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A loss-of-function polymorphism in *ATG16L1* compromises therapeutic outcome in head and neck carcinoma patients

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ABSTRACT

The anticancer immune response is shaped by immunogenic cell stress and death pathways. Thus, cancer cells can release danger-associated molecular patterns that act on pattern recognition receptors expressed by dendritic cells and their precursors to elicit an antitumor immune response. Here, we investigated the impact of single nucleotide polymorphisms (SNPs) in genes affecting this cancer-immunity dialogue in the context of head and neck squamous cell carcinoma (HNSCC). We observed that homozygosity for a loss-of-function SNP (rs2241880, leading to the substitution of a threonine residue in position 300 by an alanine) affecting autophagy related 16 like 1 *(ATG16L1)* is coupled to poor progression-free survival in platinum-treated HNSCC patients. This result was obtained on a cohort of patients enrolled at the Gustave Roussy Cancer Campus and was validated on an independent cohort of The Cancer Genome Atlas (TCGA). Homozygosity in rs2241880 is well known to predispose to Crohn's disease, and epidemiological associations between Crohn's disease and HNSCC have been reported at the levels of cancer incidence and prognosis. We speculate that rs2241880 might be partially responsible for this association.

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Introduction

Head and neck squamous cell carcinoma (HNSCC) is a frequent cancer derived from the mucosal epithelium of the upper respiratory tract (nasal cavity and paranasal sinuses, larynx) and upper digestive tract (oral cavity and pharynx).[1–7] HNSCC is determined by well-known risk factors (age, alcohol abuse, tobacco, and human papillomavirus (HPV)) that benefits from early detection, yet is difficult to treat due to the frequent incidence of comorbidities.[8–21] Surgical removal of the tumor (if operable) is usually followed by adjuvant chemotherapy and/or radiotherapy, and prognosis is determined by localization, size, histological grade, HPV status, presence of local and distant metastases, as well as comorbidities.[22–32] There is abundant evidence that infiltration of HNSCC by cytotoxic T lymphocytes (CTL) impacts prognosis in a favorable fashion, while immunosuppressive regulatory T cell (Treg) indicates poor prognosis.[33–41] Moreover, HNSCC often responds to immunotherapy targeting the programmed death protein 1 (PD1)/programmed death-ligand 1 (PD-L1) interaction.[42–52]

In the past, we observed that a set of single-nucleotide polymorphisms (SNPs) affecting a set of genes involved in the immunogenic cell death (ICD) process[1,53–65] dictate the response to adjuvant chemotherapy of breast and colorectal cancer patients.[66,67] This process involves pattern recognition receptors[68–70] (such as formyl peptide receptor 1 (FPR1);[71–76] purinergic receptor P2X, ligand-gated ion channel, 7 (P2RX7)[77–82] and toll like receptor 4 (TLR4)[83–88]) that can be mutated in substantial fraction of the world population (allelic frequency of rs867228 in *FPR1*: ~20%; rs3751143 in *P2RX7*: ~19%; rs4986790 in *TLR4*: ~6%). Moreover, ICD involves autophagy,[89–97] which can be compromised by a loss-of-function polymorphism (rs2241880, allelic frequency ~50%) in autophagy related 16 like 1 (ATG16L1).[98] This SNP, which predisposes to inflammatory bowel disease (IBD) if present in homozygosity,[99–103] compromises autophagic flux and related vesicular trafficking processes.[104–108]

Driven by this consideration, we wondered whether such SNPs might impact the therapeutic response of HNSCC patients as well. Here, we show that a loss-of-function

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polymorphism in the gene coding for *ATG16L1* is associated with poor prognosis of HNSCC patients undergoing platinum-based adjuvant chemotherapy.

Materials and methods

Patients and study design

Two-hundred forty-two head and neck squamous cell carcinoma (HNSCC) patients were enrolled in the study. In accordance with national and European legislation, the institutional review board approved the study, and written informed consent was obtained from all the included patients as to the use of their tissue samples for research purposes. A retrospective chart review followed by prospective survival data was conducted on all patients diagnosed between 2004 and 2009 at the Gustave Roussy Cancer Center. Paraffin-embedded tumor blocks (obtained at the time of surgery) were collected. The amount and quality of 193 paraffin blocks were judged adequate for histological evaluation. DNA from tumor specimens was extracted, yielding sufficient material to analyze specimens from 187 patients (180 for rs867228) related to missing information in the clinical database.

Tobacco and alcohol consumption were a common feature of all patients enrolled in this study. Tumor localization and human papilloma virus (HPV) status (for naso- and oropharyngeal cancer) were investigated to consider all relevant clinicopathological variables. Distant metastases were observed in only two patients, and this covariate has been discarded in the analysis. This cohort included mostly male patients (83.4% men *versus* 16.6% women), and tumors were usually located in the pharynx (60. 4%) and larynx (25.1%). Most (80.2%) of the patients were diagnosed with stage IV and 19.8% with stage III disease. All patients received platinum/5-fluorouracil-based induction chemotherapy, followed by platinum-based maintenance chemoradiotherapy. Almost half of the patients received taxane-based therapy (8.3% docetaxel and 42.5% paclitaxel).

The Cancer Genome Atlas (TCGA) clinical data was downloaded from Huang et al.[109]

Genotyping. Genomic DNA was isolated from paraffin-embedded tumors by means of the DNeasy blood and tissue kit (Qiagen, Valencia, CA) or Maxwell 16 FFPE Tissue LEV DNA Purification kit (Promega, Madison, WI, USA). Gene-specific primers and genotype-specific probes (Life Technologies, Carisbad, CA, USA) were used to amplify the rs2241880 single nucleotide polymorphism (SNP) affecting autophagy related 16 Like 1 (*ATG16L1*), rs867228 in the formyl peptide receptor 1 *(FPR1)* gene, rs3751143 in the purinergic receptor P2X, ligand-gated ion channel, 7 *(P2RX7)* gene and rs4986790 in the toll like receptor 4 *(TLR4)* gene. Genotypes were determined by comparing the signals from fluorescent probes (FAM and VIC) and by calculating the natural logarithm of the ratio between FAM and VIC signals (log (FAM/VIC)).

Statistical analyses. Progression-free survival (PFS) and overall survival (OS) determined from the date of diagnosis were used as primary end-points. Cox proportional hazards regression modeling was employed to check the association between survival and SNPs coded by two different models (dominant or recessive). Dominant or recessive models were evaluated independently as long as the proportion of cases in the smallest group was greater than 5% (Gustave Roussy cohort, hereafter called IGR cohort) or if there were more than 10 platinum-treated patients in the subgroup (TCGA platinum-based patients). For the IGR cohort, the most suitable model was selected on the basis of the smallest p value as determined by the likelihood ratio test (LRT). Hazard ratios alongside their 95% confidence intervals are presented for the model including the SNP alone and after accounting for nodal status (pN, N0 *versus* N1 *versus* N2 *versus* N3), tumor stage (pT, T0-1 *versus* T2 *versus* T3 *versus* T4) and tumor location (oral cavity *versus* larynx *versus* pharynx). Association with clinicopathological parameters (age at diagnosis, tumor size, nodal status, tumor stage and tumor localization) was estimated using Firth's penalized-likelihood logistic regression (dominant and recessive models) and reported as odds ratio alongside 95% confidence interval and p values. Survival rates were estimated using Kaplan-Meier method. For TCGA, as previously reported[110,111] clinical data were accessed via the TCGAbiolinks R package. The groups were compared using the two-sided Mann–Whitney U test. PFS and OS were used as primary end-points and were determined either for the entire cohort of patients or the subgroups receiving platinum-based chemotherapy. According to the number of patients and events by genotype, PFS and OS for the whole HNSCC TCGA population were plotted over 200 months while PFS and OS for the platinum-based subgroups were plotted over 80 and 100 months, respectively.

Results and discussion

Driven by previous results from our laboratory, we profiled a cohort of 187 advanced HNSCC patients (Table 1) for SNPs affecting a set of ICD-relevant genes. DNA samples from these patients, treated at the Gustave Roussy Cancer Campus (also known as Institut Gustave Roussy (IGR)) with platinum-based induction chemotherapy followed by platinum-based maintenance chemoradiotherapy, were genotyped at several loci, including *ATG16L1* (r2241880),[99,100] *FPR1* (rs867228),[66,110,67,110,112,113] *P2RX7* (rs3751143)[113–117] and *TLR4* (rs4986790).[114,115,118–123] All SNPs were found at frequencies that did not differ from those reported for the general Caucasian population.

The effect of each SNP on progression-free survival (PFS) and overall survival (OS) was determined (Table 2). Firstly, we compared patients that were homozygous for the wild type alleles of *FPR1* (Table 3) or *P2RX7* (Table 3) with

Table 1. Clinical and histopathological characteristics of HNSCC patients belonging to IGR cohort.

Variable	n	(%)
Sex		
Female	31	16.6
Male	156	83.4
Grade		
III	37	19.8
IV	150	80.2
T of TNM		
0	1	0.5
1	9	4.8
2	24	12.9
3	77	41.4
4	75	40.3
n.a.	1	0.5
N of TNM		
0	52	27.8
1	22	11.8
2	74	39.6
3	39	20.9
M of TNM		
0	187	100,0
HPV		
no	173	92.5
yes	14	7.5
Localization		
Larynx	47	25.1
Maxillofacial	5	2.7
Oral cavity	22	11.8
Pharynx	113	60.4

Abbreviations: HPV, human papilloma virus; M, metastasis; N, lymph node; n.a., not available; T, tumor size; TNM, Tumor-Node-Metastasis.

those bearing one or two copies of the loss-of-function alleles (GT/TT for *FPR1* and AC/CC for *P2RX7*), and then plotted the Kaplan–Meier survival curves for PFS and OS. Notably, *FPR1* (Table 4, **Figures S1A** and **S1B**) *P2RX7* (Table 4, **Figures S2A** and **S2B**) polymorphisms completely failed to influence progression-free or overall survival of HNSCC patients. Additionally, as previously described by Bergmann and colleagues,[124] we noticed a weak but non-significant ($p < .0658$, HR 2.2, CI [1.03;4.7]) effect, of rs4986790 in *TLR4* on PFS but not OS (Tables 3 and 4, **Figures S3A** and **S3B**). To corroborate these results in an independent cohort of patients, we interrogated The Cancer Genome Atlas (TCGA) database[125] and found that neither *FPR1* nor *TLR4* nor *P2RX7* polymorphisms impacted the investigated endpoints in HNSCC patients (Table 5**, Figures S1C, S1D, S2C, S2D, S3C**, and **S3D**). This held true for *P2RX7* and *TLR4* also upon the stratification of patients based on their allocation to platinum-based chemotherapy (Table 5**, Figures S2E, S2F, S3E** and **S3F**).

