A personalized cancer vaccine approach to treat Lynch syndrome

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ABSTRACT

Monoallelic germline mutations in the DNA mismatch repair (MMR) pathway genes cause Lynch syndrome, wherein patients have a 70-80% lifetime risk of developing colorectal cancer (CRC). Mutations in MMR genes impair DNA repair leading to a hypermutated tumor phenotype (microsatellite-instability; MSI). In this study, we report a germline mutation in the MMR pathway gene-MLH1 (MutL homolog 1) in members of two unrelated Lynch Syndrome (LS)-affected families. Three of the four affected individuals progressed to develop colorectal cancer (CRC). We analyzed one colorectal tumor by exome and RNA sequencing to identify immunogenic peptides arising from somatic mutations to explore the feasibility of developing a personalized cancer vaccine approach for treatment. Our analysis revealed that 70% of the mutations in this subject were insertions/deletions (indels) which are likely to produce frameshifted proteins that terminated prematurely, creating loss-of-function protein products. We screened for immunogenic peptides using OncoPept*VAC*, a robust immunogenic peptide-prediction pipeline that employs TCR-peptide interaction as a key criterion of immunogenicity. We have validated our pipeline by identifying several immunogenic peptides from the Lynch syndrome subject that activated $CD8^+$ T cells in an ex vivo assay using patient-derived immune cells. These immunogenic peptides qualify as candidates for a personalized neoantigen-based vaccine therapy in combination with immune- checkpoint inhibitors for Lynch syndrome-tumor clearance. We propose that a similar neoantigen-based vaccine approach may also be considered as a preventive treatment option for carriers of MMR mutations to reduce their lifetime risk of developing colorectal cancer.