Inferring the Correlation Between Incidence Rates of Melanoma and the Average Tumor-specific Epitope Binding Ability of HLA Class I Molecules in Different Populations

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TREOS CANCER VACCINE TECHNOLOGY

#1423P

Abstract

Background
Human Leucocyte Antigen (HLA) molecules are encoded by the most polymorphic genes in the human genome. The genetic variation of these genes are considerable across different geographic subpopulations. We hypothesised that this genetic variation might contribute to the risk of melanoma both at population and subject level.

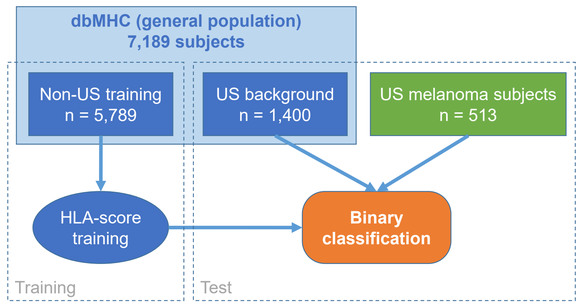
Methods
We developed a cancer risk predictor based on the complete HLA class I genotype of individuals. The HLA-score, used in the predictor describes the ability of the HLA class I alleles of an individual to bind epitopes derived from 48 selected tumor antigens as an indicator of the breadth of the tumor-specific T-cell responses. We collected HLA data for subjects from 20 different geographic regions (ethnic populations) (n = 3278) as well as the corresponding melanoma incidence rates. The average HLA-scores were compared to the incidence rates. We also classified a mixed US population consisting of melanoma and healthy subjects based on their HLA-score.

Results
On population level, we found significant correlation between the incidence rates of melanoma and average HLA-scores in different geographic regions (R^2 = 0.5005; p < 0.001; n = 20; df = 18). The highest average HLA-scores (range 75-140) were obtained for the Far East Asian and Pacific regions, where the incidence rates are low (0.4-3.4 per 100,000 per year). The lowest average HLA-scores (range 50-90) were obtained in the European and US regions, where the rates are high (12.6-13.8 per 100,000 per year). On subject level, the risk ratio between the riskiest (HLA-score <34) and the most protected groups (HLA-score ≥96) was 5.69 comparing the top and bottom 20% of the HLA-score distribution (p < 0.05). These HLA-score ranges are consistent with the threshold values separating populations with low and high incidence rates of melanoma.

Conclusions
By developing a novel HLA-score determined by autologous HLA allele binding epitopes of tumor antigens, we showed that individuals with HLA allele sets supporting broader tumor-specific T-cell responses have lower risk of developing melanoma. These results imply that the HLA genotype and HLA-score could be used to determine the immunogenetic risk of melanoma.

Study design

The 7,189 subjects in the dbMHC database[1] were split into the US (n = 1,400) and non-US (n = 5,789) subjects. The non-US subjects were used to train the HLA-score binary classifier, while the US background subjects were used for testing the method together with the US cancer subjects (n = 513).

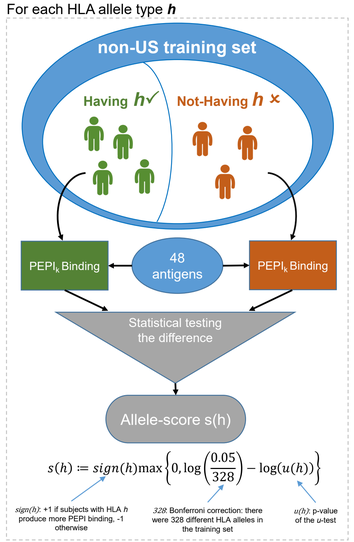


Computing the HLA-score

For each HLA allele, we computed a significance score (Allele-score) based on how significant the difference of epitope binding ability is between subjects having and not having the HLA allele in question. The more significant the difference is, the larger the significance score is in absolute value. HLA-epitopes were predicted on 48, tumor specific antigens frequently expressed in multiple tumors.
Several potential scoring schemes were considered based on how to compute epitope binding ability. We applied our PEPI (Personal EPItope) concept, where $PEPI_k$ means that only those epitopes are considered which can be bound by at least k HLA alleles of a person. The best classification has been achieved when k was set to 3.

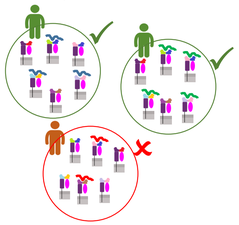
Computing the significance score

For each HLA allele type ***h***

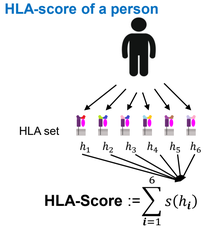


PEPI concept in computing epitope binding ability

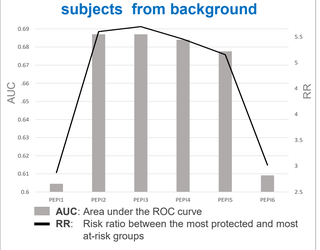
Example: PEPI (generally PEPI3): only those epitopes are considered that can be bound by at least 3 HLA alleles of a person.