Interestingly, in the TCGA dataset, patients bearing $FPR1^{GT}$ and $FPR1^{TT}$ genotypes exhibited an improved OS and PFS compared to $FPR1^{GG}$ individuals (Table 5**, Figures S1E** and **S1F**). This effect was absent in larger and more homogeneous cohorts of HNSCC cancer (such as the IGR cohort where PFS $p < .9802$, HR 1.01, CI [0.6;1.68] and OS $p < .3935$, HR 0.82, CI [0.52;1.29]). Additionally, our group has recently described that FPR1-relevant SNP E346A correlates with early diagnosis in TCGA HNSCC patients,[110] suggesting that in this cancer context only homozygosity might impact OS and PFS. Altogether, these data call for further analyses in other cohorts.

By analogy to previous results obtained for non-small cell lung carcinoma patients,[114] we hypothesized that the intrinsic characteristics of HNSCC (which near-to-always is chemoresistant and associated with poor prognosis) and/or the type of therapy that is employed to treat this malignancy (which is mainly based on cisplatin, a DNA damaging agent that is weak ICD inducer) may explain why the aforementioned SNPs fail to influence the clinical progression of the HNSCC.[126–130]

One of the ICD-relevant pathways involves the autophagy-dependent lysosomal secretion of adenosine triphosphate (ATP), the ligand of P2RX7.[131–136] The relevance of the autophagic pathway in the context of the HNSCC has already been described: rs1864183 in *ATG10*, rs3759601 in *ATG2B* and rs2241880 in *ATG16L1* were found to be associated with an higher susceptibility to develop HNSCC (laryngeal, pharyngeal, and oral carcinoma, respectively) in a Spanish population.[137] Given these premises, we decided to investigate the role of rs2241880 in our cohort of patients, knowing that rs2241880 affects *ATG16L1*, which encodes a central adaptor required for the formation of the autophagosome.[135,138–141] Moreover, rs2241880, which consists in an A > G mutation, leading to the substitution of a threonine residue in position 300 to an alanine (the risk allele), sensitizes ATG16L1 to GGhomoe-3 mediated degradation, culminating in decreased autophagy.[100,142] Since the most common genotype $ATG16L1^{AG}$ does not cause a full loss-of-function,[100,142] a recessive genetic model was applied for this gene. Patients with the $ATG16L1^{GG}$ genotype exhibited significantly reduced PFS, independently of major clinicopathological variables both in IGR and in the TCGA (platinum-based) cohorts. We found an effect of the rs2241880 SNP on PFS (Tables 3 and 4, Figure 1a, $p < .0062$, HR 1.95, CI [1.22;3.12]), but not OS (Tables 3 and 4, Figure 1b, $p < .9687$, HR 0.99, CI [0.63;1.57]) of HNSCC IGR patients. Similarly, TCGA patients treated with platinum-based chemotherapy and carrying the $ATG16L1^{GG}$ genotype displayed reduced PFS (Table 5, Figure 2c, $p < .042$, HR 0.53, CI [0.28;0.98]) and OS (Table 5, Figure 2d, $p < .005$, HR 0.36, CI [0.18;0.74]). This effect was not observed for the entire cohort (Table 5, Figure 2a and 2b). Altogether, our results confirm that an impaired autophagic machinery culminates in an unsuccessful ICD, underscoring the likely relevance of this pathway in HNSCC patients receiving platinum-based chemoradiotherapy.

It should be noted that rs2241880 has been associated with inflammatory bowel disease, in particular Crohn's disease.[143–147] Several studies have been performed to evaluate the putative association between IBD and HNSCC

Table 2. Association between clinical variables and progression-free survival or overall survival. Significant *p* values are indicated in italic.

		PFS			OS		
Variable	**Distribution (%)**	**HR CI**	**p value**	**LRT (*p* value)**	**HR CI**	**p value**	**LRT (*p* value)**
Gender							
Female	31			*5.76*			1.39
	16.6			*p<0.02*			*p*<0.24
Male	156	0.51	*0.02*		0.73 [0.44;1.22]	0.24	
	83.4	[0.3;0.86]					
Age							
0-50	40			2.17			4.21
	21.4			*p*<0.33			*p*<0.12
51-65	116	0.66	0.14		0.68	0.13	
	62	[0.38 ;1.14]			[0.41;1.11]		
>65	31	0.77	0.47		1.08	0.8	
	16.6	[0.37 ;1.59]			[0.59;1.99]		
HPV							
negative	173			3.74			2.5
	92.5			*p<0.05*			*p*<0.11
positive	14	0.35	*0.05*		0.47	0.11	
	7.5	[0.1 ;1.25]			[0.16 ;1.36]		
T of TNM							
0-1	10			*11.74*			*14.56*
	5.4			*p<0.008*			*p<0.002*
2	24	0.72 [0.2;2.54]	0.61		0.56	0.3	
	12.9				[0.19;1.63]		
3	77	0.64	0.46		0.49 [0.2 ;1.24]	0.16	
	41.4	[0.21 ;1.98]					
4	75	1.48	0.46		1.13	0.77	
	40.3	[0.49;4.48]			[0.46;2.78]		
N of TNM							
0	52			*8.83*			*12.88*
	27.8			*p<0.03*			*p<0.005*
1	22	1.42	0.38		1.3	0.48	
	11.8	[0.65;3.12]			[0.63;2.7]		
2	74	1.61	0.11		1.65	0.07	
	39.6	[0.87;2.95]			[0.95;2.85]		
3	39	2.71	*0.003*		2.91	*0.0004*	
	20.9	[1.39;5.29]			[1.6;5.3]		
Localisation							
Oral cavity	22			*13.55*			*19.83*
	11.8			*p<0.004*			*p<0.0002*
Maxillofacial	5	1.63	0.4		0.74	0.55	
	2.7	[0.54;4.95]			[0.25;2.13]		
Larynx	47	0.29	*0.004*		0.24	*<1e^{-04}*	
	25.1	[0.13;0.66]			[0.12;0.48]		
Pharynx	113	0.43	*0.02*		0.29	*<1e^{-04}*	
	60.4	[0.22;0.84]			[0.16;0.51]		

Abbreviations: CI, confidence interval; HPV, human papilloma virus; HR, hazard ratio; LRT, likelihood ratio test; M, metastasis; N, lymph node; OS, overall survival; PFS, progression-free survival; T, tumor size; TNM, Tumor-Node-Metastasis.

susceptibility, development, or outcome.[137,148–151] Particularly, in a large cohort of IBD patients (more than 7000), rs2241880 has been correlated with an increased risk of developing oral (especially tongue) carcinoma.[149] Similarly, a Dutch study reported that IBD is associated with impaired survival of patients with oral cavity carcinoma and that advanced age at IBD diagnosis can be considered as a risk factor for the development of this malignancy.[150]Additionally, IBD patients are more prone to develop mouth cancer, and the mechanisms of carcinogenesis may be linked to long-lasting inflammation, immunosuppressive treatments and to their HPV status.[151] The role of *ATG16L1* loss-of-function alleles has also been reported for other cancers than HNSCC. Indeed, rs2241880 has been described as a risk factor both for developing hepatocellular carcinoma in the context of cirrhosis,[152] breast cancer,[153] and gastric cancer.[154] Moreover, the *ATG16L1*^{AG} genotype was found to be associated with an earlier age at diagnosis of melanoma.[155] All these observations underscore the implications of *ATG16L1* T300A in several types of cancer and, more specifically, its prognostic value in HNSCC.

In summary, it appears that rs2241880 in *ATG16L1* has a negative prognostic impact on a segment of patients with HNSCC, in particular those who undergo platinum-based chemotherapy. Although there is no formal evidence for this conjecture, it is tempting to speculate that the well-studied association between IBD and poor-prognosis HNSCC is in part determined by rs2241880, knowing that this SNP is among the major predisposing factors for the development of

Table 3. Correlation between genotypes and clinicopathological parameters. Significant *p* values are indicated in italic.

