CANCER GENOMICS & PROTEOMICS *20*: 88-101 (2024)
doi:10.21873/cgp.20432

Impact of Mutations in Subunit Genes of the Mammalian SWI/SNF Complex on Immunological Tumor Microenvironment

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Abstract. *Background/Aim: Recently, inactivating somatic mutations of SWI/SNF chromatin-remodeling genes in cancers have been reported. However, few studies have been performed regarding the immunological analysis of the tumor microenvironment (TME) in chromatin remodeling complex gene-mutated tumors. In the present study, we identified cancer patients harboring various mammalian SWI/SNF complex mutations and investigated the immunological features in those mutated cancers. Patients and Methods: Cancer patients harboring any type of chromatin remodeling complex gene mutation were selected and clinicopathological features were compared between chromatin remodeling complex gene expression-low and expression-high groups. Specifically, expression levels of immune response-associated genes and cancer-associated genes were compared between the SMARCA4 expression-low and expression-high groups using volcano plot analysis. Results: Among cancers harboring PBRM1, SAMRACA4 and ARID2 gene mutations, T-cell marker and mature B-cell*

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Key Words: Immunological tumor microenvironment, iTME, mammalian SWI/SNF complex, chromatin remodeling gene, SMARCA4 mutation, tumor-infiltrating lymphocytes, TILs.

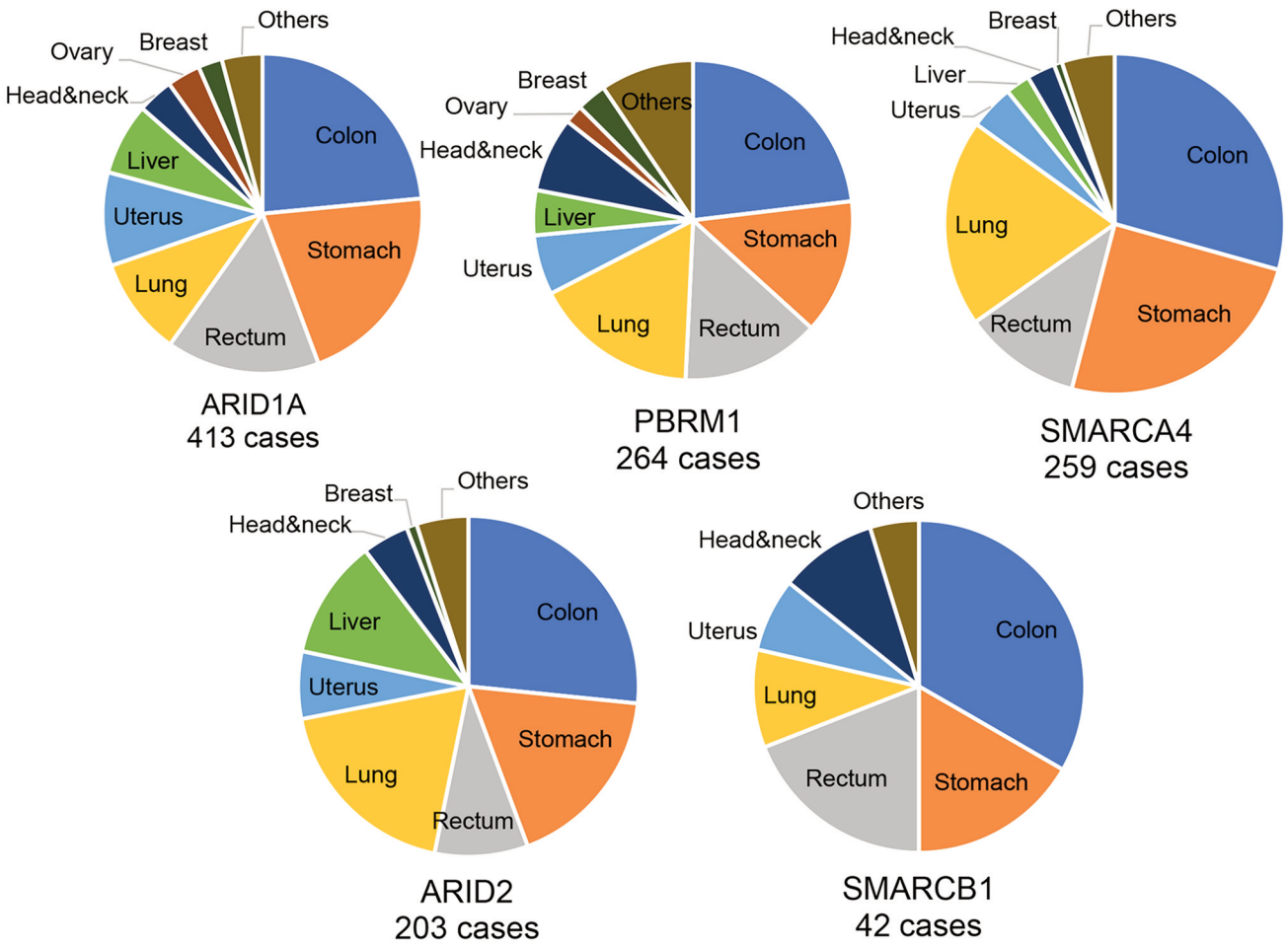

Figure 1. *Histological frequencies of various chromatin remodeling gene-mutant tumors. The number of chromatin remodeling complex gene-mutated cancer patients was 413 for ARID1A mutation, 264 for PBRM1 mutation, 259 for SMARCA4 mutation, 203 for ARID2 mutation and 42 for SMARCB1 mutation.*

marker genes were up-regulated in the tumor. Specifically, T-cell effector genes (CD8B, CD40LG), central memory marker genes (CD27, CCR7) and mature B-cell marker genes (CD20, CD38, CD79 and IRF4) were up-regulated, and cancer-associated genes including MYB, MYC and AURKB genes were down-regulated in the SMARCA4 expression-low group. Remarkably, heatmap of gene expression and immunohistochemistry (IHC) data demonstrated that the tertiary lymphoid structure (TLS) gene signature of mature B cells was up-regulated in SMACA4 gene-mutated stomach cancers. Conclusion: These results suggest that immune tumor microenvironment status, such as mature B cell recruitment featuring the TLS gene signature and immune activation mediated by cancer signal down-regulation, might contribute to the classification of SMARCA4 gene-mutated tumors as immune checkpoint blockade therapy-sensitive target tumors.

