Whole Transcriptome Sequencing Reveals Somatic HMGCR Mutation in a Case of Pancreatic Adenocarcinoma with Long-Term Therapy Response

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Context: We merged clinical history of a locally advanced pancreatic cancer (LAPC) patient with data obtained from a whole transcriptome massively parallel sequencing (RNASeq). Case report: A 56-year-old man with histological diagnosis of LAPC. After obtained informed consent, we collected a fragment of pancreatic lesion. Patient received 6 induction cycles treatment with gemcitabine and oxaliplatin (GEMOX) from November 2011, followed by chemoradiotherapy with bi-weekly gemcitabine 50 mg/m² for 6 weeks. CT-scan demonstrated partial response, so patient received additional 12 cycles of GEMOX, with further response, which currently persist since 17 months (to 3.8 cm vs. 2.5 cm). At the same time, the RNASeq was performed at 75x2 bp on a HiScanSQ (Illumina Inc., San Diego, CA, USA) platform. Single nucleotide variants (SNVs) were detected with SNVMix2 and filtered on dbSNP, 1000 Genomes Project, and Cosmic databases. Non-synonymous SNVs were analyzed with SNPs&GO and PROVEAN. We highlighted the major oncogenic hits of LAPC, confirming KRAS mutations, CDKN2A and SMAD4 deletions. RNASeq analysis showed a somatic mutation p.H672D involving the catalytic domain of hydroxymethylglutaryl coenzyme A reductase (HMGCR), the rate-limiting enzyme in the mevalonate pathway, not yet reported neither in the COSMIC nor in the ICGC databases. Furthermore, 4 new genomic rearrangements leading to fusion genes emerged: 2 in-frame gene fusions regulating RAS-MAPK and apoptotic pathways (ANKRD44-GULP1 on chromosome 2; ATXN10-TMEM49; chromosome 22 and 17) and 2 out-of-frame fusions [t(15;3) and t(19;22)] leading to SMAD3-KIAA1143 and LTBP4-SPATS2L, both disrupting genes of the TGFbeta pathway. Conclusion: We found a novel somatic alteration involving HMGCR in LAPC. Due to the key role of HMGCR in cellular transformation, we hypothesize a strong potential in the development and outcome of LAPC, whose the optimal treatment remains to be elucidated. Trials that integrate RNASeq data with clinical options are needed.