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Editorial

Acute myeloid Leukemic cells express NKG2D or shed off NKG2D Ligand to escape immune-surveillance

Keywords: organ systems, function, immune system, transformed cells, proliferation, hematopoietic

Abbreviations: AML, acute myeloid leukemia; NK, natural killer; DC, dendritic cells; HSCT, hematopoietic stem cell transplantation; MHC, major histocompatibility complex; DNAM-1, dnax accessory molecule-1

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Editorial

The core function of the immune system is to maintain a balanced healthy condition that enables cells, tissues, organs, organ systems and the organism as a whole to function properly. The immune system does this by recognizing and destroying foreign molecules (non-self) or transformed cells (transformed self) that pose danger to the health and survival of the organism. That notwithstanding, these foreign molecules or transformed cells especially cancer/tumor cells have demonstrated over time that, they are capable of escaping the immune-surveillance.[1] Escaping immune-surveillance can result in serious ailment or even death, and in such instance, the immune system is said to have been compromised. In this editorial, the spotlight is put on one of such cancers, acute myeloid leukemia (AML), which has demonstrated its ability to evade immune-surveillance. Acute myeloid leukemia is a heterogeneous group of diseases associated with the proliferation of a hematopoietic progenitor clone at a specific differentiation stage.[2] Notable immune cells that play crucial role in AML immune-surveillance are the Natural killer (NK) cells, T cells and dendritic cells (DC).[3] As such, their anti-leukemic potential have been evaluated in different potentially viable immunotherapeutic strategies. Example, NK cells exert their anti-tumor/cancer effects via direct induction of cytotoxic in the target cell, and secretion of cytokines to recruit and activate other relevant immune cells such as DC.[3] Hence, supporting the development of an effective adaptive anti-tumor/cancer immune response. The ability of NK cells to destroy AML blast has been demonstrated in the setting of allogeneic hematopoietic stem cell transplantation (HSCT) for AML patients, emphasizing further the involvement of NK cells in leukemia clearance and control.[4] The success of allogeneic hematopoietic stem-cell transplantation attributed to the graft-versus leukemia effect has demonstrated the significant role played by immune responses against leukemic cells as the best therapeutic alternative in treating this disease.[4]

In other instance, haplo-identical stem cell transplantations consisting of alloreactive NK cells and allogeneic NK cells adoptive immunotherapy has proven effective in the treatment of AML.[5] These confirm and support the fact that NK cells are involved and play important roles in immune response against AML. Evidently, both arms of the immune systems, the innate and the adaptive are capable of recognizing and eliminating AML. The leukemic cell, just like other stressed cell expresses the stress protein major histocompatibility complex (MHC) class I molecules. These stress proteins MHC class I molecules are ligands of the receptor natural killer group 2 member D (NKG2D) on NK cells.[6] The immune cells with the receptor NKG2D are therefore able to recognize and attack the MHC expressing AML blast. Thus, the MHC expressing AML blast is rendered susceptible to T and NK cells. Nevertheless, AML has demonstrated that it is capable of escaping NK cell immune-surveillance through a number of mechanisms. An impaired NK cell cytotoxic in AML patients has been reported severally in more than a decade, confirming the long assertion that AML blast is capable of escaping immune-surveillance. Hence, patients with AML will mostly require therapeutic intervention in order to be cured. Here, two notable mechanisms which aid immune-surveillance evasion by the NK cells are discussed. The first mechanism is the under-expression of the stress protein MHC by the AML blast or the shedding off the stress protein from the surface of the AML blast.[7] This obviously results in the down regulation of NK cell surface expression of the activating cytotoxicity receptors. Another important fact which has surfaced recently is the under-expression of DNAX accessory molecule-1 (DNAM-1) on NK cells from AML patients. Interestingly, DNAM-1 and activating NK cell receptor NKG2D are the main receptors involved in NK cell mediated recognition and killing of AML blasts.[8] This directly impairs the cytotoxicity role of the NK cell and therefore contributes significantly to the immune compromised state associated with AML condition. As expected, down regulation of the activating cytotoxicity receptors on NK cells has shown to be associated with poor prognosis for AML patients. One of the available therapeutic interventions that can be employed to re-activate NK cells against AML blasts is an intervention that ensures the re-introduction of the stress protein MHC on the surface of the AML. This intervention can up-regulate the cytotoxicity activating receptors of the NK cell, and thus, restore immune-surveillance against the AML blast. In a study entitled "a novel fusion antibody exhibits antiangiogenic activity and stimulates NK cell-mediated immune surveillance through fused NKG2D ligand,[9]" a novel fusion antibody was designed and constructed to be able to re-introduce MHC on tumor/cancer cells and establish close proximity between the cancer/tumor cells and effector

cells. Functional evaluation of this fusion antibody proved successful. This is a promising therapeutic agent, suitable and appropriate for AML treatment. Another mechanism that has been implicated in the AML blast immune-surveillance escape is the remote expression of tumoral NKG2D. A study with the title "tumoral NKG2D alters cell cycle of acute myeloid leukemia cells and reduces NK cell-mediated immune surveillance[10]" has sufficiently demonstrated that AML can express NKG2D. The interesting nature of this report stems from the fact that, NKG2D is a cytotoxicity activating receptor expressed by NK cells. The study further demonstrated that the tumoral NKG2D plays a crucial role in the proliferation of AML blast. The possible explanation to this tumoral NKG2D induced proliferation is attributed to the ability of AML cells to simultaneously express both ligand MHC and receptor NKG2D, which are relatively close. The AML cells therefore bind to themselves via the MHC ligand -NKG2D receptor interaction due to proximity. This in effect prevents the possible interaction between NKG2D on NK cells and the NKG2D-ligand on the AML blasts, which could result in cytotoxicity in the AML blasts. The appropriate therapeutic intervention could equally be the re-introduction of recombinant NKG2D-ligand on the AML cells via the use of the fusion antibody described above. The fusion antibody (scFv-MICA) is constituted by anti-VEGFR2 scFv and NKG2D-ligand MHC. The scFv binds to VEGFR2 on the AML blast, whereas NKG2D-ligand binds and activates the NK cells to induce cytotoxicity in the AML blast.[9] In conclusion, these two mechanisms among others could be the escape route for AML blast, and could possibly be implicated in the high incidence of AML recently. Notwithstanding, there is promising therapeutic intervention which could produce the expected outcome in the treatment of AML. The fusion antibody intervention has promising prospects and can therefore be exploited to derive the needed benefits.

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Conflict of interest

The author declares no conflict of interest.

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