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Mechanisms of immune escape in acute myeloid leukemia (AML)

Acute myeloid leukemia is a heterogeneous malignancy with generally unfavorable prognosis, which is due in particular to frequent relapses. The immune system is likely to play an important role in elimination of the residual disease. Anti-tumor immune response often develops spontaneously in humans, but it can be suppressed through a variety of mechanisms. Evasion of leukemia cells from the immune surveillance also limits the efficiency of immunotherapy protocols based on the transfer of immune cells from healthy donors or on modification of autologous lymphocytes.

Cell ability to escape from elimination by the immune system may form an integral part of leukemogenic transformation. Activation of signaling pathways enabling deregulated cell proliferation or resistance to apoptosis induction can also lead to reduced expression of HLA, which present antigens to T-cells, to enhanced expression of inhibitory receptors (like PD-L1), or to secretion of immunosuppressive molecules (like Gal-9, IDO, arginase). Our results [1] indeed indicate some recurrent mutations are associated with specific immunophenotype of leukemia blasts (Fig. 1).

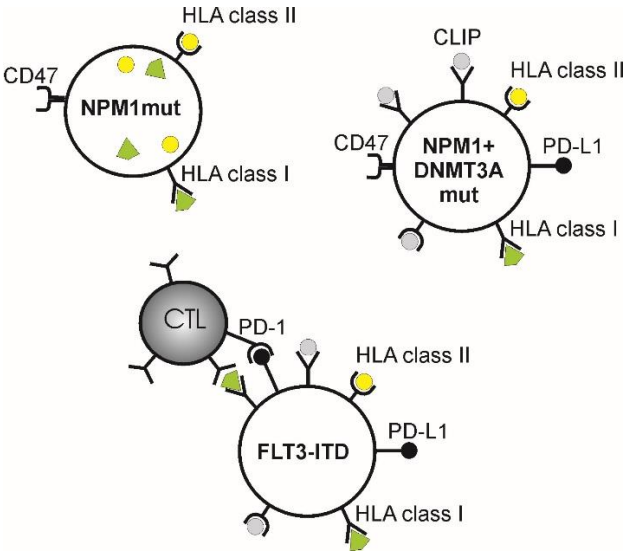

Fig. 1: Characteristic immunophenotypes of AML blasts with selected recurrent mutations. Cells with isolated mutation of nucleophosmin (NPM1) have reduced HLA expression and increased amount of CD47, which serves as an inhibitory signal for macrophages. Cells with concomitant mutation in DNA methyltransferase 3A (DNMT3A) have normal HLA levels, but increased surface amount of the invariant peptide CLIP, indicating defective antigen presentation. Internal tandem duplication in the Flt3 gene (FLT3-ITD) is also associated with increased CLIP amount. In addition, high expression of the inhibitory receptor PD-L1 predicts worse prognosis in patients with FLT3-ITD

Nucleophosmin 1 (NPM1) mutation generates neoantigens, which may be recognised by the immune system. In addition, the mutation results in NPM1 translocation from the nucleoli to the cytoplasm, possibly enhancing NPM1 processing and presentation of NPM1-derived immunopeptides. This hypothesis is corroborated by our observation that some HLA class I alleles, which present antigens to cytotoxic T-cells, are underrepresented in AML patients with NPM1 mutation compared to AML patients with wild-type NPM1 or to HLA distribution in normal population [2,3]. Individuals with suitable HLA types thus might be protected from AML development by a spontaneous immune response against mutated NPM1. In agreement with this finding, markers of immune suppression observed in this patient group are mainly related to antigen-specific immune response, i.e. decreased HLA expression or reduced antigen presentation [1].

Mutations resulting in reduced activity of DNA methyltransferase 3A (DNMT3A) have negative prognostic impact in patients with AML. In these cases, we found markers of decreased antigen presentation as well as higher expression of PD-L1, a ligand for the inhibitory receptor PD-1 on T-cells [1].

Leukemia blasts with low HLA expression, which are typical for patients with isolated NPM1 mutation, usually do not display other markers of immune escape, and this phenotype is associated with better patient outcome. In contrast, high PD-L1 levels are ofter found together with markers of additional mechanisms of immune evasion, i.e. the presence of the invariant peptide CLIP and TIM-3 protein on the cell surface. We have shown the amount of TIM-3 transcript strongly correlates not only with the surface TIM-3 protein, but also with high levels of CLIP and PD-L1. TIM-3 transcript thus could be used as a marker of activation of immunosuppressive mechanisms in patients with AML. According to our results, high TIM-3/CLIP/PD-L1 levels at diagnosis have a negative prognostic impact on the overall survival and relapse-free survival [1,4].

Our current working hypothesis is that the regulatory mechanisms of immunosuppressive processes are at least partially shared enabling parallel activation of multiple ways of immune resistance. We believe some recurrent mutations, such as internal tandem duplications in the gene for the receptor kinase FLT3 (FLT3-ITD), lead to immunophenotype changes providing increased resistance of leukemia blasts to the immune system. Such inherent activation of immune evasion mechanisms would persist under residual disease conditions, where the tumor load in the organism is not high and secretion of immunosuppressive molecules is thus limited. FLT3-ITD is known to promote signaling through mTOR, which could be responsible for immune escape. The mTOR pathway is branched according to molecular complexes formed by mTOR. The impact of FLT3-ITD thus depend on the cell context, which determines mTOR binding to mTOR complex 1 or 2 (mTORC1 or mTORC2). We presume that markers of mTORC1/mTORC2 activation could help to predict formation of immunoresistant phenotype in AML patients with FLT3-ITD.

References

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