Mgr inż. Monika Pępek

Charakterystyka nowych zmian genetycznych w przewlekłej białaczce szpikowej u chorych w różnych stadiach choroby przy zastosowaniu sekwencjonowania następnej generacji

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne

Promotor: prof. dr med. Tomasz Stokłosa

Zakład Immunologii / Zakład Biologii i Genetyki Nowotworów

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ABSTRACT

Characterization of new genetic aberrations by next-generation sequencing in patients with chronic myeloid leukemia at different stages of the disease.

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by a reciprocal chromosomal translocation t(9;22)(9q34;q11), resulting in the formation of the Philadelphia chromosome encoding the *BCR::ABL1* fusion oncogene. Despite successful therapy with tyrosine kinase inhibitors, some patients develop drug resistance that may be *BCR::ABL1*-dependent and independent. Next-generation sequencing (NGS) facilitates the search for genetic aberrations leading to the pathogenesis and progression of many diseases, including cancer. Hence, the goal of this dissertation was to characterize new genetic aberrations in CML patients with an unfavorable course of the disease. For this purpose, 45 samples from patients with CML progression to blast phase (CML-BP) and the corresponding samples, taken before the progression of CML available for 25 patients were sequenced using NGS. Mutation analysis of 193 genes related to oncogenesis and hematological malignancies revealed the presence of variants with potential prognostic and/or predictive significance. Point mutations and small insertions-deletions have been identified in genes frequently mutated in hematologic malignancies, such as *ABL1*, *ASXL1, RUNX1, DNMT3A* and *TP53*. Copy number variations (for *IKZF1, CDKN2A, CDKN2B, BCR::ABL1* genes) were observed only in CML-BP samples, while additional chromosomal abnormalities (such as monosomy of chromosome 7 and complex karyotype) were observed in CML-BP as well as in samples taken before progression of CML. Comparative analysis of point mutations, small insertions-deletions and copy number changes in 25 paired samples revealed 7 patterns of mutation dynamics resulting from mutations acquisition, persistence and clearance. In 12% of the paired samples (3/25), the germline processed pseudogene *SMAD4* (Ψ*SMAD4*) was identified, which has not yet been described in CML or other cancers. The screening study showed a significantly higher frequency of Ψ*SMAD4* in CML, but not in other types of leukemia, compared to the general Polish population. RNAseq analysis showed that Ψ*SMAD4* is not transcribed and therefore does not regulate expression of the parental gene or other unrelated genes. Except for the presence of Ψ*SMAD4*, the mutation profiles of patients with and without the pseudogene are similar.

Thus, it appears that Ψ*SMAD4* is a germline variant with no direct impact on CML progression, but its role in the pathogenesis of CML requires further research.