With the remarkable advance in genetic sequencing technologies, inactivating somatic mutations of mammalian switch/sucrose-nonfermenting (SWI/SNF) chromatin-remodeling genes in cancers, such as *BRG1/SMARCA4, PBRM1/BAF180, ARID1A/BAF250A, and ARID2/BAF200*, have been reported using clinical genome-wide sequencing and given much attention (1-4). SWI/SNF chromatin-remodeling complex genes have been demonstrated to play a role in gene transcription including epigenetic interaction and DNA double-strand repair (1, 2), and such mutations leading to loss of function are likely to be involved in cancer development and progression through a senescence or senescence-associated secretory phenotype (SASP) state (5, 6).

Mutations in SWI/SNF chromatin-remodeling complex genes are reported in many solid cancers at a rate of approximately 20% (7), such as ovarian and uterine cancer

Table I. *Clinical and genetic characterization of chromatin remodeling complex gene-mutant cancer patients.*

Categories	mARID1A			mPBRM1			mSMARCA4			mARID2		
	High	Low	*p*-Value	High	Low	*p*-Value	High	Low	*p*-Value	High	Low	*p*-Value
Sex (M/F)	110/96	116/91	0.622	74/57	89/44	0.100	75/54	89/41	0.095	48/53	74/28	0.00033**
Age	67±12	66±12	0.299	65±14	68±12	0.054	66±14	69±12	0.164	66±13	69±11	0.077
StageIII/IV	77 (37%)	102 (49%)	0.017*	44 (34%)	51 (38%)	0.444	69 (54%)	49 (38%)	0.013*	49 (49%)	43 (42%)	0.399
3-year survival rate	88.30%	85.00%	0.385	81.70%	82.70%	NS	86.00%	85.40%	NS	91.10%	82.40%	0.097
TMB	34±85	25±47	0.172	42±107	27±67	0.175	54±110	27±50	0.012*	61±101	31±65	0.013*
CNV	2.9±9.7	2.4±6.9	0.528	6.5±21	4.9±17	0.483	1.7±0.4	2.3±8.7	0.454	4.1±14	5.0±17	0.690
BRAF (%)	28 (14%)	30 (15%)	0.888	12 (9%)	16 (12%)	0.550	29 (23%)	18 (14%)	0.078	24 (24%)	16 (16%)	0.162
EGFR (%)	34 (17%)	29 (14%)	0.497	28 (21%)	17 (13%)	0.073	30 (23%)	22 (17%)	0.218	23 (23%)	24 (24%)	NS
KRAS (%)	40 (19%)	51 (25%)	0.235	36 (28%)	25 (19%)	0.109	41 (32%)	22 (17%)	0.0060**	31 (31%)	15 (15%)	0.0074**
PIK3CA (%)	52 (25%)	59 (29%)	0.506	37 (28%)	24 (18%)	0.058	40 (31%)	27 (21%)	0.066	28 (28%)	28 (27%)	NS
TP53 (%)	88 (43%)	86 (42%)	0.842	66 (50%)	65 (49%)	0.902	58 (45%)	61 (47%)	0.803	49 (49%)	52 (51%)	0.780

*p<0.05 and **p<0.01

(*ARID1A*) (8, 9), ovarian and lung cancer (*SMARCA4*) (10-12), renal cell cancer (*PBRM1*) (13) and rhabdomyosarcoma (*SMARCB1*) (14). In particular, almost all rare ovarian cancers, small-cell carcinomas of the ovary, hypercalcemic type (SCCOHTs) have *SMARCA4* mutations. In addition, many non-small cell lung cancers (10~20%) harboring *SMARCA4* mutations with reduced or absent SMARCA4 expression have recently been reported to show a refractory phenotype to standard regimens, with worse prognosis compared to wild type other non-small cell lung cancer patients (15).

Recently, synthetic lethality therapy development has been studied in SWI/SNF chromatin-remodeling complex gene-deficient cancer patients based on the past achievements of PARP inhibitors against BRCA1/BRCA2-deficient tumors (16-18). On the other hand, few studies have been performed regarding immunological analysis of the TME in chromatin remodeling complex-deficient tumors. Recently, using genome-wide genetic screening with CRISPR, the SWI/SNF chromatin-remodeling complex gene *ARID1A*, was identified as a novel immune checkpoint target, indicating that down-regulation of the *ARID1A* gene might induce immune activation through T-cell attraction (19, 20).

The HOPE genome project at Shizuoka Cancer Center is currently ongoing and has been successful since 2014 in obtaining substantial genome data leading to suitable drug selection and efficient database development. This effort enables medical researchers to search for necessary information from the genomic database derived from approximately 5,000 cancer patients enrolled in the HOPE project (21).

In the present study, we identified cancer patients harboring various mammalian SWI/SNF complex mutations and down-regulated expression of chromatin remodeling genes through the HOPE project, and investigated the immunological features of those mutant cancers.

Patients and Methods

Patient characteristics. The Shizuoka Cancer Center launched Project HOPE in 2014 using multiomic analyses including whole exome sequencing (WES) and gene expression profiling (GEP). Ethical approval for the HOPE study was obtained from the Institutional Review Board of Shizuoka Cancer Center (Authorization Number: 25–33) (21). All experiments using clinical samples were carried out in accordance with the Helsinki Declaration and the Ethical Guidelines for Human Genome and Genetic Analysis Research. The HOPE cohort comprised 5,143 patients treated at the Shizuoka Cancer Center Hospital from January 2014 to March 2019. The cancer patient cohort harboring SWI/SNF chromatin-remodeling gene mutations, such as in *SMARCA4*, *PBRM1*, *ARID1A*, *ARID2* and *SMARCB1*, was selected and divided into lower expression (below median) and higher expression groups.

