Human leukocyte antigen (HLA) typing of a broad panel of cancer patient-derived xenograft (PDX) models for immune therapies

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Background

In immune-oncology research, an appropriate microenvironment for both human tumor cells and human immune cells is an important factor to enable personalized, preclinical studies. Humanized mouse models based on matching of human leukocyte antigen (HLA) profiles of patient-derived xenograft tumors (PDX) with compatible human immune cell populations can support the establishment of such an environment.

In this study, we determined individual HLA profiles of a broad panel of 453 PDX models from 19 different tumor entities. Furthermore, we performed comprehensive HLA matching analyses of all models and 19 healthy peripheral blood mononuclear cell (PBMC) donors.

Methods

HLA profiles of 453 established PDX models were determined with seq2HLA[I] R-package and the Hapl-o-Mat[II] software based on RNA-sequencing data. To estimate the representativeness of the generated HLA profile portfolio, it was compared with HLA allele and haplotype frequencies of the representative population of 8862 healthy German stem cell donors (GSCD) provided by The Allele Frequency Net Database[III]. To enable the generation of humanized mouse models based on mutually compatible PDX models and healthy PBMC donors, HLA profile matching analyses of all PDX and 19 PBMC donors were performed according to donor-recipient HLA matching criteria recommended by the Blood and Marrow Transplant Clinical Trials Network[IV].

Results

The individual PDX HLA profiles in 4-digit resolution comprise information of HLA class I, II und non-class loci. Comparative analyses revealed that frequencies of PDX HLA alleles and haplotypes are comparable with frequencies of the representative GSCD population. More than 50 % of the PDX profiles reveal allele homozygosity at ≥1 HLA class I loci. These high proportions of homozygosity were likewise reported in the literature and may serve as prognostic markers for cancer progression[V].