	ATG16L1						FPR1						P2RX7						TLR4				
	Genotype						Genotype						Genotype						Genotype				
	AA or AG	GG	OR		LRT		GG	GT or TT	OR		LRT		AA	AC or CC	OR		LRT		AA	AG	OR		LRT	
Variable	n (%)	n (%)	CI	pvalue	p value	p value	n (%)	n (%)	CI	pvalue	p value	p value	n (%)	n (%)	CI	p value	p value	p value	n(%)	n (%)	CI	p value	p value	p value
Gender																								
Female	24	7			*0.25*	0.5669	25	6			3.26	0.0696	18	13			0.2	0.6672	26	5			6.87	*0.0035*
	17.5	14			*p < .6158*		20.8	10			*p < .0712*		15.7	18.1			*p < .06510*		14.7	50			*p < .0087*	
Male	113	43	1.25	0.6158			95	54	0.45	0.07			97	59	0.84	0.651			151	5	0.17	*0.009*		
	82.5	86	[0.535;3.239]				79.2	90	[0.164;1.069]				84.3	81.9	[0.388;1.839]				85.3	50	[0.048;0.629]			
Age																								
0–50	28	12			0.3	0.8709	30	9			2.36	0.3007	24	16			0.9	0.6451	40	0			2.91	0.2364
	20.4	24			*p < .08604*		25	15			*p < .3073*		20.9	22.2			*p < .6373*		22.6	0			*p < .2337*	
51–65	86	30	0.80	0.5871			71	41	0.54	0.13			74	42	0.85	0.6563			108	8	6.35	0.1		
	62.8	60	[0.372;1.798]				59.2	68.3	[0.226;1.187]				64.3	58.3	[0.41;1.776]				61	80	[0.761;827.383]			
>65	23	8	0.83	0.7126			19	10	0.58	0.3			17	14	1.23	0.6639			29	2	6.86	0.15		
	16.8	16	[0.287;2.29]				15.8	16.7	[0.2;1.647]				14.8	19.4	[0.481;3.153]				16.4	20	[0.533;960.621]			
HPV																								
negative	126	47			0.11	0.6407	113	53			1.89	0.1683	107	66			0.15	0.7278	163	10			0.21	0.3552
	92	94			*p < .7364*		94.2	88.3			*p < .1691*		93	91.7			*p < .6980*		92.1	100			*p < .6445*	
positive	11	3	0.81	0.7364			7	7	0.47	0.17			8	6	1.24	0.6980			14	0	0.54	0.64		
	8	6	[0.199;2.578]				5.8	11.7	[0.16;1.39]				7	8.3	[0.408;3,584]				7.9	0	[0.004;4.571]			
T of TNM																								
0–1	6	4			1.73	0.6268	8	2			2.34	0.4715	6	4			1.72	0.6375	10	0			0.04	0.898
	4.4	8			*p < .6299*		6.7	3.3			*p < .5044*		5.2	5.6			*p < .6325*		5.6	0			*p < .998*	
2	19	5	0.41	0.2521			13	10	0.38	0.22			13	11	1.23	0.7767			23	1	1.34	0.86		
	13.9	10	[0.086;1.929]				10.8	16.7	[0.061;1.755]				11.3	15.3	[0.294;5.465]				13	10	[0.066;202.326]			
3	55	22	0.59	0.4259			53	22	0.70	0.63			45	32	1.032	0.9619			73	4	1.29	0.86		
	40.1	44	[0.161;2.295]				44.2	36.7	[0.125;2.792]				39.1	44.4	[0.288;3.997]				41.2	40	[0.123;174.97]			
4	57	18	0.46	0.2624			46	25	0.54	0.39			50	25	0.729	0.6351			71	4	1.32	0.85		
	41.6	36	[0.126;1.841]				38.3	41.7	[0.096;2.132]				43.5	34.7	[0.202;2.847]				40.1	40	[0.126;179.882]			
n.a.	0	1					0	1					1	0					0	1				
	0	2					0	1.7					0.9	0					0	10				
N of TNM																								
0	37	15			2.87	0.3982	34	16			0.06	0.9961	35	17			1.44	0.6854	48	4			1.28	0.6123
	27	30			*p < .4123*		28.3	26.7			*p < .996*		30.4	23.6			*p < .6972*		27.1	40			*p < .7344*	
1	17	5	0.76	0.63			14	7	0.93	0.88			14	8	1.189	0.7404			22	0	0.24	0.26		
	12.4	10	[0.23;2.261]				11.7	11.7	[0.325;2.759]				12.2	11.1	[0.417;3.281]				12.4	0	[0.002;2.397]			
2	58	16	0.68	0.3531			47	24	0.93	0.85			42	32	1.551	0.2369			70	4	0.69	0.59		
	42.3	32	[0.304;1.535]				39.2	40	[0.428;1.981]				36.5	44.4	[0.751;3.267]				39.5	40	[0.17;2.787]			
3	25	14	1.376	0.4752			25	13	0.90	0.82			24	15	1.283	0.5679			37	2	0.72	0.68		
	18.2	28	[0.571;3.319]				20.8	21.7	[0.373;2.203]				20.9	20.8	[0.543;3.032]				20.9	20	[0.12;3.434]			
Localization																								
Oral cavity	19	3			3.9	0.2336	12	9			0.99	0.7852	13	9			2.38	0.4564	20	2			3.37	0.3869
	13.9	6			*p < .2721*		10	15			*p < .8039*		11.3	12.5			*p < .4968*		11.3	20			*p < .3385*	
Maxillofacial	4	1	0.98	0.5858			3	1	1.77	0.58			4	1	0.474	0.4533			4	1	2.73	0.4		
	2.9	2	[0.153;15.305]				2.5	1.7	[0.241;20.594]				3.5	1.4	[0.042;3.138]				2.3	10	[0.213;26.562]			
Larynx	37	10	1.56	0.5019			32	15	1.59	0.38			25	22	1.254	0.6583			45	2	0.45	0.4		
	27	20	[0.443;6.764]				26.7	25	[0.557;4.521]				21.7	30.6	[0.461;3.498]				25.4	20	[0.065;3.105]			
Pharynx	77	36	2.624	0.0888			73	35	1.57	0.35			73	40	0.783	0.602			108	5	0.42	0.3		
	56.2	72	[0.873;10.396]				60.8	58.3	[0.605;3.995]				63.5	55.6	[0.316;2.003]				61	50	[0.093;2.438]			

Abbreviations: ATG16L1, autophagy related 16-like 1; CI, confidence interval; FPR1, formyl peptide receptor 1; HPV, human papilloma virus; LRT, likelihood ratio test; M, metastasis; N, lymph node; n.a., not available; OR, odds ratio; P2RX7, purinergic receptor P2X, ligand-gated ion channel. 7; T, tumor size; TLR4, toll like receptor 4; TNM, Tumor-Node-Metastasis.

Table 4. Correlation between SNPs mutational status and progression-free survival or overall survival in IGR patients affected by HNSCC.

			PFS		OS	
Gene	ID	Genetic model	HR	p value	HR	p value
ATG16L1	rs2241880	RecessiveAA/AG *vs* GG	1.95 [1.22;3.12]	***p* < .0062**	0.99 [0.63;1.57]	*p* < .9687
FPR1	rs867228	DominantGG *vs* GT/TT	1.01 [0.6;1.68]	*p* < .9802	0.82 [0.52;1.29]	*p* < .3935
P2RX7	rs3751143	DominantAA *vs* AC/CC	2.18 [0.83;5.73]	*p* < .1536	0.75 [0.49;1.15]	*p* < .1779
TLR4	rs4986790	DominantAA *vs* AG	2.2 [1.03;4.7]	*p* < .0658	1.86 [0.87;3.98]	*p* < .1363

Abbreviations: ATG16L1, autophagy Related 16 Like 1; FPR1, formyl peptide receptor 1; HR, hazard ratio; IGR, Gustave Roussy Cancer Campus; P2RX7, purinergic receptor P2X, ligand-gated ion channel, 7; PFS; progression-free survival; OS, overall survival; TLR4, toll like receptor 4. Significant *p* values are indicated in bold.

Table 5. Correlation between SNPs mutational status and progression-free survival (PFS) or overall survival (OS) in TCGA HNSCC patients. According to the number of patients and events by genotype, PFS and OS for the whole HNSCC TCGA population were plotted over 200 months while PFS and OS for the platinum-based subgroups were plotted over 80 and 100 months, respectively. Significant *p* values are indicated in bold.

HNSCC TCGA population								Platinum-based HNSCC TCGA population							
				PFS		OS						PFS		OS	
Gene	**Genotype**			**HR**	***p* value**	**HR**	***p* value**	**Gene**	**Genotype**			**HR**	***p* value**	**HR**	***p* value**
	AA(n)	AG(n)	GG(n)	GG *versus* AA or AG		GG *versus* AA or AG			AA(n)	AG(n)	GG(n)	GG *versus* AA or AG		GG *versus* AA or AG	
ATG16L1	130	277	118	1.05 (0.78–1.4)	0.776	0.92 (0.67–1.26)	0.604	***ATG16L1***	25	42	20	0.53 (0.28–0.98)	**0.042**	0.36 (0.18–0.74)	**0.005**
FPR1	GG(n)	GT(n)	TT (n)	GG *versus* GT or TT		GG *versus* GT or TT		***FPR1***	GG (n)	GT (n)	TT (n)	GG *versus* GT or TT		GG *versus* GT or TT	
	320	179	26	0.88 (0.69–1.13)	0.318	0.88 (0.67–1.16)	0.364		54	26	7	0.43 (0.22–0.82)	**0.011**	0.4 (0.18–0.89)	**0.026**
P2RX7	AA (n)	AC (n)	CC (n)	AA *versus* AC or CC		AA *versus* AC or CC		***P2RX7***	AA (n)	AC (n)	CC (n)	AA *versus* AC or CC		AA *versus* AC or CC	
	356	156	13	1.01 (0.78–1.31)	0.924	0.98 (0.73–1.31)	0.902		58	27	2	0.76 (0.41–1.4)	0.378	0.5 (0.23–1.13)	0.095
TLR4	AA (n)	AG (n)	GG (n)	AA *versus* AC or CC		AA *versus* AC or CC		***TLR4***	AA (n)	AG (n)	GG (n)	AA *versus* AC or CC		AA *versus* AC or CC	
	458	67	0	0.74 (0.49–1.09)	0.134	0.7 (0.44–1.11)	0.134		74	13	0	1.24 (0.55–2.8)	0.603	1.84 (0.75–4.51)	0.185

Abbreviations: ATG16L1, autophagy related 16-like 1; FPR1, formyl peptide receptor 1; HR, hazard ratio; P2RX7, purinergic receptor P2X, ligand-gated ion channel. 7; OS, overall survival; PFS, progression-free survival; TLR4, toll like receptor 4).