DNA microarray-based GEP and WES using next-generation sequencing. The method used to perform GEP and WES analyses

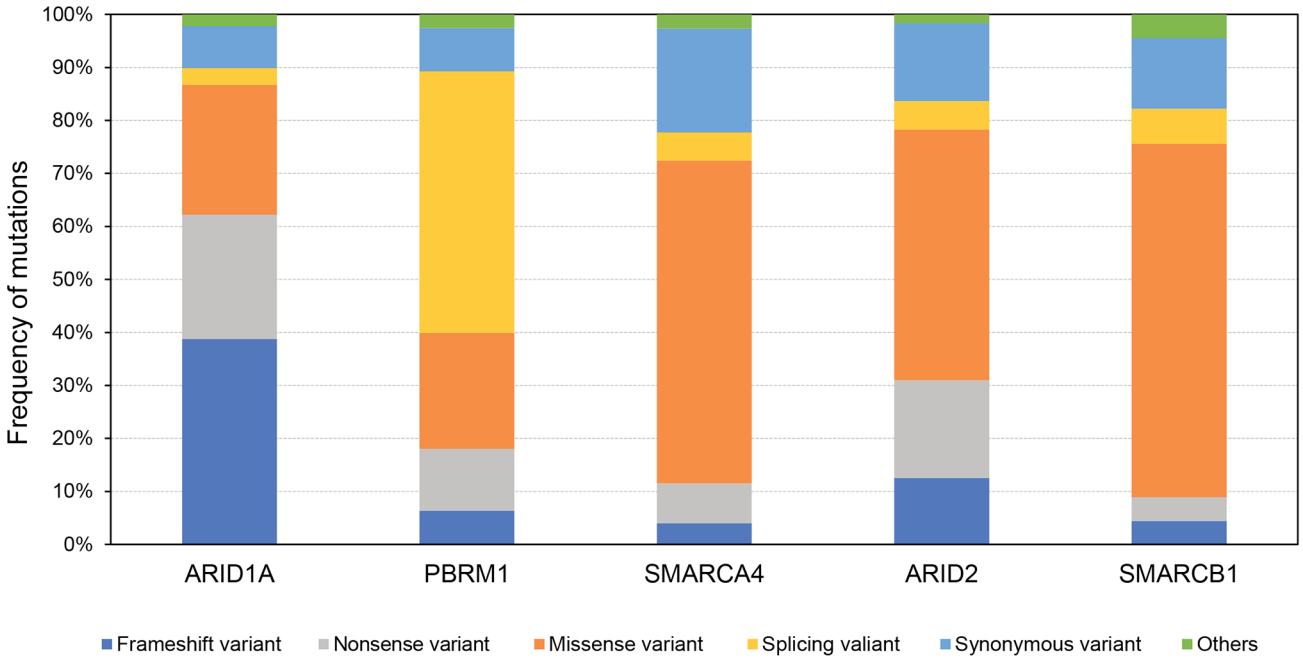

Figure 2. *Profiling of various mutations in chromatin remodeling gene-mutant tumors. Frequencies of various patterns of mutations in each chromatin remodeling gene-mutant tumor are shown. The mutation patterns are as follows: frameshift variant, nonsense variant, missense variant, splicing variant, synonymous variant and others.*

has been described previously (20). Mutations that were identified in tumor samples and not observed in matched normal samples were identified as somatic mutations. The methods for determining tumor mutation burden (TMB) and copy number variation (CNV) number have been described previously (21).

Immunohistochemistry (IHC). For analysis of tumor-infiltrating immune cells (TILs), antibodies against SMARCA4 (Abcam, cat. ab110641, Cambridge, UK), CD8 (Leica Microsystems GmbH, cat. NCL-CD8-4B11, Wetzlar, Germany), PD-1 (Abcam, cat. Ab52587) and CD20 (Leica Microsystems, cat. NCL-CD20-L26) were purchased. Three representative marker-positive or -negative cases from the SMARCA4 expression-high or -low group were selected and their formalin-fixed, paraffin-embedded (FFPE) specimens were used for immunohistochemistry.

Immune response-associated genes and SCC820 panel gene expression profiling. The lists of genes in the 204 immune response-associated gene panel and the SCC820 cancer-associated panel have been shown previously (22). Briefly, expression levels of 204 immune response-associated genes and the SCC820 cancer-associated genes of *SMARCA4*-mutant cancers were compared between the SMARCA4 expression-high (above median) group and SMARCA4 expression-low (below median) group with volcano plot analysis. Genes with altered expression (more than 2-fold) were identified.

Statistical analysis. Comparison of the proportion of categorical variables between each gene expression-high group and expression-low group was performed with the Mann-Whitney *U*-test. $p<0.05$ was considered significant. Data analysis using the volcano plot was performed with GeneSpring GX software version 14.9.1 (Agilent Technologies, Santa Clara, CA, USA). Overall survival was calculated using the Kaplan-Meier method and statistical significance between each gene expression-high group and expression-low group was evaluated by the log-rank test.

Results

Clinical and genetic characteristics of chromatin remodeling complex gene-mutated cancers. The number of chromatin remodeling complex gene-mutated cancer patients was 413 for *ARID1A* mutation, 264 for *PBRM1* mutation, 259 for *SMARCA4* mutation, 203 for *ARID2* mutation and 42 for *SMARCB1* mutation. The number of cancer patients harboring any type of chromatin remodeling complex gene mutation was 1,181 and comprised 23.0% of all patients. The histological types of those gene-mutated cancers are summarized in Figure 1. There was no significant difference in the frequency of cancer types among each gene-mutated cancer (Figure 1).