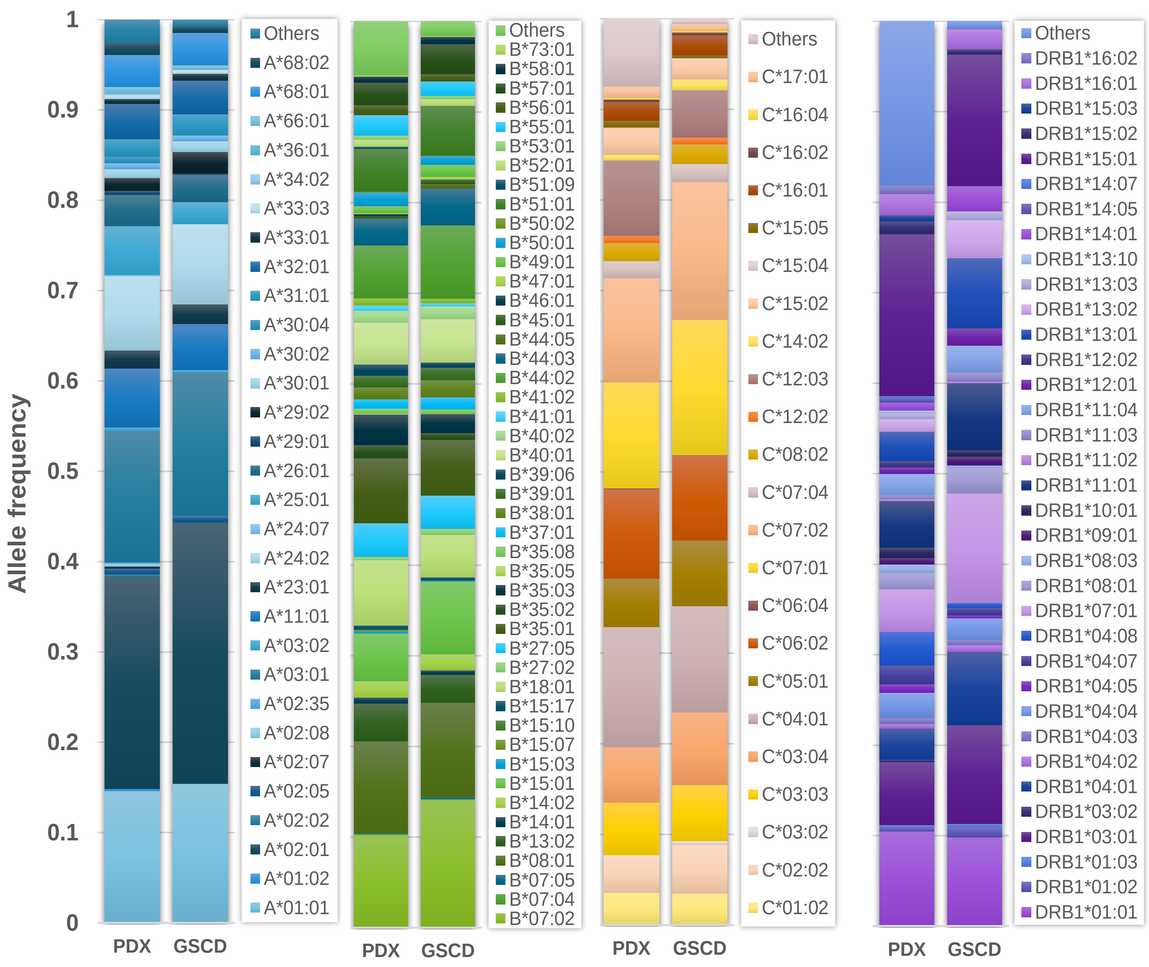

Fig. 1: Comparison of HLA-A, -B, -C (class I) and -DRB1 allele frequencies (AF) of PDX and GSCD. 30 out of 37 PDX HLA-A alleles match those of the GSCD population and account for 99.3 % GSCD-AF (HLA-B: 46/79 PDX alleles ≙ 98.4 % GSCD-AF; HLA-C: 23/27 PDX alleles ≙ 99.5 % GSCD-AF; HLA-DRB1: 35/56 PDX alleles ≙ 99.3 % GSCD-AF)

Table 1: Comparison of class I~DRB1 haplotype frequencies (HF > 1%) of PDX and GSCD

PDX HLA haplotypes	PDX HF (%)	GSCD HLA haplotypes	GSCD HF (%)
A*02:01~B*07:02~C*07:02~DRB1*15:01	**4.095**	**A*01:01-B*08:01-C*07:01-DRB1*03:01**	**5.826**
A*01:01~B*08:01~C*07:01~DRB1*03:01	**3.381**	**A*02:01-B*07:02-C*07:02-DRB1*15:01**	**2.181**
A*03:01~B*07:02~C*07:02~DRB1*15:01	**2.381**	A*02:01-B*15:01-C*03:04-DRB1*04:01	1.286
A*03:01~B*35:01~C*04:01~DRB1*01:01	**2.000**	A*02:01-B*44:02-C*05:01-DRB1*04:01	1.207
A*01:01~B*08:01~C*07:06~DRB1*03:01	1.667	**A*03:01-B*07:02-C*07:02-DRB1*15:01**	**3.843**
A*01:01~B*08:01~C*07:01~DRB1*15:01	1.143	**A*03:01-B*35:01-C*04:01-DRB1*01:01**	**1.540**
A*01:01~B*50:01~C*06:02~DRB1*07:01	1.143	A*29:02-B*44:03-C*16:01-DRB1*07:01	1.005
A*25:01~B*67:02~C*12:03~DRB1*15:01	1.143		

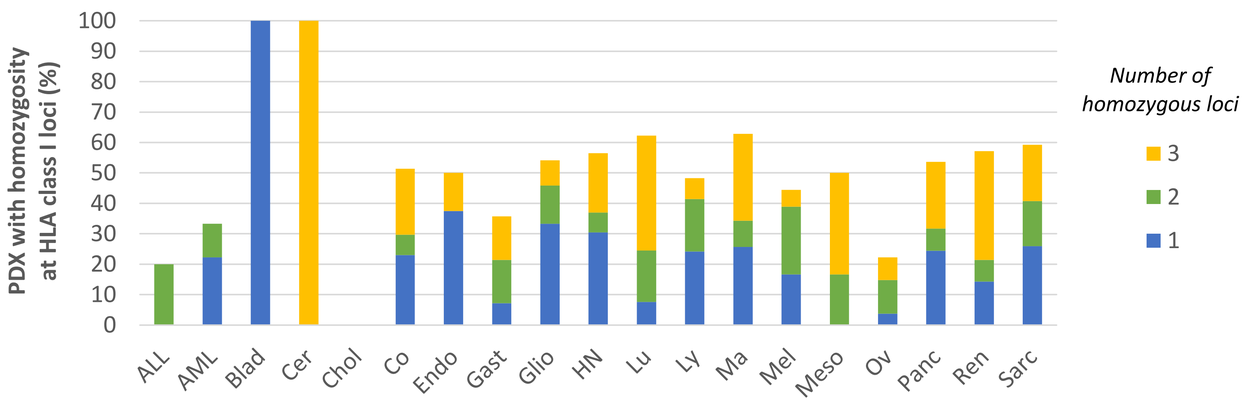

Fig. 2: Homozygosity at HLA class I loci. ≥ 50 % of PDX models from bladder, cervical, colon, endometrial, head and neck, lung, mammary, pancreatic and renal cell carcinoma as well as from glioma, mesothelioma and sarcoma are homozygous at ≥ 1 class I loci.

HLA profile matching of PDX models and PBMC donors resulted in 121 matches including PDX from 16 tumor entities. Exemplarily, the dependence of HLA-matching for the therapy efficacy was shown for a head and neck squamous cell cancer (HNSCC) PDX mouse model humanized with PBMCs from 3 different donors.

