ALLELIC POLYMORPHISM OF KIRS IN JAK2V617F AND CALR MUTATION DRIVEN MYELOPROLIFERATIVE NEOPLASMS.

Milena Ivanova[1], Angelina Mladenova[1], Gergana Tsvetkova[2], Ilina Micheva[3], Evgueni Hadjiev[2], Velizar Shivarov[4]

[1] Department of Clinical Immunology, Alexandrovska University Hospital, Medical University Sofia, Sofia, Bulgaria

[2]Department of Clinical Hematology, Alexandrovska University Hospital, Medical University Sofia, Sofia, Bulgaria

[3]Department of Clinical Hematology, Saint Marina University Hospital, Medical University Varna, Varna, Bulgaria

[4]Department of Experimental Research, Medical University Pleven, Pleven, Bulgaria

We showed that *HLA-I* genotype might differentially restrict *JAK2V617F* and *CALRmut*-driven oncogenesis and potentially explain the mutual exclusivity of the two mutations in myeloproliferative neoplasms (MPNs). The positive associations with *HLA-I* alleles suggest that HLA molecules could also mediate immunoedditing in MPN through interaction with KIRs. To explore further this hypothesis we analysed allele level polymorphism of 8 *KIR* genes in 167 MPN patients (137 JAK2V617F+ and 30 CALRmut+) and 96 healthy controls from the Bulgarian population. *KIR* genotyping was performed by NGS using NGSgo-AmpX KIR. By fitting additive generalized linear model with age and gender as covariables we observed statistically significant increased frequency of KIR2DL4*00801 (OR-2,56;P-0,006) while KIR3DL1*00501 (OR-0,583;P-0,034) and KIR3DL3*104 (OR-0,171;P-0,013) alleles we significantly depleted in MNP patients. When analysis was performed according to the presence of driving mutations, JAK2V617F+ patients had a significantly higher frequency of KIR3DL3*00801(OR-13,356;P-0,029), KIR2DL4*00801(OR-3,083;P-0,003), KIR3DL1*00101(OR-1,788;P-0,034) and lower frequencies of KIR2DL3*104 (OR-0,159;P-0,021) and KIR3DL1*00501 (OR-0,541;P-0,025) alleles compared to the controls. Alleles KIR3DL3*00701 (OR-7,212;P-0,042) and KIR2DL2*00301 (OR-2,817;P-0,029) were enriched while KIR2DL4*01101 (OR-0,256;P-0,034) was depleted in CALRmut+ patients. In both cohort of patients, we observed significant protective effect of KIR2DL2 absence. Analysis of HLA-KIR interactions showed that presence of KIR2DL2 receptor and absence of their C1 ligands had predisposing association in MPN. These data suggest possible role of KIR alleles and KIR/ligand interactions in JAK2V617F and CALRmut driven MPN. These findings might have implications for better understanding the molecular mechanisms of mmunosurveillance and cancer invasion in MPN. Supported by grant Supported by grants KP-06-H41/2, KP-06-H83/3 and GenDx.

E-mail: mivanova@intech.bg