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Short Communication

Natural Killer Cell Phenotype at Diagnosis of Acute Lymphoblastic Leukemia Predicts Disease Prognosis

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ABSTRACT

Studies on Natural Killer (NK) cells have demonstrated their potential in treating hematological malignancies and solid tumors. Because they are potentially safer and easier to engineer than T cell-based therapies, NK cells are a particularly attractive platform for developing off-the-shelf cellular treatments. Development of allogeneic NK cell-based therapies requires a detailed understanding of how autologous NK cells are suppressed in patients with cancers.

Keywords: Natural killer cell; B and T-cell acute lymphoblastic leukemia; Clinical prognosis

ABBREVIATIONS

NK: Natural Killer Cells; ALL: Acute Lymphoblastic Leukemia; GVHD: Graft vs. Host Disease; AML: Acute Myeloid Leukemia; MRD: Minimal Residual Disease; CNS: Central Nervous System; GVL: Graft vs. Leukemia; CAR: Chimeric Antigen Receptor; MHCI: Major Histocompatibility Complex Class I

INTRODUCTION

In our recently published study in Blood [1], Authors identified the defects in NK surveillance in patients with B and T-cell Acute Lymphoblastic Leukemia (ALL) at diagnosis. The study showed that defective NK surveillance is a reliable predictor of clinical outcome in ALL and can be applied to decide course of ALL treatment and to develop NK cell-based therapies.

Innate immune Natural Killer (NK) cells are one of the first lines of defense against infections and cancers. NK cells can kill abnormal target cells without prior sensitization. In contrast to cytotoxic T cells that bind to target cell antigen presented with surface Major Histocompatibility Complex Class I (MHCI) molecules, NK cells use activating and inhibitory receptors to detect and lyse abnormal target cells lacking MHCI [2]. Therefore, NK cells are attractive candidates for the development of cell-based immunotherapies for cancer [3,4].

The potential of allogeneic NK cells as cancer therapies has been defined in seminal studies. For example, Ruggeri, et al. demonstrated that donor-derived NK cells from allogeneic hematopoietic transplants exert potent Graft *vs.* Leukemia (GVL) effect in patients with Acute Myeloid Leukemia (AML) [5]. Unlike T cells, allogeneic NK cells reduce graft *vs.* host disease (GVHD) [5,6] making them particularly attractive as off-the-shelf cellular immunotherapies. Furthermore, the reduced induction of cytokine release syndrome and neurotoxicity by NK cell-based therapies [7] make them more attractive than cytotoxic T cell-based therapies. Given the advantages of allogeneic NK cells, multiple clinical trials are underway to test the safety and efficacy of off-the-shelf Chimeric Antigen Receptor (CAR)-NK cells in patients with hematopoietic malignancies and solid tumors [7].

The rational development of effective allogeneic NK cell-based cancer treatments requires investigations into whether and how NK cells are perturbed in different cancer types. More recently, study defined the mechanisms underlying the suppressed antileukemia NK surveillance in patients with B and T-cell Acute Lymphoblastic Leukemia (ALL) using high-dimensional mass, flow, and *in silico* cytometry [1]. The study found that NK cells are reduced in the ALL microenvironment and that residual NK cells in patients with ALL are impaired in their cytotoxic function. The study showed that reduced cytotoxicity of NK cells in patients with ALL potentially results from a developmental arrest in the NK effector maturation pathway that produces cytotoxic NK cells. This developmental defect results in the accumulation of immature, dysfunctional, and hyperactivated cytokine-producing NK cells in ALL patients. In addition to

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defective maturation of NK cells, other factors not explored in our study including, defective processing, release, and target cell membrane binding potential of NK cell lytic granules and/or resistance of the leukemia cells to NK cell-mediated lysis could result in impaired NK cell-mediated immune surveillance in patients with ALL. In the future, it would be worthwhile to investigate the extent to which these other mechanisms contribute to suppressed NK surveillance in ALL and apply this knowledge to develop effective NK cell-based therapies.

Our studies [1] are relevant for diagnosis and treatment of ALL in the clinic. Our findings support the development of allogeneic NK cell-based therapies because reduced numbers and dysfunctionality of NK cells in ALL patients would make isolation and engineering of autologous NK cells difficult. Ours is the first study to correlate NK cell phenotype at ALL diagnosis with clinical prognosis of the patient. The study found that ALL patients with increased relative frequencies of activated cytokine-producing NK cells compared to resting NK cells at diagnosis had poor clinical outcomes. Reduced relapse-free survival rates of ALL patients with high proportions of activated NK cells occurred independently of known predictors of ALL prognosis including, the presence of Minimal Residual Disease (MRD) after induction therapy and Central Nervous System (CNS) involvement. Therefore, this study infer that cytometry-based NK cell profiling at ALL diagnosis could be a powerful tool to predict clinical outcome and identify patients who can be treated with NK cell-based therapies.

A limitation of our study [1] is the inability to conduct genetic experiments to determine whether restoring NK cell maturation in human ALL can promote sustained leukemia regression. The study addressed this by conducting genetic experiments in transgenic mouse models of ALL [8], and found that NK suppression in mouse ALL recapitulated that seen in ALL patients [1]. The study also showed that adoptive transfer of NK cells can slow down growth and recurrence of mouse T-ALL [8].

CONCLUSION

In conclusion, our studies underscore the importance of developing approaches to profile NK cells at ALL diagnosis and applying this information to restore NK cell-mediated immune surveillance for sustained remission of B and T-ALLs.

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AUTHOR CONTRIBUTIONS

Anil Kumar and Srividya Swaminathan wrote the commentary.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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