Regarding clinicopathological factors, such as sex, age, pathological staging and performance status, there was no significant difference between the chromatin remodeling gene-mutated cancer groups (Table I). However, in genomic analysis among chromatin remodeling gene-mutated tumors, high TMB and more *KRAS*-mutated cases were identified in

Table II. *Profiling of immune cell marker and immune checkpoint genes in chromatin remodeling complex gene-mutant cancer patients.*

Categories	mARID1A			mPBRM1			mSMARCA4			mARID2		
	High	Low	*p*-Value	High	Low	*p*-Value	High	Low	*p*-Value	High	Low	*p*-Value
CD3E	–2.37	–2.27	0.599	–2.17	–2.00	0.060	–2.49	–1.91	2.4E-04**	–2.46	–1.99	0.174
CD8B	–2.80	–2.60	0.178	–2.52	–2.39	0.280	–3.00	–2.28	1.4E-04**	–2.70	–2.49	0.432
PD-1	–0.09	–0.04	0.500	–0.03	0.31	0.0254	–0.10	0.23	0.0021**	0.00	0.31	0.102
PD-L1	–2.57	–2.50	0.605	–2.48	–2.07	0.050	–2.13	–2.23	0.807	–2.27	–1.96	0.178
HAVCR2	–1.52	–1.42	0.630	–1.44	–0.99	0.0011**	–1.49	–1.13	0.031*	–1.35	–1.01	0.015*
LAG3	0.46	0.56	0.769	0.63	0.84	0.123	0.62	0.90	0.022*	0.63	1.00	0.523
CD19	–0.19	0.19	0.338	–0.06	0.18	0.838	–0.73	0.95	1.0E-05**	–0.23	–0.06	0.778
CD20	–3.17	–3.08	0.527	–3.06	–3.18	0.756	–3.72	–2.48	3.3E-05**	–3.18	–3.31	0.804
CD38	0.16	0.41	0.393	0.53	0.65	0.153	0.14	0.87	0.0013**	0.44	0.64	0.973

The expression level of each gene is indicated in log2-transformed scale between the SMARCA4 expression-low and high groups. *p<0.05 and **p<0.01.

Table III. *Profiling of immune cell marker and immune checkpoint genes in various types of SMARCA4 gene-mutant cancer patients.*

Categories	Colon			Stomach			Lung			Rectum		
	High	Low	*p*-Value	High	Low	*p*-Value	High	Low	*p*-Value	High	Low	*p*-Value
Case numbers	38	38		32	32		25	26		14	15	
CD3E	–2.69	–2.27	0.207	–2.33	–1.53	0.0010**	–1.96	–1.69	0.241	–2.05	–2.12	0.252
CD8B	–3.59	–2.62	0.032*	–3.30	–2.07	0.0011**	–2.44	–2.15	0.192	–2.75	–2.37	0.354
PD-1	–0.55	–0.30	0.405	0.04	0.99	0.023*	0.57	0.58	0.290	–0.17	–0.36	0.715
PD-L1	–1.73	–2.60	0.104	–1.86	–1.74	0.580	–1.17	–1.69	0.262	–2.32	–2.33	0.477
HAVCR2	–1.73	–1.88	0.294	–1.44	–0.91	0.112	–0.47	–0.19	0.828	–1.65	–1.70	0.847
LAG3	0.41	0.65	0.435	0.81	1.22	0.090	1.15	1.22	0.647	0.64	0.58	0.715
CD19	–1.57	0.09	0.0079**	–0.73	2.05	2.4E-06**	0.65	1.03	0.519	–0.16	1.14	0.146
CD20	–4.51	–3.08	0.123	–4.54	–0.93	4.5E-06**	–2.49	–2.28	0.495	–3.19	–2.74	0.190
CD38	–0.48	0.43	0.045*	0.09	1.29	0.0014**	1.16	1.17	0.688	0.15	0.63	0.715

The expression level of each gene is indicated in log2-transformed scale between the SMARCA4 expression-low and high groups. *p<0.05 and **p<0.01