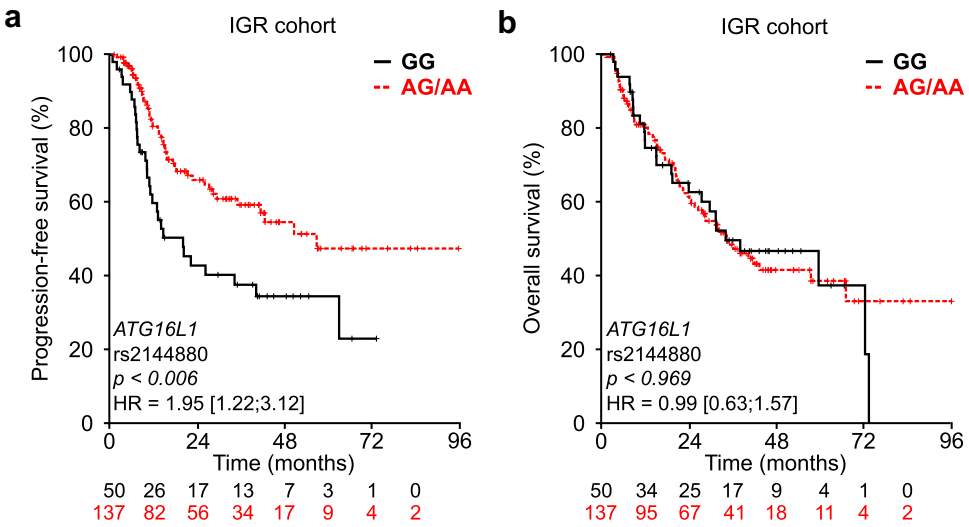

Figure 1. Kaplan-Meier estimates of progression-free survival (a) and overall survival (b) in HNSCC patients belonging to the IGR cohort and harboring AG (Thr300Ala) or AA (Thr300Thr) genotype of *ATG16L1* rs2144880 SNP compared to patients carrying the variant alleles GG (Ala300Ala).

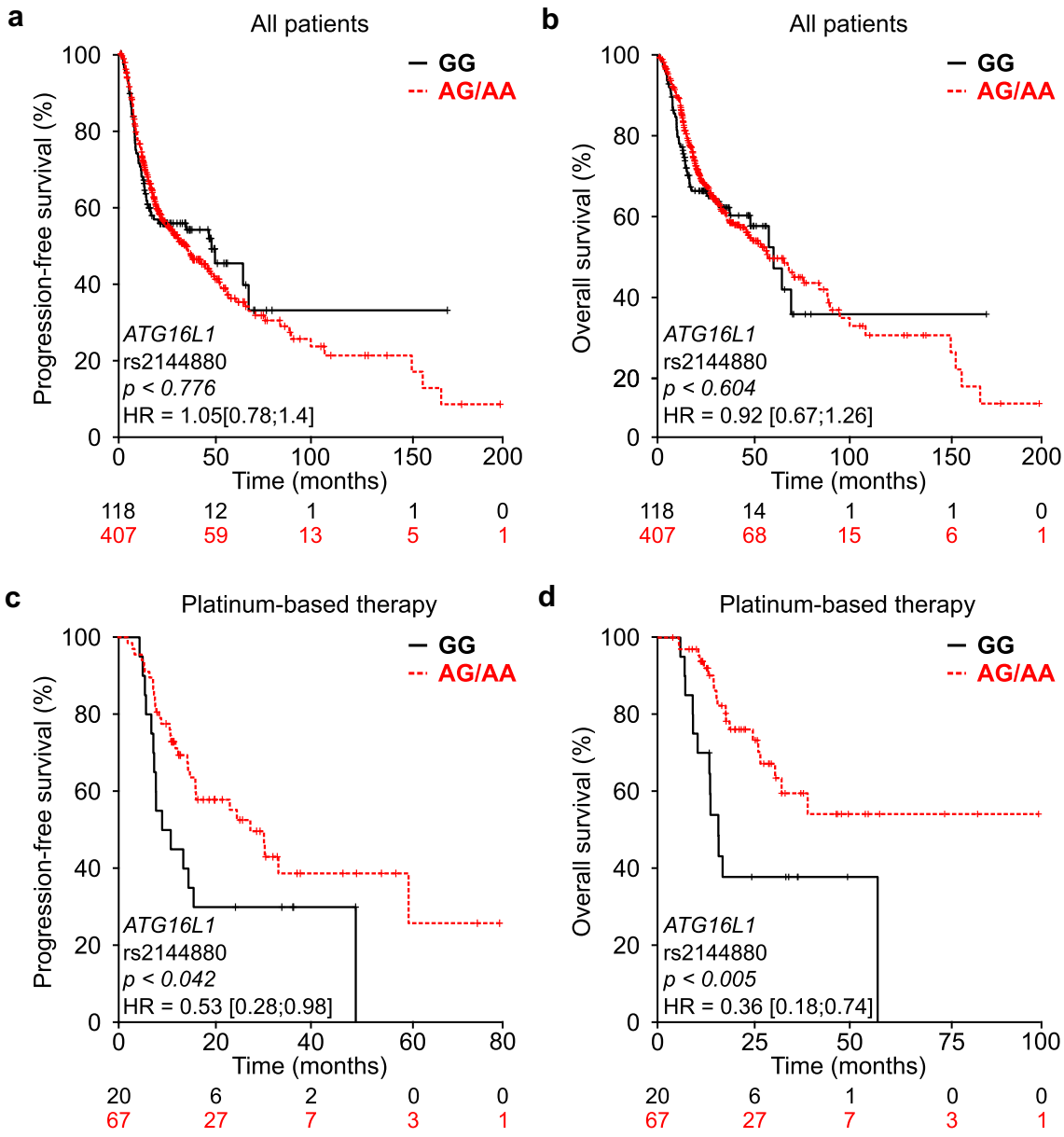

Figure 2. Kaplan-Meier estimates of progression-free survival (PFS) and overall survival (OS) in HNSCC TCGA patients and harboring AG (Thr300Ala) or AA (Thr300Thr) genotype of *ATG16L1* rs2144880 SNP compared to patients carrying the variant alleles GG (Ala300Ala). PFS (a and c) or OS (b and d) according to *ATG16L1* genotype in all HNSCC (a and b) or platinum-based therapy treated (c and d) patients.

Crohn's disease. Future studies should investigate this possible mechanistic link.

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E.V., J.L.N. performed the experiments. V.M. cut the paraffin blocks. Z.S., V.C. and S.Z., performed clinical analysis. L.G., S.T. helped in designing the clinical studies. O.C evaluated the amount and quality of the tumor material and the HPV status. E.V., L.G. and G.K. conceived and directed the project. J.L.N., E.V. and G.K. wrote the manuscript.

Data availability

The IGR data that support the findings of this study are available on reasonable request from the corresponding authors. Patient-specific IGR data are not publicly available due to ethical restrictions. The TCGA data that support the findings of this study are openly available at http://cancergenome.nih.gov.

References

1. Leemans CR, Snijders PJF, Brakenhoff RH. The molecular landscape of head and neck cancer. Nat Rev Cancer. 2018;18(5):269–282. doi:10.1038/nrc.2018.11.
2. Mody MD, Rocco JW, Yom SS, Haddad RI, Saba NF. Head and neck cancer. Lancet. 2021;398(10318):2289–2299. doi:10.1016/S0140-6736(21)01550-6.
3. Sundermann BV, Uhlmann L, Hoffmann J, Freier K, Thiele OC. The localization and risk factors of squamous cell carcinoma in the oral cavity: a retrospective study of 1501 cases. J Craniomaxillofac Surg. 2018;46:177–182. doi:10.1016/j.jcms.2017.10.019.
4. Orru G, Mameli A, Demontis C, Rossi P, Ratto D, Occhinegro A, Piras V, Kuqi L, Berretta M, Taibi R, et al. Oral human papilloma virus infection: an overview of clinical-laboratory diagnosis and treatment. Eur Rev Med Pharmacol Sci. 2019;23(18):8148–8157. doi:10.26355/eurrev_201909_19035.
5. Gregoire V, Grau C, Lapeyre M, Maingon P. Target volume selection and delineation (T and N) for primary radiation treatment of oral cavity, oropharyngeal, hypopharyngeal and laryngeal squamous cell carcinoma. Oral Oncol. 2018;87:131–137. doi:10.1016/j.oraloncology.2018.10.034.
6. Economopoulou P, de Bree R, Kotsantis I, Psyrri A. Diagnostic tumor markers in head and neck squamous cell carcinoma (HNSCC) in the clinical setting. Front Oncol. 2019;9:827. doi:10.3389/fonc.2019.00827.
7. Kline ER, Muller S, Pan L, Tighiouart M, Chen ZG, Marcus AI. Localization-specific LKB1 loss in head and neck squamous cell carcinoma metastasis. Head Neck. 2011;33(10):1501–1512. doi:10.1002/hed.21638.
8. Szturz P, Cristina V, Herrera Gomez RG, Bourhis J, Simon C, Vermorken JB. Cisplatin eligibility issues and alternative regimens in locoregionally advanced head and neck cancer: recommendations for clinical practice. Front Oncol. 2019;9:464. doi:10.3389/fonc.2019.00464.
9. Dillon MT, Harrington KJ. Human Papillomavirus-Negative Pharyngeal Cancer. J Clin Oncol. 2015;33(29):3251–3261. doi:10.1200/JCO.2015.60.7804.
10. Ragin CC, Modugno F, Gollin SM. The epidemiology and risk factors of head and neck cancer: a focus on human papillomavirus. J Dent Res. 2007;86(2):104–114. doi:10.1177/154405910708600202.
11. Sturgis EM, Wei Q, Spitz MR. Descriptive epidemiology and risk factors for head and neck cancer. Semin Oncol. 2004;31(6):726–733. doi:10.1053/j.seminoncol.2004.09.013.
12. Isayeva T, Li Y, Maswahu D, Brandwein-Gensler M. Human papillomavirus in non-oropharyngeal head and neck cancers: a systematic literature review. Head Neck Pathol. 2012;6(S1):S104–20. doi:10.1007/s12105-012-0368-1.
13. Stein AP, Saha S, Kraninger JL, Swick AD, Yu M, Lambert PF, Kimple RJ. Prevalence of human papillomavirus in oropharyngeal cancer: a systematic review. Cancer J. 2015;21(3):138–146. doi:10.1097/PPO.0000000000000115.
14. Bulbul MG, Genovese TJ, Hagan K, Rege S, Qureshi A, Varvares MA. Salvage surgery for recurrent squamous cell carcinoma of the head and neck: systematic review and meta-analysis. Head Neck. 2022;44(1):275–285. doi:10.1002/hed.26898.
15. Silverman DA, Lin C, Tamaki A, Puram SV, Carrau RL, Seim NB, Eskander A, Rocco JW, Old MO, Kang SY, et al. Respiratory and pulmonary complications in head and neck cancer patients: evidence-based review for the COVID-19 era. Head Neck. 2020;42(6):1218–1226. doi:10.1002/hed.26217.
16. Akhter M, Rahman QB, Rahman QB, Molla MR. A study on histological grading of oral squamous cell carcinoma and its co-relationship with regional metastasis. J Oral Maxillofac Pathol. 2011;15(2):168–176. doi:10.4103/0973-029X.84485.
17. Dougherty MI, Dougherty W, Kain JJ, Hughley BB, Shonka DC Jr., Fedder KL, Jameson MJ. Non-HPV-related head and neck squamous cell carcinoma in a young patient cohort. Ear Nose Throat J. 2021;100(10_suppl):1101S–6S. doi:10.1177/0145561320935839.
18. Goldstein DP, Irish JC. Head and neck squamous cell carcinoma in the young patient. Curr Opin Otolaryngol Head Neck Surg. 2005;13(4):207–211. doi:10.1097/01.moo.0000170529.04759.4c.
19. van Monsjou Hs, Wreesmann VB, van den Brekel Mw, Balm AJ, van Monsjou HS, van den Brekel MWM. Head and neck squamous cell carcinoma in young patients. Oral Oncol. 2013;49(12):1097–1102. doi:10.1016/j.oraloncology.2013.09.001.
20. Zatterstrom UK, Wennerberg J, Ewers SB, Willen R, Attewell R. Prognostic factors in head and neck cancer: histologic grading, DNA ploidy, and nodal status. Head Neck. 1991;13(6):477–487. doi:10.1002/hed.2880130603.
21. Cardin GB, Bernard M, Bahig H, Nguyen-Tan PF, Ballivy O, Filion E, Soulieres D, Philouze P, Ayad T, Guertin L, et al. Single nucleotide polymorphism rs6942067 is a risk factor in young and in non-smoking patients with hpv negative head and neck squamous cell carcinoma. Cancers (Basel). 2019;12.
22. Guidi A, Codeca C, Ferrari D. Chemotherapy and immunotherapy for recurrent and metastatic head and neck cancer: a systematic review. Med Oncol. 2018;35(3):37. doi:10.1007/s12032-018-1096-5.

23. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nat Rev Dis Primers. 2020;6(1):92. doi:10.1038/s41572-020-00224-3.
24. Maxwell JH, Grandis JR, Ferris RL. HPV-associated head and neck cancer: unique features of epidemiology and clinical management. Annu Rev Med. 2016;67(1):91–101. doi:10.1146/annurev-med-051914-021907.
25. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, Jones CU, Sur R, Raben D, Jassem J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006;354(6):567–578. doi:10.1056/NEJMoa053422.
26. Gillison ML, Trotti AM, Harris J, Eisbruch A, Harari PM, Adelstein DJ, Jordan RCK, Zhao W, Sturgis EM, Burtness B, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. Lancet. 2019;393(10166):40–50. doi:10.1016/S0140-6736(18)32779-X.
27. Aggarwal N, Yadav J, Thakur K, Bibban R, Chhokar A, Tripathi T, Bhat A, Singh T, Jadli M, Singh U, et al. Human papillomavirus infection in head and neck squamous cell carcinomas: transcriptional triggers and changed disease patterns. Front Cell Infect Microbiol. 2020;10:537650. doi:10.3389/fcimb.2020.537650.
28. Kobayashi K, Hisamatsu K, Suzui N, Hara A, Tomita H, Miyazaki T. A Review of HPV-Related Head and Neck Cancer. J Clin Med. 2018;7(9):241. doi:10.3390/jcm7090241.
29. Lee YG, Kang EJ, Keam B, Choi JH, Kim JS, Park KU, Lee KE, Kwon JH, Lee K-W, Kim MK, et al. Treatment strategy and outcomes in locally advanced head and neck squamous cell carcinoma: a nationwide retrospective cohort study (KCSG HN13-01). BMC Cancer. 2020;20(1):813. doi:10.1186/s12885-020-07297-z.
30. McDermott JD, Bowles DW. Epidemiology of head and neck squamous cell carcinomas: impact on staging and prevention strategies. Curr Treat Options Oncol. 2019;20(5):43. doi:10.1007/s11864-019-0650-5.
31. Sabatini ME, Chiocca S. Human papillomavirus as a driver of head and neck cancers. Br J Cancer. 2020;122(3):306–314. doi:10.1038/s41416-019-0602-7.
32. Tumban E. A current update on human papillomavirus-associated head and neck cancers. Viruses. 2019;11.
33. Nguyen N, Bellile E, Thomas D, McHugh J, Rozek L, Virani S, Peterson L, Carey TE, Walline H, Moyer J, et al. Tumor infiltrating lymphocytes and survival in patients with head and neck squamous cell carcinoma. Head Neck. 2016;38(7):1074–1084. doi:10.1002/hed.24406.
34. Wang WL, Chang WL, Yang HB, Chang IW, Lee CT, Chang CY, Lin J-T, Sheu B-S. Quantification of tumor infiltrating Foxp3+ regulatory T cells enables the identification of high-risk patients for developing synchronous cancers over upper aerodigestive tract. Oral Oncol. 2015;51(7):698–703. doi:10.1016/j.oraloncology.2015.04.015.
35. Uppaluri R, Dunn GP, Lewis JS Jr. Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in head and neck cancers. Cancer Immunity. 2008;8:16.
36. Fialova A, Koucky V, Hajduskova M, Hladikova K, Spisek R. Immunological network in head and neck squamous cell carcinoma-a prognostic tool beyond HPV status. Front Oncol. 2020;10:1701. doi:10.3389/fonc.2020.01701.
37. Sun X, Zhang L, Liu S, Khalaf OI. The immune infiltration in HNSCC and its clinical value: A comprehensive study based on the TCGA and GEO databases. Comput Math Methods Med. 2021;2021:1163250. doi:10.1155/2021/1163250.
38. Lechner A, Schlosser H, Rothschild SI, Thelen M, Reuter S, Zentis P, Shimabukuro-Vornhagen A, Theurich S, Wennhold K, Garcia-Marquez M, et al. Characterization of tumor-associated T-lymphocyte subsets and immune checkpoint molecules in head and neck squamous cell carcinoma. Oncotarget. 2017;8(27):44418–44433. doi:10.18632/oncotarget.17901.
39. Wang G, Zhang M, Cheng M, Wang X, Li K, Chen J, Chen Z, Chen S, Chen J, Xiong G, et al. Tumor microenvironment in head and neck squamous cell carcinoma: functions and regulatory mechanisms. Cancer Lett. 2021;507:55–69. doi:10.1016/j.canlet.2021.03.009.
40. Jie HB, Gildener-Leapman N, Li J, Srivastava RM, Gibson SP, Whiteside TL, Ferris RL. Intratumoral regulatory T cells upregulate immunosuppressive molecules in head and neck cancer patients. Br J Cancer. 2013;109(10):2629–2635. doi:10.1038/bjc.2013.645.
41. Seminerio I, Descamps G, Dupont S, de Marrez L, Laigle JA, Lechien JR, Kindt N, Journe F, Saussez S. Infiltration of FoxP3+ regulatory T cells is a strong and independent prognostic factor in head and neck squamous cell carcinoma. Cancers (Basel). 2019;2:11.
42. Burtness B, Harrington KJ, Greil R, Soulieres D, Tahara M, de Castro G Jr., Psyrri A, Basté N, Neupane P, Bratland Å, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet. 2019;394(10212):1915–1928. doi:10.1016/S0140-6736(19)32591-7.
43. Zolkind P, Uppaluri R. Checkpoint immunotherapy in head and neck cancers. Cancer Metastasis Rev. 2017;36(3):475–489. doi:10.1007/s10555-017-9694-9.
44. Sacco AG, Chen R, Worden FP, Wong DJL, Adkins D, Swiecicki P, Chai-Ho W, Oppelt P, Ghosh D, Bykowski J, et al. Pembrolizumab plus cetuximab in patients with recurrent or metastatic head and neck squamous cell carcinoma: an open-label, multi-arm, non-randomised, multicentre, phase 2 trial. Lancet Oncol. 2021;22(6):883–892. doi:10.1016/S1470-2045(21)00136-4.
45. Ferris RL, Blumenschein G Jr., Fayette J, Guigay J, Colevas AD, Licitra L, Harrington K, Kasper S, Vokes EE, Even C, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 2016;375(19):1856–1867. doi:10.1056/NEJMoa1602252.
46. Seiwert TY, Burtness B, Mehra R, Weiss J, Berger R, Eder JP, Heath K, McClanahan T, Lunceford J, Gause C, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol. 2016;17(7):956–965. doi:10.1016/S1470-2045(16)30066-3.
47. Gavrielatou N, Doumas S, Economopoulou P, Foukas PG, Psyrri A. Biomarkers for immunotherapy response in head and neck cancer. Cancer Treat Rev. 2020;84:101977. doi:10.1016/j.ctrv.2020.101977.
48. Lin W, Chen M, Hong L, Zhao H, Chen Q. Crosstalk between PD-1/PD-L1 blockade and its combinatorial therapies in tumor immune microenvironment: a focus on HNSCC. Front Oncol. 2018;8:532. doi:10.3389/fonc.2018.00532.
49. Cohen EEW, Bell RB, Bifulco CB, Burtness B, Gillison ML, Harrington KJ, Le Q-T, Lee NY, Leidner R, Lewis RL, et al. The society for immunotherapy of cancer consensus statement on immunotherapy for the treatment of squamous cell carcinoma of the head and neck (HNSCC). J Immunother Cancer. 2019;7(1):184. doi:10.1186/s40425-019-0662-5.
50. Cramer JD, Burtness B, Ferris RL. Immunotherapy for head and neck cancer: recent advances and future directions. Oral Oncol. 2019;99:104460. doi:10.1016/j.oraloncology.2019.104460.
51. Patel JJ, Levy DA, Nguyen SA, Knochelmann HM, Day TA. Impact of PD-L1 expression and human papillomavirus status in anti-PD1/PDL1 immunotherapy for head and neck squamous cell carcinoma-Systematic review and meta-analysis. Head Neck. 2020;42(4):774–786. doi:10.1002/hed.26036.
52. Zhang W, Yan C, Zhang T, Chen X, Dong J, Zhao J, Han D, Wang J, Zhao G, Cao F, et al. Addition of camrelizumab to docetaxel, cisplatin, and radiation therapy in patients with locally advanced esophageal squamous cell carcinoma: a phase 1b study. Oncoimmunology. 2021;10(1):1971418. doi:10.1080/2162402X.2021.1971418.

