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HLA traits linked to development of head and neck squamous cell carcinoma affect the progression-free survival of patients

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ABSTRACT

Background: Personalized medicine and treatment stratification of patients with head and neck squamous cell carcinoma (HNSCC) today mostly ignore genetic heterogeneity in HNSCC but especially the patient's genetic background. We hypothesized that particular human leukocyte antigen (HLA) class I (HLA-A, B, Cw) and II proteins (DR, DQ) confer susceptibility for and influence development of HNSCC and may be prognostic factors for progression-free survival (PFS).
Methods: 90 consecutive HNSCC patients of the prospective observational cohort study LIFE treated between 08/2010 and 05/2011 at the University Leipzig underwent low resolution typing of HLA-A, B, Cw, DR, and DQ. Antigen and haplotype frequencies were compared to those in German blood donors. Effects on PFS were analyzed using Kaplan-Meier curves and Cox models.
Results: HNSCC patients had overall altered HLA-B frequencies ($P < 0.05$); frequencies of B∗44 were lower, those of B∗13, B∗52, and B∗57 increased ($P < 0.05$). Almost all other antigen frequencies showed no deviation. Homozygous HLA-Cw and DRB4 were frequent and associated with reduced PFS ($P < 0.05$). Altered haplotype frequencies were common and particular haplotypes accompanied by differing PFS. B∗13/Cw∗06 carriers had poorest outcome ($P = 0.011$). However, multivariate Cox proportional hazard models revealed 3 clinical covariates (localization oropharynx, loco-regional metastasis, and T4 category), HPV16-DNA positivity, and 10 HLA traits as independent predictors for PFS.
Conclusions: The relevance of the genetic background of HNSCC patients calls for future research to clarify the role of HLA traits in HNSCC and if PFS depends on HLA.
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Introduction

Main risk factors for carcinogenesis of head and neck squamous cell carcinoma (HNSCC) are tobacco and/or alcohol consumption. Since exposure to both lifestyle factors is followed by immunotoxicity, genotoxicity, mutagenesis plus increased expression of cytokines and growth factors resulting in loss of proliferation control, the reasons for developing HNSCC and relapses appear to be obvious. Also the sexually transmitted and persistent infection with oncogenic high-risk subtypes of the human papillomavirus (HPV) poses a risk for developing oropharyngeal HNSCC. However, not every person with oropharyngeal HPV infection or a risky lifestyle regarding alcohol and tobacco consumption suffers later from HNSCC. Moreover, the risk for development of HNSCC is increased by genetic variants in genes encoding enzymes involved in DNA repair or metabolism of alcohol [1–4]. They also increase the risk independent of lifestyle-associated risk factors. For instance, Fanconi anemia patients have a 700-fold increased risk for HNSCC and high rate of relapses [5,6]. Therefore, genetic heterogeneity may account for altered risk of developing HNSCC but also affect progression-free survival (PFS).

Genetic instability leads to somatic mutations which mostly are controlled by the immune system. Higher cancer incidences accompany immune defects in the T-cell system. Since T-cell responses to peptides of oncogenes critically depend on binding and proper presentation [7] by human leukocyte antigen (HLA) class I (HLA-A, B, Cw) and II proteins (DR, DQ, DP), particular HLA antigens and their combinations (haplotypes) could be involved

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in immune escape of HNSCC. Tumor-associated antigens (TAA) and in particular neoantigens generated by somatic mutations or viruses (*e.g.* antigens from HPV) might escape immune surveillance due to inability of particular HLA proteins to sufficiently bind peptides of TAA leading to severely diminished or even absent presentation of these peptides. The varying capability of particular HLA proteins to sufficiently present peptides [7] might specifically lower or increase immune surveillance and be responsible for altered allele and haplotype frequencies in HNSCC and different PFS. Homozygous HLA alleles should limit immune surveillance further, wherefore homozygous HLA alleles could increase the risk for development of HNSCC and affect PFS of HNSCC patients. Only a few studies investigated HLA antigen frequencies in HNSCC and moreover ended up with inconclusive results [8,9]. Therefore, the potential impact of HLA traits on development of HNSCC and also the risk for relapse is almost completely ignored in HNSCC clinical trials but might partly explain unresolved issues of unexpected outcome variance. To assess allele frequencies and the potential impact of HLA traits on PFS, low resolution HLA typing of leukocytes from consecutively recruited 90 HNSCC patients was performed.