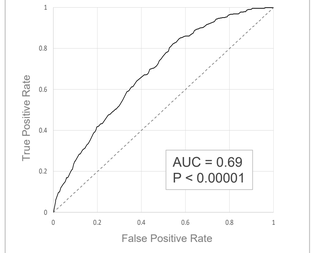
HLA-score of a person



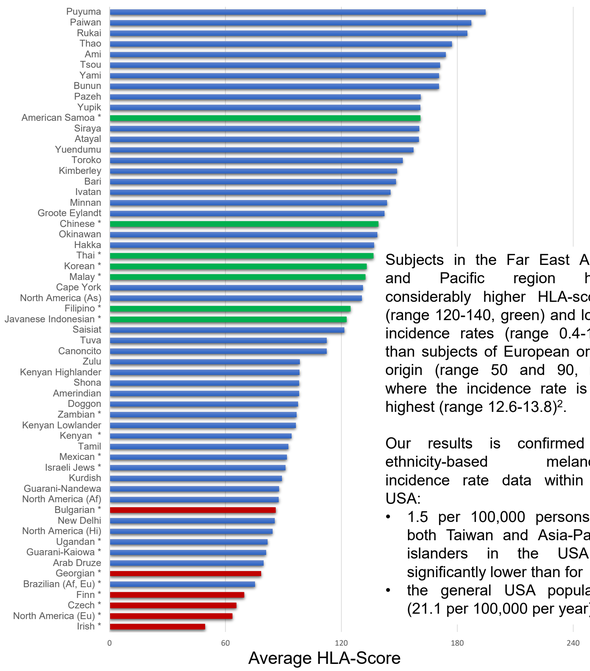
Best classification achieved with PEPI3 for separation of US melanoma subjects from background



ROC curve of the HLA score with PEPI3



HLA score in different ethnic populations



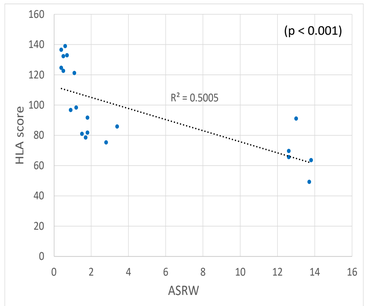
Subjects in the Far East Asian and Pacific region have considerably higher HLA-scores (range 120-140, green) and lower incidence rates (range 0.4-1.8)[2] than subjects of European or US origin (range 50 and 90, red) where the incidence rate is the highest (range 12.6-13.8)[2].

Our results is confirmed by ethnicity-based melanoma incidence rate data within the USA:

- 1.5 per 100,000 persons for both Taiwan and Asia-Pacific islanders in the USA is significantly lower than for
- the general USA population (21.1 per 100,000 per year),

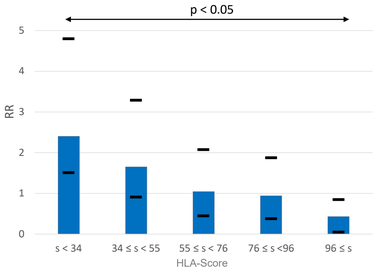
Significant correlation between HLA score and melanoma incidence rates in 20 countries

We identified 20 countries (***on the figure above***) with HLA genotype data from their dominant ethnicity, for which we determined the mean HLA-scores and compared them with the incidence rates of melanoma[2]. The countries with low and high melanoma incidence rates are well separated by an apparent HLA-score of >80 threshold, which is consistent with the threshold values separating low and high risk subjects in the US (HLA-score ≥96).



The Relative Risk (RR) in different subgroups of a mix US population based on HLA-score

Test population, n=1913 (general and melanoma subjects) were divided into five equal-size subgroups based on their HLA-score (s). The Relative Risk (RR) of each subgroup was computed.



- Subjects with the highest immunological risk of developing melanoma (6.1%) are in the lowest HLA-score subgroup (s<34). Since the average lifetime risk of melanoma in the USA is 2.6%[3], a subject in the s<34 subgroup has 2.3 fold higher risk for melanoma than an average USA subject.
- In contrast, the subgroup with the highest HLA-score (96<s) represents subjects with the lowest immunological risk of developing melanoma (1.1%). A subject in this subgroup has 0.42 fold lower risk than an average subject in the USA.

HLA-score for the prediction of cancer risk in different indications

We also tested the HLA-score method for other indicators. In 5 from the 6 other indications, the achieved AUC value was significant

Cancer type	Cohort Size	Relative Risk (RR)		$RR_{extremities}$	AUC	p
		Risk Grp*	Protected Grp*			
Melanoma	513	2.34	0.41	5.69	0.69	<0.001
Lung (NSCLC)	370	1.84	0.41	4.49	0.66	<0.001
Renal cell	129	1.73	0.51	3.41	0.63	<0.001
Colorectal	121	1.28	0.55	2.35	0.55	0.008
Bladder	87	1.89	0.46	4.14	0.66	<0.001
Glioma	82	1.83	0.48	3.81	0.63	<0.001
Head and neck	58	1.21	0.51	2.38	0.62	0.001

Conclusions

- We showed here that HLA genotype affects a person's risk of developing cancer through an immunological mechanism – ie. epitope binding ability of the autologous HLA alleles
- This further confirms our PEPI concept for the prediction of patient's antigen-specific immune responses based on their complete HLA-genotype[4,5].
- HLA-score predictor can be used as biomarker to identify subjects with increased immunological cancer risk.
- Eg: the 2.35–5.69 $RR_{extremities}$ for different cancers is either comparable or exceeds the 2.64 risk ratio of BRCA2 carriers comparing the top and bottom 5%[6,7].
- Genetic testing should include determining the subject's HLA genotype and calculating the HLA-score to better assess hereditary risks of cancer.

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