53. Galluzzi L, Yamazaki T, Kroemer G. Linking cellular stress responses to systemic homeostasis. Nat Rev Mol Cell Biol. 2018;19(11):731–745. doi:10.1038/s41580-018-0068-0.
54. Rufo N, Garg AD, Agostinis P. The unfolded protein response in immunogenic cell death and cancer immunotherapy. Trends Cancer. 2017;3(9):643–658. doi:10.1016/j.trecan.2017.07.002.
55. Galluzzi L, Buque A, Kepp O, Zitvogel L, Kroemer G. Immunogenic cell death in cancer and infectious disease. Nat Rev Immunol. 2017;17(2):97–111. doi:10.1038/nri.2016.107.
56. Galluzzi L, Vitale I, Warren S, Adjemian S, Agostinis P, Martinez AB, Chan TA, Coukos G, Demaria S, Deutsch E, et al. Consensus guidelines for the definition, detection and interpretation of immunogenic cell death. J Immunother Cancer. 2020;1:8.
57. Vanmeerbeek I, Sprooten J, De Ruysscher D, Tejpar S, Vandenberghe P, Fucikova J, Spisek R, Zitvogel L, Kroemer G, Galluzzi L, et al. Trial watch: chemotherapy-induced immunogenic cell death in immuno-oncology. Oncoimmunology. 2020;9(1):1703449. doi:10.1080/2162402X.2019.1703449.
58. Ahmed A, Tait SWG. Targeting immunogenic cell death in cancer. Mol Oncol. 2020;14(12):2994–3006. doi:10.1002/1878-0261.12851.
59. Zhou J, Wang G, Chen Y, Wang H, Hua Y, Cai Z. Immunogenic cell death in cancer therapy: present and emerging inducers. J Cell Mol Med. 2019;23(8):4854–4865. doi:10.1111/jcmm.14356.
60. Hazenberg MP, Pennock-Schroder AM, van de Merwe JP. Reversible binding of polymyxin B and neomycin to the solid part of faeces. J Antimicrob Chemother. 1986;17(3):333–339. doi:10.1093/jac/17.3.333.
61. Deng H, Yang W, Zhou Z, Tian R, Lin L, Ma Y, Song J, Chen X. Targeted scavenging of extracellular ROS relieves suppressive immunogenic cell death. Nat Commun. 2020;11(1):4951. doi:10.1038/s41467-020-18745-6.
62. Krysko DV, Garg AD, Kaczmarek A, Krysko O, Agostinis P, Vandenabeele P. Immunogenic cell death and DAMPs in cancer therapy. Nat Rev Cancer. 2012;12(12):860–875. doi:10.1038/nrc3380.
63. Minute L, Teijeira A, Sanchez-Paulete AR, Ochoa MC, Alvarez M, Otano I, Etxeberrria I, Bolaños E, Azpilikueta A, Garasa S, et al. Cellular cytotoxicity is a form of immunogenic cell death. J Immunother Cancer. 2020;1:8.
64. Ruan H, Leibowitz BJ, Zhang L, Yu J. Immunogenic cell death in colon cancer prevention and therapy. Mol Carcinog. 2020;59(7):783–793. doi:10.1002/mc.23183.
65. Kroemer G, Kepp O. Radiochemotherapy-induced elevations of plasma HMGB1 levels predict therapeutic responses in cancer patients. Oncoimmunology. 2021;10(1):2005859. doi:10.1080/2162402X.2021.2005859.
66. Vacchelli E, Enot DP, Pietrocola F, Zitvogel L, Kroemer G. Impact of Pattern Recognition Receptors on the Prognosis of Breast Cancer Patients Undergoing Adjuvant Chemotherapy. Cancer Res. 2016;76(11):3122–3126. doi:10.1158/0008-5472.CAN-16-0294.
67. Vacchelli E, Ma Y, Baracco EE, Sistigu A, Enot DP, Pietrocola F, Yang H, Adjemian S, Chaba K, Semeraro M, et al. Chemotherapy-induced antitumor immunity requires formyl peptide receptor 1. Science. 2015;350(6263):972–978. doi:10.1126/science.aad0779.
68. Bai L, Li W, Zheng W, Xu D, Chen N, Cui J. Promising targets based on pattern recognition receptors for cancer immunotherapy. Pharmacol Res. 2020;159:105017. doi:10.1016/j.phrs.2020.105017.
69. Pandey S, Singh S, Anang V, Bhatt AN, Natarajan K, Dwarakanath BS. Pattern recognition receptors in cancer progression and metastasis. Cancer Growth Metastasis. 2015;8:25–34. doi:10.4137/CGM.S24314.
70. Zeromski J, Kaczmarek M, Boruczkowski M, Kierepa A, Kowala-Piaskowska A, Mozer-Lisewska I. Significance and role of pattern recognition receptors in malignancy. Arch Immunol Ther Exp (Warsz). 2019;67(3):133–141. doi:10.1007/s00005-019-00540-x.
71. Osei-Owusu P, Charlton TM, Kim HK, Missiakas D, Schneewind O. FPR1 is the plague receptor on host immune cells. Nature. 2019;574(7776):57–62. doi:10.1038/s41586-019-1570-z.
72. Otani T, Ikeda S, Lwin H, Arai T, Muramatsu M, Sawabe M. Polymorphisms of the formylpeptide receptor gene (FPR1) and susceptibility to stomach cancer in 1531 consecutive autopsy cases. Biochem Biophys Res Commun. 2011;405(3):356–361. doi:10.1016/j.bbrc.2010.12.136.
73. Li SQ, Yu Y, Zhang Y, Sun YP, Li XX, Su N. The role of formyl peptide receptor 1 gene polymorphisms in human colorectal cancer. J Cancer. 2020;11(12):3580–3587. doi:10.7150/jca.36355.
74. Liu X, Ma B, Malik AB, Tang H, Yang T, Sun B, Wang G, Minshall RD, Li Y, Zhao Y, et al. Bidirectional regulation of neutrophil migration by mitogen-activated protein kinases. Nat Immunol. 2012;13(5):457–464. doi:10.1038/ni.2258.
75. Chiang SF, Huang KC, Chen WT, Chen TW, Ke TW, Chao KSC. Polymorphism of formyl peptide receptor 1 (FPR1) reduces the therapeutic efficiency and antitumor immunity after neoadjuvant chemoradiotherapy (CCRT) treatment in locally advanced rectal cancer. Cancer Immunol Immunother. 2021;70(10):2937–2950. doi:10.1007/s00262-021-02894-8.
76. Liu M, Zhao J, Chen K, Bian X, Wang C, Shi Y, Wang JM. G protein-coupled receptor FPR1 as a pharmacologic target in inflammation and human glioblastoma. Int Immunopharmacol. 2012;14(3):283–288. doi:10.1016/j.intimp.2012.07.015.
77. Di Virgilio F, Dal Ben D, Sarti AC, Giuliani AL, Falzoni S. The P2X7 Receptor in Infection and Inflammation. Immunity. 2017;47(1):15–31. doi:10.1016/j.immuni.2017.06.020.
78. Lili W, Yun L, Tingran W, Xia W, Yanlei S. P2RX7 functions as a putative biomarker of gastric cancer and contributes to worse prognosis. Exp Biol Med (Maywood). 2019;244(9):734–742. doi:10.1177/1535370219846492.
79. Di Virgilio F. P2RX7: a receptor with a split personality in inflammation and cancer. Mol Cell Oncol. 2016;3(2):e1010937. doi:10.1080/23723556.2015.1010937.
80. Zhang WJ, Zhu ZM. Association between the rs3751143 polymorphism of P2RX7 gene and chronic lymphocytic leukemia: a meta-analysis. Purinergic Signal. 2020;16(4):479–484. doi:10.1007/s11302-020-09737-8.
81. Wang BJ, Chen JY, Guan Y, Liu DC, Cao ZC, Kong J, Wu ZS, Wu WY. Predicted the P2RX7 rs3751143 polymorphism is associated with cancer risk: a meta-analysis and systematic review. Biosci Rep. 2021;2;41.
82. Zhu X, Li Q, Song W, Peng X, Zhao R. P2X7 receptor: a critical regulator and potential target for breast cancer. J Mol Med (Berl). 2021;99(3):349–358. doi:10.1007/s00109-021-02041-x.
83. Li J, Yang F, Wei F, Ren X. The role of toll-like receptor 4 in tumor microenvironment. Oncotarget. 2017;8:66656–66667. doi:10.18632/oncotarget.19105.
84. Kashani B, Zandi Z, Pourbagheri-Sigaroodi A, Bashash D, Ghaffari SH. The role of toll-like receptor 4 (TLR4) in cancer progression: a possible therapeutic target? J Cell Physiol. 2021;236(6):4121–4137. doi:10.1002/jcp.30166.
85. Ou T, Lilly M, Jiang W. The pathologic role of toll-like receptor 4 in prostate cancer. Front Immunol. 2018;9:1188. doi:10.3389/fimmu.2018.01188.
86. Fang H, Ang B, Xu X, Huang X, Wu Y, Sun Y, Wang W, Li N, Cao X, Wan T, et al. TLR4 is essential for dendritic cell activation and anti-tumor T-cell response enhancement by DAMPs released from chemically stressed cancer cells. Cell Mol Immunol. 2014;11(2):150–159. doi:10.1038/cmi.2013.59.
87. Pandey N, Chauhan A, Jain N. TLR4 polymorphisms and expression in solid cancers. Mol Diagn Ther. 2018;22(6):683–702. doi:10.1007/s40291-018-0361-9.
88. Shetab Boushehri MA, Lamprecht A. TLR4-Based Immunotherapeutics in Cancer: a Review of the Achievements and Shortcomings. Mol Pharm. 2018;15(11):4777–4800. doi:10.1021/acs.molpharmaceut.8b00691.

