Lower degree of microsatellite instability in colorectal carcinomas from *MSH6*-associated Lynch syndrome patients

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Abstract

Background: Numerous observational and molecular studies focusing on Lynch syndrome (LS) have revealed significant variation in the phenotype and molecular characteristics among carriers of pathogenic variants in mismatch repair genes (*path_MMR*). Recently, we demonstrated that colorectal carcinomas in *path_MSH6* carriers exhibit fewer insertion/deletion mutations compared to CRCs from other MMR groups, raising the question of whether *MSH6*-mutated CRCs might display a lower degree of microsatellite instability (MSI).

Methods: Mutations at twenty coding microsatellites (cMS) were analyzed in 39 *MSH6-*, 18 *MLH1-*, 16 *MSH2-* and 22 *PMS2*-mutated CRCs and 35 sporadic MSI CRCs, and mutation frequencies and mutant allele ratios were compared among the different MMR-deficient groups. Considering factors such as *HLA-A**02:01 type, *B2M* status, and the anticipated immunogenicity of frameshift peptides derived from cMS mutations, the identified cMS mutation profiles of *MSH6*-mutated CRCs were further investigated to assess their potential impact on immunotherapeutic strategies.

Results: *MSH6*-mutated CRCs exhibited lower mutation frequencies and mutant allele ratios across most cMS. The cMS mutations in *MSH6*-mutated CRCs demonstrated inverse correlations with the

predicted immunogenicity of the resulting frameshift peptides, which may suggest negative selection of cell clones bearing highly immunogenic frameshift peptides.

Conclusions: *MSH6*-mutated CRCs display a lower degree of MSI, which may be connected to lower penetrance and later onset of the disease in *path_MSH6* carriers. Moreover, this lower MSI level may implicate an altered immune response compared to other MSI CRCs, which could have implications for the success of immunotherapy in *MSH6*-mutated CRCs. Future studies should carefully evaluate this possibility. If confirmed, these results would reinforce the notion of classifying LS as distinct syndromes associated with specific MMR genes.

Acknowledgements

The authors sincerely thank all patients and their families for their participation in this study. We gratefully acknowledge the PALGA-Group Collaborators/participating pathology centers for providing patient samples. The excellent technical assistance by Ricarda Mehr, Vera Fuchs, Jonathan Dörre, Nina Nelius, Marieke E. IJsselsteijn and Manon van der Ploeg are gratefully acknowledged. The authors thank Noel F.C.C. de Miranda for reviewing this work.