. If required, these activated cells can also be genetically modified to express tumor-specific recognition molecules, such as chimeric antigen receptors (CAR) or T cell receptors (TCR) [1].

Effector cells used for adoptive immunotherapy strategies must meet several requirements to ensure a successful outcome of the treatment. First, they must be easily expandable *ex vivo* to get sufficient numbers to achieve relevant clinical responses. Second, they must have a high specificity for the cancer cells to traffic to the tumor site and avoid any damage to healthy tissues. Third, they should be able to proliferate and persist significantly *in vivo*, exerting a sustained and prolonged antitumor response. Importantly, ACT should be safe and well tolerated in patients, generating only mild adverse effects or toxicities.

Several effector cell populations have been developed for ACT purposes, such as Lymphokine-activated killer cells, Tumor-infiltrating lymphocytes, CAR- or TCR-transduced T cells, NK cells, $\gamma\delta$ T cells, Natural Killer T cells and Cytokine-Induced Killer cells. This review will focus on CIK cells highlighting

differences with other cell populations, as well as the involvement and importance of cytokines in shaping CIK cell features [2].

CIK cells are a very promising cell population for ACT approaches. They were essentially obtained by the optimization of LAK cell expansion protocol, but they differ from these latter cells for some critical aspects.

In the early 1980s, Rosenberg's group described the generation of LAK cells from both murine and human lymphocytes, as a cell population capable of lysing cancer cells after a short-term incubation (from 3 to 5 days) in interleukin-2 (IL-2). These cells were able to lyse a wide array of autologous and allogeneic fresh tumors, and NK-resistant cells. However, LAK cells did not expand efficiently *ex vivo* and therefore alternative culture conditions were investigated, to allow long-term culturing and higher proliferation of effector cells [3]. The use of activation signals such as OKT3, a mitogenic anti-CD3 monoclonal antibody (mAb), in combination with IL-2 led to a significant expansion of effectors with an improved lytic activity. Moreover, the incubation of cells with IFN- γ further increased the cytotoxic activity but only if the cytokine was added 24 h before IL-2; IFN- γ priming at the same time or following incubation with OKT3 and IL-2 was much less effective in generating cytotoxic cells. Likewise, IL-1 alone had no effect on cytotoxic activity, unless it was combined with IFN- γ and anti-CD3. Thus, the optimization of the LAK expansion protocol through the definition of a time-

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sensitive schedule for the addition of IFN- γ , OKT3 and IL-2, led to the obtainment of CIK cells [4].

CIK cells are a heterogeneous subset of polyclonal CD3+CD56+ T cells with phenotypic and functional properties of NK cells. They derive from CD3+ T cell precursors that acquire the expression of CD56 during expansion. CIK cells show a higher proliferation rate than LAK cells, up to 1000 folds, and can be obtained from PBMCs, bone marrow mononuclear cells and umbilical cord blood. After 2 weeks of expansion, the bulk population is mainly composed by CD3+CD56+ CIK cells and CD3+CD56- T cells, and only a small fraction of CD3-CD56+ NK cells. Cytotoxic activity is mainly associated with the CD3+CD56+ subset, differently from LAK cells in which the major effectors express conventional NK markers (CD3-CD56+) [5].

Expanded CIK cells also differ from NKT cells, which are mainly defined accordingly to their ability to recognize a relatively monomorphic non-classical class I-like MHC molecule, CD1d, which presents a wide range of lipid antigens from bacterial lipids to mammalian self-lipids.

CIK cells, similarly to LAK cells, do not require antigen-specific stimuli to be activated and proliferate, and exert a potent MHC-unrestricted antitumor activity against both hematological and solid malignancies, but not against normal tissues and hematopoietic precursors [6,7].

CONCLUSION

CIK cells are a very attractive tool for adoptive immunotherapy approaches against hematological and solid tumors. They can be

easily expanded using a straightforward and inexpensive expansion protocol, and are safe as they only require GMP-grade cytokines to obtain very high amounts of cytotoxic cells.

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