89. Senovilla L, Vitale I, Martins I, Tailler M, Pailleret C, Michaud M, Galluzzi L, Adjemian S, Kepp O, Niso-Santano M, et al. An immunosurveillance mechanism controls cancer cell ploidy. Science. 2012;337(6102):1678–1684. doi:10.1126/science.1224922.
90. Garg AD, Agostinis P. Cell death and immunity in cancer: from danger signals to mimicry of pathogen defense responses. Immunol Rev. 2017;280(1):126–148. doi:10.1111/imr.12574.
91. Garg AD, Agostinis P. ER stress, autophagy and immunogenic cell death in photodynamic therapy-induced anti-cancer immune responses. Photochem Photobiol Sci. 2014;13(3):474–487. doi:10.1039/C3PP50333J.
92. Gupta G, Borglum K, Chen H. Immunogenic Cell Death: a Step Ahead of Autophagy in Cancer Therapy. Journal of Cancer Immunology. 2021;3(1):47–59. doi:10.33696/cancerimmunol.3.041.
93. Zhong Z, Sanchez-Lopez E, Karin M. Autophagy Inflammation, and Immunity: a Troika Governing Cancer and Its Treatment. Cell. 2016;166(2):288–298. doi:10.1016/j.cell.2016.05.051.
94. Arensman MD, Yang XS, Zhong W, Bisulco S, Upeslacis E, Rosfjord EC, Deng S, Abraham RT, Eng CH. Anti-tumor immunity influences cancer cell reliance upon ATG7. Oncoimmunology. 2020;9(1):1800162. doi:10.1080/2162402X.2020.1800162.
95. Pervaiz S, Bellot GL, Lemoine A, Brenner C. Redox signaling in the pathogenesis of human disease and the regulatory role of autophagy. Int Rev Cell Mol Biol. 2020;352:189–214.
96. Yamazaki T, Buque A, Ames TD, Galluzzi L. PT-112 induces immunogenic cell death and synergizes with immune checkpoint blockers in mouse tumor models. Oncoimmunology. 2020;9(1):1721810. doi:10.1080/2162402X.2020.1721810.
97. Klionsky DJ, Petroni G, Amaravadi RK, Baehrecke EH, Ballabio A, Boya P, Bravo-San Pedro JM, Cadwell K, Cecconi F, Choi AMK, et al. Autophagy in major human diseases. EMBO J. 2021;40(19):e108863. doi:10.15252/embj.2021108863.
98. Yang C, Mei H, Peng L, Jiang F, Xie B, Li J, Lu P. Prognostic correlation of an autophagy-related gene signature in patients with head and neck squamous cell carcinoma. Comput Math Methods Med. 2020;2020:7397132. doi:10.1155/2020/7397132.
99. Lavoie S, Conway KL, Lassen KG, Jijon HB, Pan H, Chun E, Michaud M, Gallini Comeau CA, Dreyfuss JM, Glickman JN, et al. The Crohn's disease polymorphism, ATG16L1 T300A, alters the gut microbiota and enhances the local Th1/Th17 response. Elife. 2019;8.
100. Murthy A, Li Y, Peng I, Reichelt M, Katakam AK, Noubade R, Roose-Girma M, DeVoss J, Diehl L, Graham RR, et al. A Crohn's disease variant in Atg16l1 enhances its degradation by caspase 3. Nature. 2014;506(7489):456–462. doi:10.1038/nature13044.
101. Salem M, Ammitzboell M, Nys K, Seidelin JB, Nielsen OH. ATG16L1: a multifunctional susceptibility factor in Crohn disease. Autophagy. 2015;11(4):585–594. doi:10.1080/15548627.2015.1017187.
102. Younis N, Zarif R, Mahfouz R. Inflammatory bowel disease: between genetics and microbiota. Mol Biol Rep. 2020;47(4):3053–3063. doi:10.1007/s11033-020-05318-5.
103. Wildenberg ME, Koelink PJ, Diederen K, Te Velde AA, Wolfkamp SC, Nuij VJ, Peppelenbosch MP, Nobis M, Sansom OJ, Anderson KI, et al. The ATG16L1 risk allele associated with Crohn's disease results in a Rac1-dependent defect in dendritic cell migration that is corrected by thiopurines. Mucosal Immunol. 2017;10(2):352–360. doi:10.1038/mi.2016.65.
104. Kuballa P, Huett A, Rioux JD, Daly MJ, Xavier RJ, Gay N. Impaired autophagy of an intracellular pathogen induced by a Crohn's disease associated ATG16L1 variant. PLoS One. 2008;3(10):e3391. doi:10.1371/journal.pone.0003391.
105. Wang C, Bauckman KA, Ross ASB, Symington JW, Ligon MM, Scholtes G, Kumar A, Chang H-W, Twentyman J, Fashemi BE, et al. A non-canonical autophagy-dependentrole of the ATG16L1T300A variant in urothelial vesicular trafficking and uropathogenic *Escherichia coli* persistence. Autophagy. 2019;15(3):527–542. doi:10.1080/15548627.2018.1535290.
106. Lotsberg ML, Wnuk-Lipinska K, Terry S, Tan TZ, Lu N, Trachsel-Moncho L, Røsland GV, Siraji MI, Hellesøy M, Rayford A, et al. AXL targeting abrogates autophagic flux and induces immunogenic cell death in drug-resistant cancer cells. J Thorac Oncol. 2020;15(6):973–999. doi:10.1016/j.jtho.2020.01.015.
107. Vassilieva EV, Nusrat A. Vesicular trafficking: molecular tools and targets. Methods Mol Biol. 2008;440:3–14.
108. Zavodszky E, Vicinanza M, Rubinsztein DC. Biology and trafficking of ATG9 and ATG16L1, two proteins that regulate autophagosome formation. FEBS Lett. 2013;587(13):1988–1996. doi:10.1016/j.febslet.2013.04.025.
109. Huang K-L, Mashl RJ, Wu Y, Ritter DI, Wang J, Oh C, Paczkowska M, Reynolds S, Wyczalkowski MA, Oak N, et al. Pathogenic Germline Variants in 10,389 Adult Cancers. Cell. 2018;173(2):355–70 e14. doi:10.1016/j.cell.2018.03.039.
110. Le Naour J, Liu P, Zhao L, Adjemian S, Sztupinszki Z, Taieb J, Mulot C, Silvin A, Dutertre CA, Ginhoux F, et al. A TLR3 ligand reestablishes chemotherapeutic responses in the context of FPR1 deficiency. Cancer Discov. 2020;2.
111. Sztupinszki Z, Le Naour J, Vacchelli E, Laurent-Puig P, Delaloge S, Szallasi Z, Kroemer G. A major genetic accelerator of cancer diagnosis: rs867228 in FPR1. Oncoimmunology. 2021;10(1):1859064. doi:10.1080/2162402X.2020.1859064.
112. Gray V, Briggs S, Palles C, Jaeger E, Iveson T, Kerr R, Saunders MP, Paul J, Harkin A, McQueen J, et al. Pattern recognition receptor polymorphisms as predictors of oxaliplatin benefit in colorectal cancer. J Natl Cancer Inst. 2019;111(8):828–836. doi:10.1093/jnci/djy215.
113. Ghiringhelli F, Apetoh L, Tesniere A, Aymeric L, Ma Y, Ortiz C, Vermaelen K, Panaretakis T, Mignot G, Ullrich E, et al. Activation of the NLRP3 inflammasome in dendritic cells induces IL-1beta-dependent adaptive immunity against tumors. Nat Med. 2009;15(10):1170–1178. doi:10.1038/nm.2028.
114. Vacchelli E, Galluzzi L, Rousseau V, Rigoni A, Tesniere A, Delahaye N, Schlemmer F, Menger L, Sukkurwala AQ, Adjemian S, et al. Loss-of-function alleles of P2RX7 and TLR4 fail to affect the response to chemotherapy in non-small cell lung cancer. Oncoimmunology. 2012;1(3):271–278. doi:10.4161/onci.18684.
115. Vacchelli E, Semeraro M, Enot DP, Chaba K, Poirier Colame V, Dartigues P, Perier A, Villa I, Rusakiewicz S, Gronnier C, et al. Negative prognostic impact of regulatory T cell infiltration in surgically resected esophageal cancer post-radiochemotherapy. Oncotarget. 2015;6(25):20840–20850. doi:10.18632/oncotarget.4428.
116. Duan S, Yu J, Han Z, Cheng Z, Liang P. Association between P2RX7 gene and Hepatocellular Carcinoma Susceptibility: a case-control study in a chinese han population. Med Sci Monit. 2016;22:1916–1923. doi:10.12659/MSM.895763.
117. Dardano A, Falzoni S, Caraccio N, Polini A, Tognini S, Solini A, Berti P, Virgilio FD, Monzani F. 1513A>C polymorphism in the P2X7 receptor gene in patients with papillary thyroid cancer: correlation with histological variants and clinical parameters. J Clin Endocrinol Metab. 2009;94(2):695–698. doi:10.1210/jc.2008-1322.
118. Vacchelli E, Ma Y, Baracco EE, Zitvogel L, Kroemer G. Yet another pattern recognition receptor involved in the chemotherapy-induced anticancer immune response: formyl peptide receptor-1. Oncoimmunology. 2016;5(5):e1118600. doi:10.1080/2162402X.2015.1118600.

