A FC-OPTIMIZED B7-H3 ANTIBODY FOR INDUCTION OF NK CELL REACTIVITY AGAINST ACUTE MYELOID LEUKEMIA

Background: Acute myeloid leukemia (AML) is the most frequent acute leukemia in adults. Although treatment options of AML have improved during the last decade, so far, no anti-tumor antibodies are clinically approved for AML therapy. The crucially important factor for the therapeutic success of monoclonal antibodies (mAbs) in cancer treatment is their ability to mediate antibody-dependent cellular cytotoxicity (ADCC) through natural killer (NK) cells. Recently, the coreceptor of immune-checkpoint B7 family B7-H3 (CD276) has emerged as a promising target for AML immunotherapy, due to its profound expression on leukemic blasts of AML patients.

Methods: Here we provide preclinical characterization of our previously developed B7-H3 mAb 8H8 in AML. By introduction of amino acid substitutions (S239D/I332E) in the Fc part, 8H8-SDIE provides enhanced affinity to the activating Fc receptor CD16 on NK cells. We characterized B7-H3 expression and binding of 8H8 on AML cell lines (n=12) and patient samples (n=64) and employed 8H8-SDIE in various in vitro assays.

Results: Flow cytometric analyses showed that 8H8-SDIE bound specifically to the target antigen at saturating doses of approximately 1 µg/mL on primary AML patients' samples. Co-cultures of allogeneic peripheral blood mononuclear cells (PBMC) with B7-H3-positive primary AML cells, revealed that B7-H3-SDIE induced significant NK cell activation measured by CD69 and CD25 expression. In line, determination of CD107a upregulation confirmed significant induction of NK cell degranulation by our construct. Additional analysis of the supernatants by LegendPlex showed 8H8-SDIE treatment-induced secretion of immunomodulatory IFNγ and TNF as well as enhanced levels of Granzyme B, Granulysin, and Perforin mediating NK cell effector functions. No effects were observed in the presence of the corresponding iso-SDIE control. Target cell-restricted lysis of AML cell lines and primary AML patients' samples by 8H8-SDIE was potently induced in Europium and FACS-based cytotoxicity assays, while iso-SDIE treatment did not induce lysis of leukemic cells.

Conclusions: Taken together, we here introduce a novel attractive immunotherapeutic compound potently inducing NK cell anti-leukemic reactivity as a beneficial treatment option for AML.

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