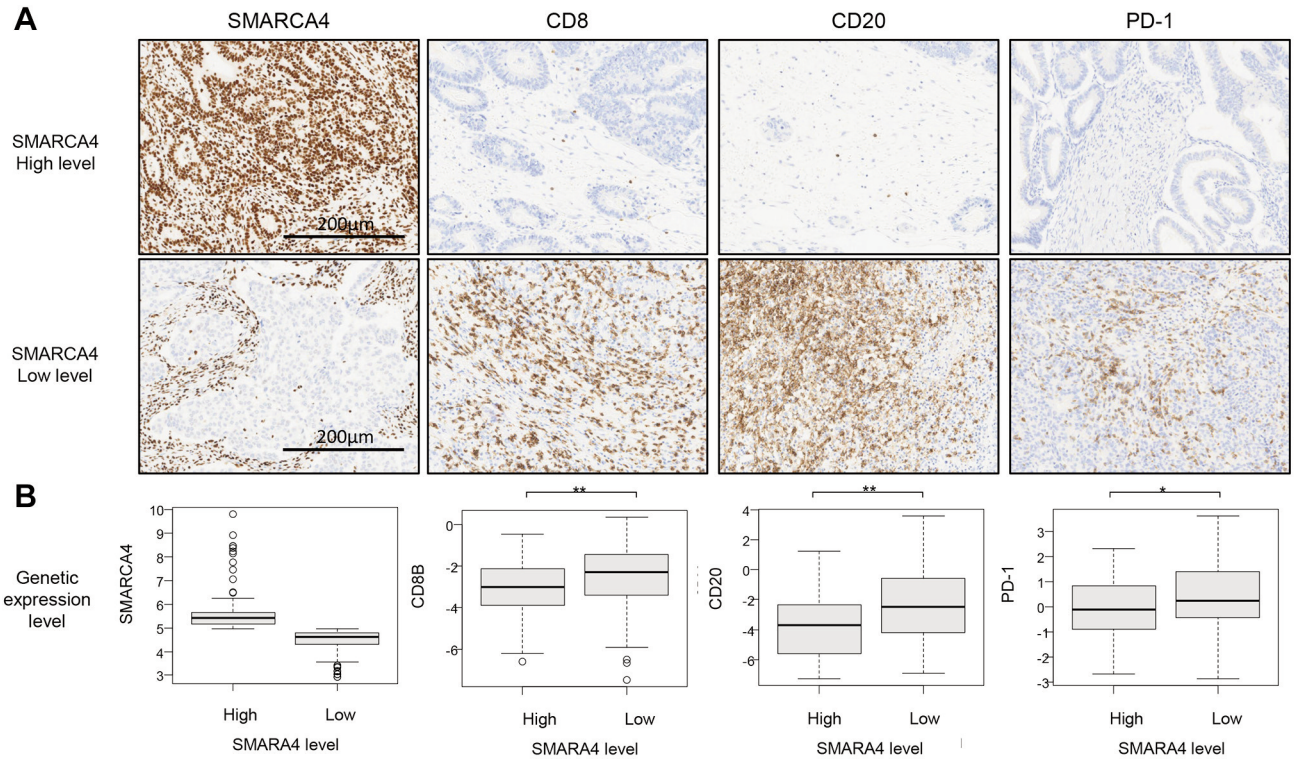

Figure 3. *Representative immunohistochemical images of SMARCA4-mutant solid cancer. (A) Antibodies against SMARCA4, CD8, CD20 and PD-1 were used for immunohistochemical (IHC) staining. Images of SMARCA4 and each immune marker staining are shown between SMARCA4 expression-low and -high tumor groups in the upper panel. Magnification: ´200. (B) SMARCA4 and immune marker gene expression levels are shown. The vertical axis shows the expression levels indicated on a log2-transformed scale between the SMARCA4 expression-low and -high groups at the bottom. *p<0.01 and *p<0.05 using the Mann-Whitney U-test.*

gene expression-high groups for *SMARCA4*-mutated and *ARID2*-mutated tumors. Moreover, profiling of mutation patterns in chromatin remodeling gene-mutated tumors indicated that frameshift variants and splicing variants were most frequent in *ARID1A*- and *PBRM1*-mutated tumors, respectively, and a higher frequency of missense variants was identified in *SMARCA4*-, *ARID2*- and *SMARCB1*-mutated tumors (Figure 2).

Immune cell-associated marker gene expression of chromatin remodeling complex gene-mutated cancers. Among cancers harboring *PBRM1*, *SAMRACA4* and *ARID2* gene mutations, T-cell marker and mature B-cell marker genes were up-regulated in each gene-expression-low group compared with the expression-high group, particularly in *SMARCA4*-mutated cancers (Table II). Marker genes of exhausted T-cell, such as *HAVCR2* and *LAG3*, were also up-regulated. Regarding the histological type of tumors, PD-1^+ T-cell marker and $CD38^+$ mature B-cell marker genes were up-regulated in colon cancers and stomach cancers with *SMARCA4* gene-low expression, but not in non-small cell lung and rectal cancers (Table III).

IHC analysis and TMB levels in SMARCA4-mutated cancers. Among SMARCA4-mutated cancers, $CD8^+PD1^+$ T cells and $CD20^+$ B cells were increased in SMARCA4 expression-low specimens (Figure 3).

TMB levels were significantly higher in *SMARCA4*-mutated colon cancers and stomach cancers than in wild-type colon cancers (Figure 4A). Microsatellite instability-high (MSI-H) colon cancers were excluded from all colorectal cancer patients. TMB levels were also higher in the *SMARCA4* expression-high group of *SMARCA4*-mutated stomach cancers; however, TMB levels were not different between the *SMARCA4* expression-high and -low groups of *SMARCA4*-mutated colorectal cancers (Figure 4B).

Expression profiling of immune response-associated genes and SCC820 panel genes in SMARCA4-mutated cancers. Volcano plot analysis showed 35 up-regulated and 10 down-regulated genes among immune response-associated genes (Figure 5A, Table IV), and 29 up-regulated and 30 down-regulated genes among the SCC820 cancer-associated genes (Figure 5B, Table V) in the *SMARCA4* expression-low group.