119. Vacchelli E, Semeraro M, Adam J, Dartigues P, Zitvogel L, Kroemer G. Immunosurveillance in esophageal carcinoma: the decisive impact of regulatory T cells. Oncoimmunology. 2016;5 (2):e1064581. doi:10.1080/2162402X.2015.1064581.
120. Apetoh L, Ghiringhelli F, Tesniere A, Obeid M, Ortiz C, Criollo A, Mignot G, Maiuri MC, Ullrich E, Saulnier P, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med. 2007;13(9):1050–1059. doi:10.1038/nm1622.
121. Tesniere A, Schlemmer F, Boige V, Kepp O, Martins I, Ghiringhelli F, Aymeric L, Michaud M, Apetoh L, Barault L, et al. Immunogenic death of colon cancer cells treated with oxaliplatin. Oncogene. 2010;29 (4):482–491. doi:10.1038/onc.2009.356.
122. Semlali A, Reddy Parine N, Arafah M, Mansour L, Azzi A, Al Shahrani O, Al Amri A, Shaik JP, Aljebreen AM, Alharbi O, et al. Expression and polymorphism of toll-like receptor 4 and effect on NF-kappaB mediated inflammation in colon cancer patients. PLoS One. 2016;11(1):e0146333. doi:10.1371/journal.pone.0146333.
123. Gast A, Bermejo JL, Claus R, Brandt A, Weires M, Weber A, Plass C, Sucker A, Hemminki K, Schadendorf D, et al. Association of inherited variation in Toll-like receptor genes with malignant melanoma susceptibility and survival. PLoS One. 2011;6 (9):e24370. doi:10.1371/journal.pone.0024370.
124. Bergmann C, Bachmann HS, Bankfalvi A, Lotfi R, Putter C, Wild CA, Schuler PJ, Greve J, Hoffmann TK, Lang S, et al. Toll-like receptor 4 single-nucleotide polymorphisms Asp299Gly and Thr399Ile in head and neck squamous cell carcinomas. J Transl Med. 2011;9(1):139. doi:10.1186/1479-5876-9-139.
125. Cancer Genome Atlas N. Comprehensive molecular portraits of human breast tumours. Nature. 2012;490(7418):61–70. doi:10.1038/nature11412.
126. Ortiz-Cuaran S, Bouaoud J, Karabajakian A, Fayette J, Saintigny P. Precision medicine approaches to overcome resistance to therapy in head and neck cancers. Front Oncol. 2021;11:614332. doi:10.3389/fonc.2021.614332.
127. Picon H, Guddati AK. Mechanisms of resistance in head and neck cancer. Am J Cancer Res. 2020;10:2742–2751.
128. Robinson AM, Rathore R, Redlich NJ, Adkins DR, VanArsdale T, Van Tine BA, Michel LS. Cisplatin exposure causes c-Myc-dependent resistance to CDK4/6 inhibition in HPV-negative head and neck squamous cell carcinoma. Cell Death Dis. 2019;10 (11):867. doi:10.1038/s41419-019-2098-8.
129. Oosting SF, Haddad RI. Best Practice in Systemic Therapy for Head and Neck Squamous Cell Carcinoma. Front Oncol. 2019;9:815. doi:10.3389/fonc.2019.00815.
130. Lev Z, Kimchie Z, Hessel R, Segev O. Expression of ras cellular oncogenes during development of Drosophila melanogaster. Mol Cell Biol. 1985;5(6):1540–1542. doi:10.1128/mcb.5.6.1540-1542.1985.
131. Janho Dit Hreich S, Benzaquen J, Hofman P, Vouret-Craviari V. To inhibit or to boost the ATP/P2RX7 pathway to fight cancer-that is the question. Purinergic Signalling. 2021;17(4):619–631. doi:10.1007/s11302-021-09811-9.
132. Ma Y, Adjemian S, Yang H, Catani JP, Hannani D, Martins I, Michaud M, Kepp O, Sukkurwala AQ, Vacchelli E, et al. ATP-dependent recruitment, survival and differentiation of dendritic cell precursors in the tumor bed after anticancer chemotherapy. Oncoimmunology. 2013;2(6):e24568. doi:10.4161/onci.24568.
133. Martins I, Wang Y, Michaud M, Ma Y, Sukkurwala AQ, Shen S, Kepp O, Métivier D, Galluzzi L, Perfettini J-L, et al. Molecular mechanisms of ATP secretion during immunogenic cell death. Cell Death Differ. 2014;21(1):79–91. doi:10.1038/cdd.2013.75.
134. Michaud M, Martins I, Sukkurwala AQ, Adjemian S, Ma Y, Pellegatti P, Shen S, Kepp O, Scoazec M, Mignot G, et al. Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice. Science. 2011;334 (6062):1573–1577. doi:10.1126/science.1208347.
135. Pietrocola F, Pedro JM B-S, Galluzzi L, Kroemer G. Autophagy in natural and therapy-driven anticancer immunosurveillance. Autophagy. 2017;13(12):2163–2170. doi:10.1080/15548627.2017.1310356.
136. Wang Y, Martins I, Ma Y, Kepp O, Galluzzi L, Kroemer G. Autophagy-dependent ATP release from dying cells via lysosomal exocytosis. Autophagy. 2013;9(10):1624–1625. doi:10.4161/auto.25873.
137. Fernandez-Mateos J, Seijas-Tamayo R, Klain JCA, Borgonon MP, Perez-Ruiz E, Mesia R, Del Barco E, Coloma CS, Dominguez AR, Daroqui JC, et al. Analysis of autophagy gene polymorphisms in Spanish patients with head and neck squamous cell carcinoma. Sci Rep. 2017;7(1):6887. doi:10.1038/s41598-017-07270-0.
138. He C, Klionsky DJ. Regulation mechanisms and signaling pathways of autophagy. Annu Rev Genet. 2009;43(1):67–93. doi:10.1146/annurev-genet-102808-114910.
139. Lamb CA, Yoshimori T, Tooze SA. The autophagosome: origins unknown, biogenesis complex. Nat Rev Mol Cell Biol. 2013;14 (12):759–774. doi:10.1038/nrm3696.
140. Nakatogawa H. Mechanisms governing autophagosome biogenesis. Nat Rev Mol Cell Biol. 2020;21(8):439–458. doi:10.1038/s41580-020-0241-0.
141. Stolz A, Ernst A, Dikic I. Cargo recognition and trafficking in selective autophagy. Nat Cell Biol. 2014;16(6):495–501. doi:10.1038/ncb2979.
142. Kaser A, Blumberg RS. Stressful genetics in Crohn's disease. Nature. 2014;506(7489):441–442. doi:10.1038/nature13060.
143. Rioux JD, Xavier RJ, Taylor KD, Silverberg MS, Goyette P, Huett A, Green T, Kuballa P, Barmada MM, Datta LW, et al. Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. Nat Genet. 2007;39(5):596–604. doi:10.1038/ng2032.
144. Zhang HF, Qiu LX, Chen Y, Zhu WL, Mao C, Zhu LG, Zheng M-H, Wang Y, Lei L, Shi J, et al. ATG16L1 T300A polymorphism and Crohn's disease susceptibility: evidence from 13,022 cases and 17,532 controls. Hum Genet. 2009;125(5–6):627–631. doi:10.1007/s00439-009-0660-7.
145. Grant SF, Baldassano RN, Hakonarson H. Classification of genetic profiles of Crohn's disease: a focus on the ATG16L1 gene. Expert Rev Mol Diagn. 2008;8(2):199–207. doi:10.1586/14737159.8.2.199.
146. Hampe J, Franke A, Rosenstiel P, Till A, Teuber M, Huse K, Albrecht M, Mayr G, De La Vega FM, Briggs J, et al. A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG16L1. Nat Genet. 2007;39(2):207–211. doi:10.1038/ng1954.
147. Ngoh EN, Brugger HK, Monajemi M, Menzies SC, Hirschfeld AF, Del Bel KL, Jacobson K, Lavoie PM, Turvey SE, Sly LM, et al. The Crohn's disease-associated polymorphism in ATG16L1 (rs2241880) reduces SHIP gene expression and activity in human subjects. Genes Immun. 2015;16(7):452–461. doi:10.1038/gene.2015.30.
148. Moazeni-Roodi A, Tabasi F, Ghavami S, Hashemi M. Investigation of ATG16L1 rs2241880 polymorphism with cancer risk: a meta-analysis. Medicina (Kaunas). 2019;8:55.
149. Katsanos KH, Roda G, McBride RB, Cohen B, Colombel JF. Increased risk of oral cancer in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2016;14(3):413–420. doi:10.1016/j.cgh.2015.09.041.
150. Nissen LHC, Derikx L, Jacobs AME, van Herpen CM, Kievit W, Verhoeven R, van den Broek E, Bekers E, van den Heuvel T, Pierik M, et al. Risk factors and clinical outcomes of head and neck cancer in inflammatory bowel disease: a nationwide cohort study. Inflamm Bowel Dis. 2018;24(9):2015–2026. doi:10.1093/ibd/izy096.
151. Giagkou E, Christodoulou DK, Katsanos KH. Mouth cancer in inflammatory bowel diseases. Oral Dis. 2016;22(4):260–264. doi:10.1111/odi.12420.

152. Reuken PA, Lutz P, Casper M, Al-Herwi E, Stengel S, Spengler U, Stallmach A, Lammert F, Nischalke HD, Bruns T, et al. The ATG16L1 gene variant rs2241880 (p.T300A) is associated with susceptibility to HCC in patients with cirrhosis. Liver Int. 2019;39(12):2360–2367. doi:10.1111/liv.14239.
153. El-Amir MI, Wahman MM, Khaled HA, El-Feky MA. Role of ATG16LI (rs2241880) and Interleukin 10 (rs1800872) Polymorphisms in Breast Cancer Among Egyptian Patients. The Egyptian Journal of Immunology. 2020;27:65–76.
154. Burada F, Ciurea ME, Nicoli R, Streata I, Vilcea ID, Rogoveanu I, Ioana M. ATG16L1 T300A polymorphism is correlated with gastric cancer susceptibility. Pathol Oncol Res. 2016;22(2):317–322. doi:10.1007/s12253-015-0006-9.
155. White KA, Luo L, Thompson TA, Torres S, Hu CA, Thomas NE, Lilyquist J, Anton-Culver H, Gruber SB, From L, et al. Variants in autophagy-related genes and clinical characteristics in melanoma: a population-based study. Cancer Med. 2016;5(11):3336–3345. doi:10.1002/cam4.929.