Title: ***Beta-2-microglobulin defects are associated with somatic mutations of DNA repair genes in Lynch syndrome-associated colorectal cancer***

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Abstract
Lynch Syndrome (LS) is caused by pathogenic germline variants in DNA mismatch repair genes. LS carriers have a high risk of developing colorectal cancers (CRC) displaying high levels of microsatellite instability (MSI). MSI leads to accumulation of frameshift insertions/deletions (indels) giving rise to neoantigens with high immunological potential.

We present a cohort of 58 CRCs from LS patients detected during colorectal surveillance (38 first and 20 metachronous cancers). Tumors were characterized by whole exome sequencing. We analyzed two different parameters on mutation load: the conventional tumor mutational burden (TMB) and the number of mononucleotide repeats (MNR), i.e. indels occurring at selected loci in coding genes.

Presence of a somatic DNA repair mutation (*MSH3, MSH6, POLD1, POLE*) correlated with a higher mutational load. *B2M* was mutated in 22.4% of tumors with an allele frequency average of 24.3% [min:11%; max:36%], indicative for presence of the mutation either in heterozygosis or in a fraction of tumor cells. *B2M* was mutated more frequently in first than metachronous tumors. *B2M* mutations were associated with the presence of a concomitant mutation in at least one of the DNA repair genes. Tumors bearing mutations in both *B2M* and in one of the DNA repair genes showed higher TMB and accumulation of indels than those with only the mutation in the DNA repair gene

The loss of function of *B2M* could be an immune evasion mechanism linked to the presence of excess neoantigens, suggesting that treatment during the early stages of tumor development could avoid immune evasion.