Methodology for identification of clinically relevant targets for TCR-immunotherapy in hepatocellular carcinoma

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Background

Hepatocellular carcinoma (HCC) is a primary type of liver cancer that ranks as the fourth most leading cause of cancer-related deaths world-wide. Treatment options including ablation and chemotherapies are not always efficient to eliminate advanced HCC. Immunotherapies have general low response rates in advanced HCC patients, indicating that new approaches are needed in order to improve the current clinical responses.

Our main objective is to identify mutations that can be clinically relevant targets for T cell immunotherapy in HCC patients.

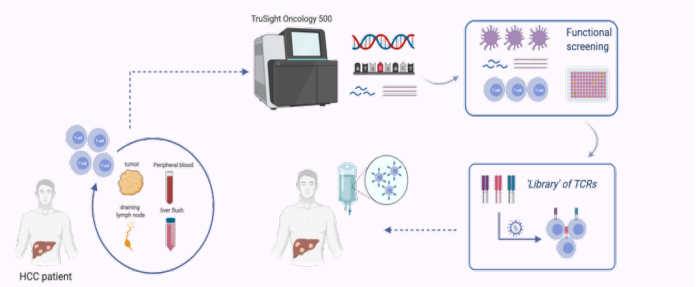

Figure 1. Methodology overview. From the explanted liver of HCC patients tumors, peripheral blood, lymph nodes and liver flush are collected as source for T cells. Here we present data from three advanced HCC patients that underwent liver transplantation. Tumors from the explanted livers were sequenced with the Illumina Trusight Oncology 500 platform. This platform allows to focus on clinically relevant tumor mutations and at the same time acquire information on the patient HLA restriction, in order to perform HLA binding prediction analysis. The mutations were ranked according to their specific relevance for HCC, presence of frequent substitutions (hot-spot) and likelihood of HLA binding. The screening of the synthesized peptides and minigenes encoding the top-ranking mutations for their ability to activate T cells is ongoing.

Results

The top ranking somatic mutations identified respectively for the three patients, are shown on table 1. Among those, we identified 'hot-spot' mutations in driver oncogenes such as the CTNNB1 and highly frequent HCC associated genes including the PIK3CA, CDKN2A and KMT2C.

For each frequent HLA allele such as A*01, A*02, A*03, B*47 and C*03 we identified peptides with high predicted binding affinity (figure 2).

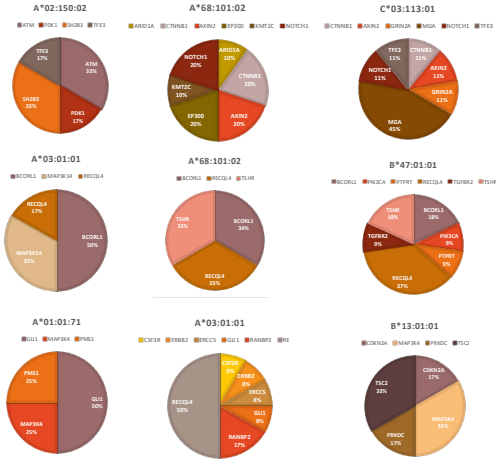

Figure 2. Representative charts on HLA binding prediction for each patient using the NetMHCpan 4.1 server. Different percentages of predicted binders based on the number of peptides identified at specific genes including driver oncogenes and highly relevant HCC genes.

Tumor 1	Tumor 2	Tumor 3
ARID1A	*BCORL1**	*CDKN2A**
*CTNNB1**	MAP3K14	*BRCA2**
ATM	*PIK3CA**	*CSF3R**
AXIN2	PTPRT	*ERBB2**
EP300	RECQL4	ERCC5
GRIN2A	TGFBR2	GLI1
KMT2B	TSHR	IRS2
*KMT2C**		KDM6A
MGA		IRS2
NOTCH1		KDM6A
NOTCH1		MAP3K4
*NOTCH2**		PMS1
PDK1		PRKDC
RPS6KB2		RANBP2
*SH2B3**		RECQL4
TFE3		TSC2

Table 1. Top ranking somatic mutations identified by Illumina Trusight Oncology 500 platform. Driver oncogenes in which 'hot-spot' mutations identified are underlined and pointed with asterisk (*).

Conclusions

Main findings:

- Identification of hot-spot mutations in driver oncogenes and highly frequent HCC associated genes.
- Potential high affinity binders for frequently expressed HLA class I alleles.

These data are increasing the likelihood of identifying T cell receptors that can be used for T cell-based immunotherapy broadly in a high number of cancer patients. The immunological testing of these mutations and the identification of specific T cell receptors is ongoing.

References

Eishiro Mizukosh & Shuichi Kaneko, 'Immune cell therapy for hepatocellular carcinoma', (2019) J Hematol Oncol.

Figure 1 was made in BioRender (BioRender.com)

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