Large HLA disease association study with more than 50,000 controls shows protective effects for HLA-B*40:01 and C*03:04 in NPM1 mutated AML

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Background

Mutations in the *nucleophosmin 1* gene (NPM1) are common and recurrent molecular abnormalities in acute myeloid leukemia (AML). They are considered to be positive prognostic factors potentially due to immune responses mediated by NPM1 mutation (NPM1mut)-specific cytotoxic T cells and thereby suppressing NPM1mut-positive hematopoiesis. Here, in a large HLA association study we compared the distribution of HLA class I alleles at 2-field-resolution between *NPM1mut* AML patients (n=471) and a control group of healthy individuals (n=51,890). HLA class I molecules of alleles which are underrepresented might present *NPM1*mut-derived neoepitopes more effectively and have the potential to elicit an anti-leukemic immune response.

Geno-type

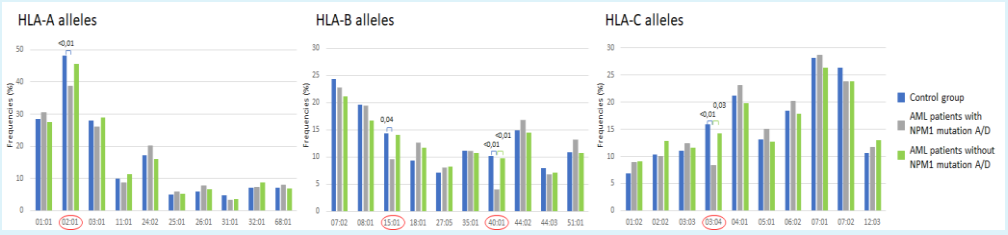
NPM1 genotyping of patient samples with polymerase chain reaction (PCR) amplification of *NPM1* exon 12

HLA genotyping with high-resolution amplicon-based approach using Illumina devices

Data Samples

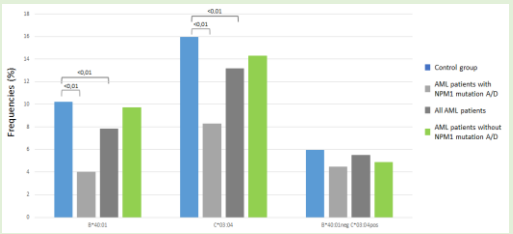
Condition	AML patients	Healthy Donor (Lifetime Risk of AML < 1%)
Sample Size	1,704	51,890
Population	German, 18-79	German, 19-59
Source	SAL Biobank and CoBi www.cobi-biobank.de	DKMS donor registry

Protective effect of HLA-A*02:01, B*15:01, B*40:01 and C*03:04 in AML patients with NPM1 mutation



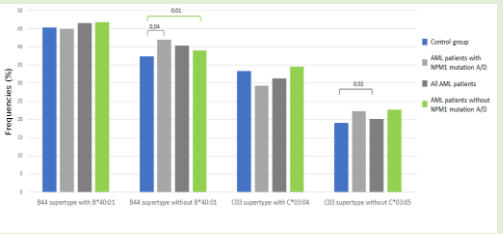
Frequencies of the ten most frequent HLA-A, -B and -C alleles in AML patients with (grey bars) and without (green bars) NPM1 mutation A/D and in healthy donors (blue bars). Adjusted p-values are depicted above the columns.

Who is the driver of immune surveillance?



Frequencies of HLA-B*40:01-positive, HLA-C*03:04-positive, and HLA-B*40:01-negative-HLA-C*03:04-positive AML patients (grey and green bars) in comparison to healthy donors (blue bars). Adjusted p-values are given above the columns.

HLA supertypes do not have a protective effect.



Frequencies of HLA-B44 and HLA-C03 supertypes positive AML patients (grey and green bars) in comparison to healthy donors (red bars). Adjusted p-values are depicted above the columns.

Conclusions

We found HLA-B*40:01 and HLA-C*03:04 underrepresented in NPM1 mutated AML suggesting that neoepitopes presented by these HLA alleles trigger T cell responses. NetMHCpan version 4.1 predicts that NPM1mut-derived immunopeptides bind strongly HLA-B*40:01 and weakly C*03:04. Relative linkage disequilibrium was shown for HLA-B*40:01 and HLA-C*03:04, but we could not identify a strong impact for either HLA-B*40:01 or HLA-C*03:04. Our findings suggest that further studies are warranted to confirm the presence and functionality of neo-epitope specific T-cells.

Next Step

Identification and isolation of HLA-B*40:01 and HLA-C*03:04 restricted NPM1mut-specific CD8+ T cell clones