**Genomic Landscape of Pleural and Peritoneal Mesothelioma Tumors**

Stefanie Hiltbrunner1,2, Zoe Fleischmann3, Ethan S. Sokol3, Martin Zoche4,5, Emanuela Felley-Bosco6,2, Alessandra Curioni-Fontecedro1,2

Malignant pleural and peritoneal mesotheliomas are rare malignancies with an unacceptably poor prognosis and limited treatment options. The genomic landscape is mainly characterized by loss of tumor suppressor genes and mutations in DNA repair genes. Currently, data from next-generation sequencing (NGS) of mesothelioma tumors is restricted to a limited number of cases; moreover, data comparing molecular features of mesothelioma from pleural and peritoneal origin with NGS are lacking. Here, we have analyzed the largest cohort of patients with mesothelioma so far, for molecular alterations by NGS. These results indicate that molecular analysis for mesothelioma may inform clinical routine.

This analysis revealed 19 genes with an overall prevalence of at least 2%. Alterations in BAP1, CDKN2A, CDKN2B, NF2, MTAP, TP53, and SETD2 occurred with a prevalence of at least 10%. A) prevalence of alterations in the entire cohort, B) in pleural mesothelioma and C) in peritoneal mesothelioma. The alterations include short variants (short nucleotide variants (SNV) and insertion-deletions (indels)), gene rearrangements, copy number variations and multiple alterations.

**Background**

Malignant pleural and peritoneal mesotheliomas are rare malignancies with an unacceptably poor prognosis and limited treatment options. The genomic landscape is mainly characterized by loss of tumor suppressor genes and mutations in DNA repair genes. Currently, data from next-generation sequencing (NGS) of mesothelioma tumors is restricted to a limited number of cases; moreover, data comparing molecular features of mesothelioma from pleural and peritoneal origin with NGS are lacking. Here, we have analyzed the largest cohort of patients with mesothelioma so far, for molecular alterations by NGS. These results indicate that molecular analysis for mesothelioma may inform clinical routine.

**Materials and Methods**

We analyzed 1113 pleural mesothelioma and 355 peritoneal mesothelioma samples from patients sequenced through December 2020. All tumors were sequenced with the FoundationOne® or FoundationOne®CDx test for detection of substitutions, insertion-deletions, copy-number alterations and selected rearrangements in at least 324 cancer genes. Microsatellite instability was called on at least 95 loci and tumor mutational burden (TMB) was calculated on 0.8-1.2 Mb.

**Results**

1. Prevalence of genomic alterations

This analysis revealed 19 genes with an overall prevalence of at least 2%. Alterations in BAP1, CDKN2A, CDKN2B, NF2, MTAP, TP53, and SETD2 occurred with a prevalence of at least 10%. A) prevalence of alterations in the entire cohort, B) in pleural mesothelioma and C) in peritoneal mesothelioma. The alterations include short variants (short nucleotide variants (SNV) and insertion-deletions (indels)), gene rearrangements, copy number variations and multiple alterations.

2. Overview on genomic subgroups according to CDKN2A/B and BAP1 expression

Based on the most common alterations occurring, four distinct subgroups in pleural and peritoneal mesothelioma were identified. Due to large differences in the prevalence of the genomic alterations between pleural and peritoneal mesothelioma, the subgroups in pleural and peritoneal mesothelioma are defined by their different genomic makeup. In pleural mesothelioma, group 1 had alterations in CDKN2A/B and BAP1, group 2 in CDKN2A/B, group 3 in BAP1 only and group 4 neither in BAP1 nor in CDKN2A/B but in TP53. NF2 alterations were identified across all four groups. In peritoneal mesothelioma, group 1 was characterized by BAP1 expression, group 2 by NF2, group 3 by no expression of BAP1 and NF2. CDKN2A/B is expressed homogeneously throughout group 1-3. Group 4 had none of the major alterations.

3. Expression levels of targetable alterations

We have previously reported the case of a patient with peritoneal mesothelioma harboring an ALK translocation. The patient underwent targeted treatment and achieved a very good partial response (Rüschoff et al., 2019). Thus, we analysed the cohort for the presence of different druggable alterations and found targetable alterations in A) KRAS, EGFR, PDGFRA/B, ERBB2 and FGFR3, and B) alterations in genes part of the Hedgehog pathway PTCH1, PTCH2, SUFU, GLI1, and C) alterations in ALK.

**Conclusion**

Precision medicine including comprehensive genomic profiling has tremendously improved the outcome of patients, especially in lung cancer, breast cancer and melanoma. Nevertheless, rare malignancies and in malignancies with a low numbers of somatic mutations need to be analyzed to identify new therapeutic options for these difficult to treat cancers.