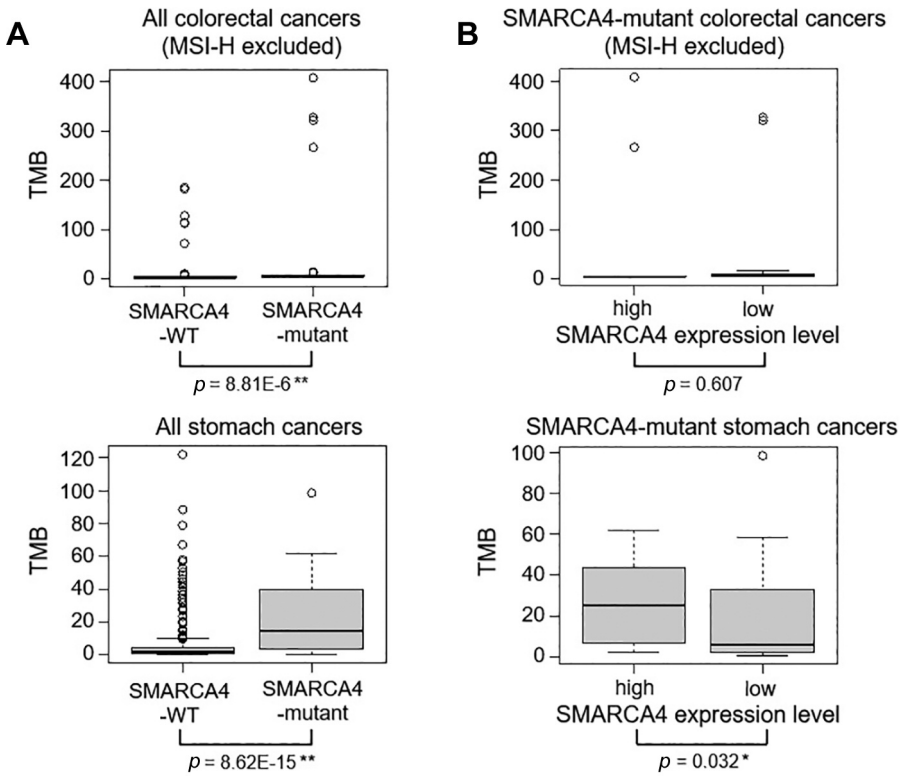

Figure 4. *Tumor mutational burden (TMB) levels in SMARCA4-mutant colon cancers and stomach cancers. Microsatellite instability-high (MSI-H) colon cancers were excluded from all colon cancer patients. (A) Comparison of TMB levels was performed between the SMARCA4-WT and -mutant colon cancer groups and between the SMARCA4-WT and -mutant stomach cancer groups. (B) Comparison of TMB levels was performed between the SMARCA4-high and SMARCA4-low groups of SMARCA4-mutant colon cancers, and between the SMARCA4-high and SMARCA4-low groups of SMARCA4-mutant stomach cancers. *p<0.05 and **p<0.01 using the Mann-Whitney U-test.*

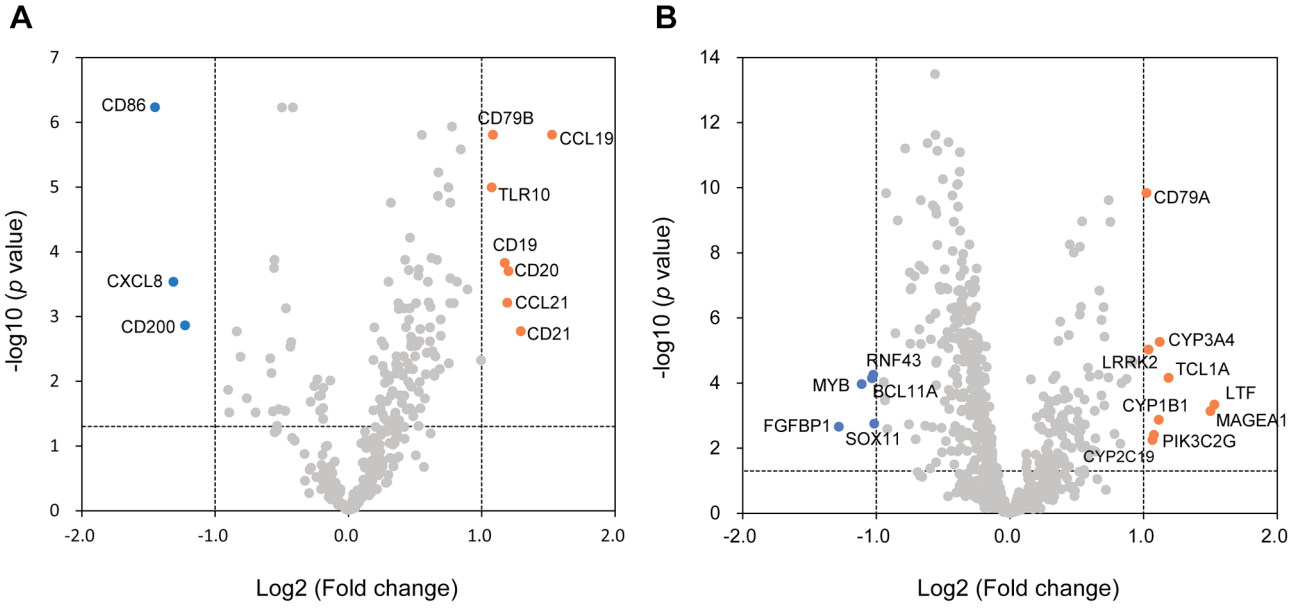

Figure 5. *Comparison of gene expression between the SMARCA4 expression-low and -high groups of SMARCA4 gene-mutant solid cancers. (A) Immune response-associated genes and (B) cancer-associated SCC820 genes. Up-regulated or down-regulated genes with changes greater than 1.5-fold were identified using volcano plots with Benjamini-Hochberg correction. The horizontal gray line represents a p-value of 0.05. The vertical lines show 2-fold changes in gene expression. Filled circles in orange and blue represent up-regulated and down-regulated genes, respectively.*

Table IV. *Expression-alterd immune response-associated gene list in SMARCA4-mutant cancers with lower SMARCA4 gene expression.*

