PB1752 ANALYSIS OF HLA-PEPTIDE BINDING POCKETS IN PATIENTS WITH ACUTE LEUKEMIA UNDERGOING UMBILICAL CORD BLOOD TRANSPANTATION

**Topic:** 01. Acute lymphoblastic leukemia - Biology & Translational Research

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**Background:** Despite a better understanding of the genetic heterogeneity of both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), relapse rates remain high and long-term survival is suboptimal. In this context, the association between these malignancies and the human leukocyte antigens (HLA) has been widely studied. The highly polymorphic HLA loci have significance and relevance for disease susceptibility thanks to their peptide-binding grooves-dependent antigen presentation to effector cells. Such processes trigger an algorithm of immune responses based on multiple fine-tuned combinations of amino acid sequence interactions. Thus, the HLA genetic diversity has been a focus of interest in acute leukemia settings as exemplified by studies showing the implication of both HLA class I and II polymorphisms. However, there is scarce data regarding the diversity of peptide-binding pockets per se especially in the context of umbilical cord blood transplantation (UCBT).

**Aims:**

To analyze whether variants of HLA-DQB1 and -DRB1 peptide-binding groove pockets 4 and 9 and/or their amino acid positions are associated with the diagnosis of ALL or AML among patients undergoing UCBT.

**Methods:** A retrospective analysis was performed including 849 patients with ALL and AML undergoing an UCBT. Demographics and genotyping data were obtained from the Eurocord database. Pockets and amino acids were imputed from the four-digit HLA genotypes of patients. Easy-HLA was used for haplotype inference when needed. Descriptive statistics were applied. Risk ratios (RRs) and 95% confidence intervals (CI) were estimated by applying log-binomial regression to compare the allelic frequencies between both types of leukemia.

**Results:** ALL and AML were diagnosed in 50.2% and 49.8%, respectively. The median age at UCBT was 8.7 and 17.9 years. Overall, they were mostly pediatric patients (61.8%), males (52%), and in first complete remission (58.7%). From the ten variants analyzed in pocket 9 of the HLA-DQB1 allele, only the variant YYVSY, corresponding to the allele HLA-DQB1*05:02/04, was more frequent in ALL when compared to AML (RR=2.12, 95% CI: 1.30-3.44; p=0.001). Also, within the 21 analyzed pocket 4 variants of the HLA-DRB1 allele, RFDRAY, corresponding to DRB1*16:01/02, was the only variant with a significant higher frequency among AML patients versus AML patients (RR=3.26, 95% CI: 1.81-5.99; p=0.001). No differences were observed when comparing ALL and AML at either pocket 4 of HLA-DQB1 allele or pocket 9 of HLA-DRB1 allele. Further amino acid analysis revealed that the frequency of serine 57 of the HLA-DQB1 pocket 9 was higher in ALL (RR=2.03, 95% CI: 1.26-3.27; p=0.037). None of the analyzed amino acid positions in HLA-DRB1 pockets was statistically enriched neither in ALL or AML.

**Summary/Conclusion:** Our analyses suggest that specific variants in terms of HLA pockets and amino acids might be unique to ALL. As a result of expressing HLA molecules on their surface, leukemic cells may participate to the disease development and/or to immune evasion. Thus, the immune and genetic expression profile of the leukemic microenvironment has been described as a potential useful biomarker in guiding therapeutic approaches. Interestingly, peptide binding to HLA class II molecules is frequently viewed as a merger of detached anchor residue preferences for pockets 4 and 9. In our study, these associations, at a genotypic level, might be a stepping stone towards analyzing results in acute leukemia after UCBT as there is robust evidence supporting the impact of HLA on
important post-transplant outcomes.