Materials and methods

Patients and study population

Blood samples were from histopathologic confirmed HNSCC patients of white Caucasian genetic descent treated between 08/2010 and 05/2011 at the ENT Department of the University Hospital Leipzig. 21 of the 90 patients participated in the induction-chemotherapy trials DeLOS-II (NCT00508664; n = 12) and TISOC-1 (NCT01108042; n = 9) [10,11], while the other where treated according to guidelines and decision of the interdisciplinary head & neck tumor conference of the University Hospital Leipzig (Table 1). For HLA typing, genomic DNA was isolated from leukocytes [12] of blood samples taken after obtaining written patient's informed consent as approved by the ethics committee of the Medical Faculty of the University Leipzig (votes 201-10-12072010 & 202-10-12072010). The HPV status was assessed as described [13]. At time of analyses, patients were under follow up for about three years (median 35.1 months; IQR 19.6–40.3 months).

HLA typing

Low-resolution DNA-typing by PCR-SSP for HLA-A, B, Cw, HLA-DRB1/3/4/5, and DQB1 was performed using Histo Type ABC low and Histo Type DR/DQB low (BAG, Lich, Germany) according to the manufacturer's protocols. All samples with homozygous or ambiguous result underwent second low-resolution typing using AllSet+™ Gold low resolution SSP (Invitrogen, Darmstadt, Germany) according to the manufacturer's protocols by using the software UniMatch® Plus 5.0 (Invitrogen).

Calculation of allele and haplotype frequencies and statistical analysis

Frequencies (f) of HLA in HNSCC patients were compared to published frequencies in German stem cell [14] and blood donors [15] using Pearson's χ^2-test [16]. Odds ratios (OR = ad/bc) and the relative risk (RR = ac/bd) inclusive their 95% confidence intervals (95% CI) were calculated [16]. $P \leq 0.05$ was considered significant. The numbers of distinguishable alleles were 22 (HLA-A), 34 (HLA-B), 14 (HLA-Cw), 5 (DQB1), 13 (HLA-DRB1), plus presence of DRB3, DRB4, and DRB5. Phenotypic combinations of antigens coded by different loci were used as estimated haplotypes [17–19].

Table 1
Main characteristics of the 90 head and neck squamous cell carcinoma (HNSCC) patients investigated.

Covariate	Category	n	(%)
Sex	Female	12	(13.3)
	Male	78	(86.7)
Localization	Oropharynx	28	(31.1)
	Other	62	(68.9)
	Oropharynx	28	(31.1)
	Hypopharynx	20	(22.2)
	Larynx	24	(26.7)
	Other	18	(20.0)
T category	Tx	1	(1.1)
	T1	13	(14.4)
	T2	21	(23.3)
	T3	21	(23.3)
	T4a	32	(35.6)
	T4b	2	(2.2)
N category	N0	32	(35.6)
	N1	7	(7.8)
	N2a	5	(5.6)
	N2b	22	(24.4)
	N2c	9	(10.0)
	N3	5	(5.6)
N category	N0	32	(35.6)
	N+	58	(64.4)
M category	M0	87	(96.7)
	M1	3	(3.3)
Stage	UICC I	8	(8.9)
	UICC II	11	(12.2)
	UICC III	9	(10.0)
	UICC IVA	53	(58.9)
	UICC IVB	6	(6.7)
	UICC IVC	3	(3.3)
Stage	Early	19	(21.1)
	Advanced	71	(78.9)
Tobacco smoking behavior	Nonsmoker	19	(21.1)
	Smoker	70	(77.8)
	Missing	1	(1.1)
	Nonsmoker	19	(21.1)
	<10 pack years	2	(2.2)
	10 < 20 pack years	5	(5.6)
	20 < 30 pack years	8	(8.9)
	30 < 40 pack years	26	(28.9)
	≥40 pack years	29	(32.2)
	Missing	1	(1.1)
Alcohol consumption	No	9	(10.0)
	Yes	80	(88.9)
	Missing	1	(1.1)
Alcohol consumption category	0	10	(11.1)
	>0 < 30 g/d	31	(34.4)
	30 < 60 g/d	24	(26.7)
	≥60 g/d	24	(26.7)
	Missing	1	(1.1)
HPV status	High-risk HPV-DNA+	17	(18.9)
	HPV16-DNA+	13	(14.4)
	HPV16 DNA+RNA+	8	(8.9)
Therapy	Surgery (Op)	19	(21.1)
	Radiotherapy (RT)	6	(6.7)
	Op+PORT	19	(21.1)
	Op+PORChT	16	(17.8)
	Primary concurrent RChT	3	(3.3)
	DeLOS-II (IC+RT)	12	(13.3)
	TISOC 1	13	(14.4)
	Best supportive care (BSC)	2	(2.2)
Therapies applied	Monomodal	25	(27.8)
	Multimodal	63	(70.0)
	BSC	2	(2.2)
	Received Op	68	(75.6)
	No	22	(24.4)
	Received RT	69	(76.7)
	No	21	(23.3)

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