35 Up-regulated genes			10 Down-regulated genes		
Gene symbol	FC	*p*-Value	Gene symbol	FC	*p*-Value
CCL19	2.88	1.6E-06	CD86	–2.73	5.9E-07
CR2 (CD21)	2.45	1.7E-03	CXCL8	–2.48	2.9E-04
MS4A1 (CD20)	2.30	2.0E-04	CD200	–2.34	1.4E-03
CCL21	2.29	6.1E-04	CCL20	–1.87	1.4E-02
CD19	2.26	1.5E-04	CSF3	–1.86	3.0E-02
CD79B	2.12	1.6E-06	IL20RA	–1.79	1.7E-03
TLR10	2.11	1.0E-05	EDAR	–1.75	4.2E-03
TNFRSF17	1.99	4.7E-03	CSF2	–1.70	1.8E-02
CXCL12	1.86	3.8E-04	TNFSF9	–1.62	3.0E-02
IL6R	1.79	2.6E-06	ULBP1	–1.50	4.4E-03
CD27 (TNFRSF7)	1.76	2.9E-04			
CD40LG (TNFSF5)	1.73	6.2E-04			
CD40 (TNFRSF5)	1.71	1.2E-06			
TLR7	1.70	1.7E-05			
TNFSF14	1.70	2.6E-04			
CCL5	1.70	6.2E-04			
NGFR	1.69	5.3E-03			
CD79A	1.68	1.0E-05			
LTB	1.62	1.1E-03			
CCR7	1.62	2.0E-03			
IRF4	1.61	6.5E-03			
TNFSF10	1.60	6.0E-06			
EBI3	1.59	1.4E-05			
HLA-DPA1 (HLA-DPA)	1.59	1.3E-04			
KLRK1 (CD314. NKG2D)	1.57	4.1E-03			
TIMD4	1.57	7.5E-03			
CD38	1.56	8.3E-03			
LAMA2	1.55	3.4E-03			
IL10RA	1.54	1.2E-04			
TNFRSF13B	1.53	7.1E-04			
CD8B	1.53	2.4E-03			
LEPR	1.53	1.5E-03			
HLA-DRB1	1.52	6.1E-04			
CCR10	1.51	2.9E-04			
CD3D	1.50	3.6E-03			

FC, Fold change.

Briefly, T-cell effector genes *(CD8B, CD40LG*), central memory marker genes (*CD27, CCR7*) and mature B-cell marker genes (*CD20, CD38, CD79, IRF4*) were up-regulated. In addition, the *CCL19* and *CCL21* chemokine genes, which attract functional T- and B-cells inside tumors, increased in expression in the *SMARCA4* expression-low group. In contrast, the *IL20RA, CD200* and *CXCL8* genes, which induce an immunosuppressive TME, were down-regulated.

Cancer-associated genes, including *MYB*, *MYC* and *AURKB*, which correlate with oncogenic signaling and immunosuppression, were down-regulated in the *SMARCA4* expression-low group.

Scheme for the immune-activating state induced by SMARCA4 down-regulation in SMARCA4-mutated cancers. The hypothesis that *SMARCA4* down-regulation induces immune-activation events in an immune-suppressive TME is shown in Figure 6. Down-regulation of 3 main genes in the TME, *MYC*, *AURKB* and *IL20R*, might trigger TIL (effector T-cell and mature B-cell) induction, cell cycle arrest and chromatin remodeling insufficiency, which may contribute to immune activation.

Heatmap of 23 tertiary lymphoid structure (TLS)-associated gene expression between SMARCA4 expression-high and -low groups in SMARCA4-mutated stomach cancers. Among 23 TLS-associated genes, mature B cell marker genes (CD19, CD20, CD27, CD38, CD40), follicular DC marker genes (CD21, CCR7) and chemokine genes (CCL19, CCL21, CXCL13) were up-regulated in the

Table V. *Expression-alterd cancer-associated gene list in SMARCA4-mutant cancers with lower SMARCA4 gene expression.*

29 Up-regulated genes			30 Down-regulated genes		
Gene symbol	FC	*p*-Value	Gene symbol	FC	*p*-Value
LTF	2.89	4.6E-04	FGFBP1	–2.43	2.2E-03
MAGEA1	2.83	7.3E-04	MYB	–2.16	1.1E-04
TCL1A	2.28	6.9E-05	BCL11A	–2.04	7.1E-05
CYP3A4	2.18	5.4E-06	RNF43	–2.03	5.6E-05
CYP1B1	2.17	1.3E-03	SOX11	–2.02	1.8E-03
PIK3C2G	2.11	3.9E-03	ETV4	–1.92	9.3E-05
CYP2C19	2.10	5.6E-03	APCDD1	–1.91	3.4E-04
LRRK2	2.05	9.5E-06	AXIN2	–1.91	3.0E-04
CD79A	2.03	1.5E-10	RAD54L	–1.90	1.5E-10
CD79B	1.89	2.3E-05	GRM8	–1.89	2.6E-03
IGF1	1.83	7.4E-05	PMAIP1	–1.81	3.0E-06
GATA3	1.78	1.0E-04	BUB1B	–1.79	1.0E-09
POU2AF1	1.77	7.3E-03	FANCB	–1.72	6.2E-12
LIFR	1.72	3.6E-03	ZNF703	–1.69	1.8E-03
CRLF2	1.68	1.1E-09	RECQL4	–1.68	4.0E-08
BCL2L11	1.67	2.4E-10	MYC	–1.68	6.2E-06
NTRK3	1.67	6.7E-05	RAD51	–1.67	1.3E-07
MAP4K1	1.63	3.8E-06	AURKB	–1.67	1.2E-07
FLT3	1.63	4.9E-04	CHEK1	–1.64	5.2E-08
SETBP1	1.63	4.6E-07	SOX9	–1.63	5.3E-03
RET	1.61	2.4E-04	TPX2	–1.60	2.2E-06
PLCG2	1.61	1.2E-06	FANCA	–1.60	2.5E-08
FCGR1A	1.59	1.5E-07	EZH2	–1.59	2.4E-10
ESR2	1.59	5.5E-05	BIRC5	–1.59	6.3E-06
CYP2C8	1.56	1.3E-02	FANCI	–1.56	3.3E-08
ASXL3	1.56	5.0E-03	CCND2	–1.55	2.0E-03
HGF	1.55	7.2E-04	MSH2	–1.53	4.3E-12
IRF4	1.53	1.2E-02	PTGS2	–1.51	4.2E-02
SOX10	1.51	6.3E-05	BCR	–1.51	1.1E-06
			POLQ	–1.51	4.6E-06

FC, Fold change.

SMARCA4-low group compared to the SMARCA4-high group (Figure 7).

