Somatic mutations in HLA loci in patients with myeloid leukemia

Půbalová , Neupauerová, Vraná, Šálek, Nazarová

HLA Department, Institute of Hematology and Blood Transfusion (IHBT), Prague, Czech Republic; Institute of Experimental Cellular Therapy, University Hospital Essen, Essen, Germany

INTRODUCTION

Acute myeloid leukemia (AML)

- The most common acute leukemia in adults
- Genetically heterogeneous disorder characterized by the accumulation of somatic genetic variants in hematopoietic progenitor cells
- HLA somatic mutations allow tumour cells to escape from the immune response against acute myeloid leukemia
- Allogeneic hematopoetic stem cell transplantation (aHSCT) is an effective treatment for AML

Human Leukocyte Antigens (HLA)

- Peptide-presenting proteins, play a key role in immune system
- For transplantation, HLA is routinely matched between recipient and donor
- Our HLA Department of IHBT is focussing on HLA typing of hematooncological patients and their donors before HSCT

METHODS

Next-generation sequencing: Holotype kit 24/7 (Omixon, Hungary), MiSeq platform (Illumina, USA)
Sanger sequencing (Innotrain, Germany; CareDx, USA)

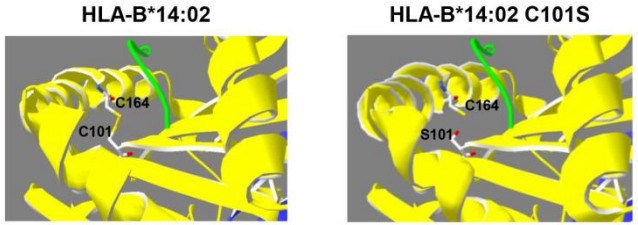
RESULTS

In our cohort of patients indicated for HSCT (2017-2020) from the 23 new alleles detected, 2 were somatic.

Somatic HLA-B*14:02 variant

- Somatic variant occured when the patient was 37 years old
- **Cys101Ser** (codon change **T**GC-**A**GC) in exon 3
- causes the disruption of the disulphide bond between C101 and C164 (Figure 1.)
- May cause an abberant expression
- New variant arose during the development of the disease from aplastic anemia to AML
- Other somatic changes present during the dissease progression: trisomy of chr8 and point mutations in *PHF6, RUNX1, SETBP1* and *ASXL1* genes

Figure 1. (Neupauerová et al., 2019)
Homology modelling of C101S in HLA-B*14:02
https://doi.org/10.1111/tan.13762



Somatic HLA-C*04:01 variant

- Somatic variant occured when the patient was 42 years old
- Somatic mutation was present in the leukemic cells at the time of diagnosis
- **Thr118Thr** (codon change AC**C**-AC**A**) in exon 3
- Synonymous substitution – possibly has no effect on protein function

CONCLUSION

- In our cohort of patients, 2 somatic variants were detected
- Findings are in agreement with the known genome instability in AML
- Both somatic variants are in patients suffering from AML, arosed later with the progress of the disease in the leukemic clone only
- The identified somatic variants are present in the coding exons of the HLA I.genes. The HLA-B variant may also effect protein function

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