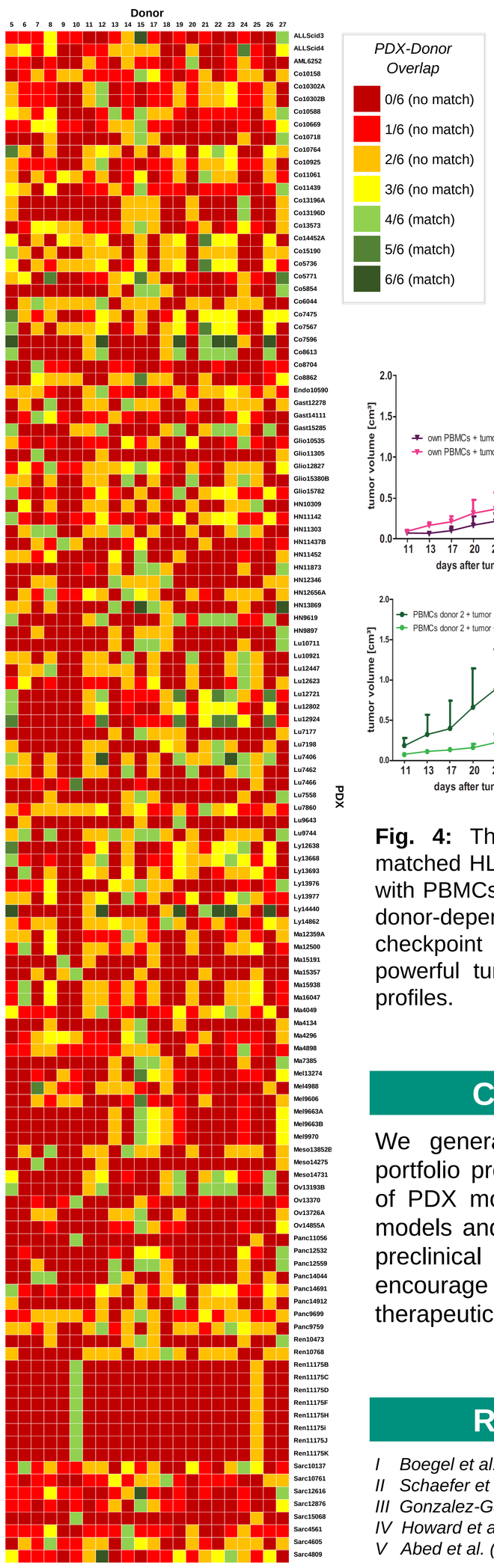

Fig. 3: HLA profile matching analyses resulted in 121 PDX-donor matches in 16 entities. For a match, PDX and donor should be ≥ 4/6 match at HLA-A (2-digit resolution), HLA-B (2-digit resolution) and HLA-DRB1 (4-digit resolution).

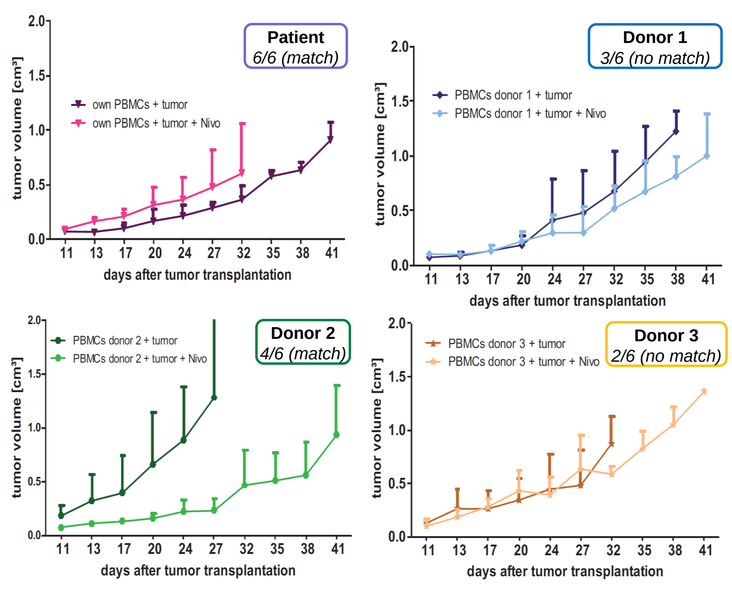

Fig. 4: The comparison of matched and non-matched HLA profiles of a HNSCC PDX humanized with PBMCs from the patient and 3 donors shows a donor-dependent tumor growth. Treatment with checkpoint inhibitor Nivolumab caused a more powerful tumor growth inhibition in matched HLA profiles.

Conclusion

We generated a comprehensive HLA profile portfolio providing information on a broad panel of PDX models. Matched HLA profiles of PDX models and PBMC donors enable personalized, preclinical immune-oncology studies to encourage the development of novel immune-therapeutic strategies.

References

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