Scheme for TLS signature contributing lymphoid structure development and TLS-associated antitumor effect. Lymphoid stromal fibroblasts and follicular dendritic cells producing lymphotoxins and CXCL13 could be developing the budding of lymphoid follicles. CXCL19 and CXCL21 produced by stromal fibroblasts can attract T-cells like follicular helper (FH) T-cells and memory B-cells to form mature TLS with germinal centers. Memory B-cells can proliferate and become mature plasma cells producing specific antibodies, which can migrate, mediated by CXCL12, to tumor tissues leading to antibody-based antitumor effects (Figure 8).

Discussion

The SWI/SNF complex is a conserved ATP-dependent chromatin remodeling complex that is closely involved in gene transcription and DNA damage repair mechanisms (23). Each complex comprises approximately 15 subunits and is classified into 3 categories: the BRG1/BRM-associated factor (BAF) complex, polybromo-associated BAF (PBAF) complex and noncanonical BAF (ncBAF) complex. The component genes comprise *SMARCA4*, *ARID1A, ARID2, PBRM1* and *SMARCB1*. Based on the observation that the SWI/SNF complex shows tumor suppressor function, it has been reported that approximately 20% of human cancers harbor any type of mutations in the SWI/SNF complex (24, 25). Briefly, more than 95% of malignant rhabdoid tumors and epithelioid sarcomas harbor *SMARCB1* mutations leading to loss of SMARCB1 protein expression (14). Recently, an inactivating *SMARCA4* mutation has been demonstrated in almost all small-cell carcinomas of the ovary, hypercalcemic type (SCCOHTs) (8).

Furthermore, very recently, rare round-cell thoracic sarcomas harboring *SMARCA4*-inactivated mutations have been defined as having the following features: rapid course

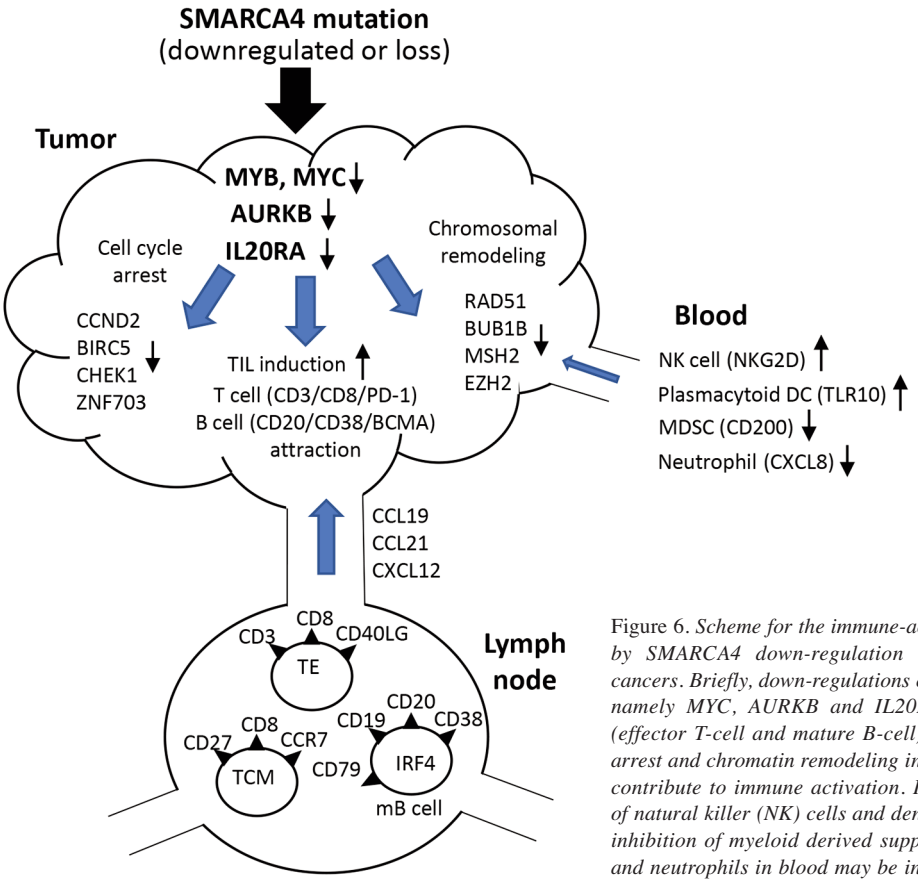

Figure 6. *Scheme for the immune-activating state induced by SMARCA4 down-regulation in SMARCA4-mutant cancers. Briefly, down-regulations of 3 genes in the TME, namely MYC, AURKB and IL20R, might trigger TIL (effector T-cell and mature B-cell) induction, cell cycle arrest and chromatin remodeling insufficiency, which can contribute to immune activation. In addition, activation of natural killer (NK) cells and dendritic cells (DCs) and inhibition of myeloid derived suppressor cells (MDSCs) and neutrophils in blood may be induced.*

and worse prognosis, heavy smoking exposure, frequent presentation at a younger age, *SOX2* up-regulation and claudin-4 loss (26, 27). However, thoracic sarcoma tumors are distinguishable from other *SMARCA4*-mutated (down-regulated) lung adenocarcinomas showing characteristics, such as SMARCA4-deficient adenocarcinoma, CK-positivity and TTF-1 negativity, absence of EGFR driver mutations, and concurrent *SMARCA4* and *TP53* mutations (28).

Next, synthetic lethality-based therapies should be evaluated because SWI/SNF chromatin remodeling complex-deficient tumors are considered to be good targets for those approaches, particularly in *ARID1A*-, *SMARCA2*- and *SMARCA4*-mutant tumors, which have resulted in the development of PARP and EZH2 inhibitors (17, 18). From a cancer metabolic point of view, OXPHOS inhibitors have been demonstrated to be effective for *SMARCA4*-mutated tumors (29).

Importantly, the SWI/SNF chromatin remodeling complex-deficient state leads to chromatin instability, which activates or triggers the cGAS-STING pathway to sensitize the immune system to broken DNA or RNA released from collapsed nuclei (30-32). Our preliminary genomic analysis data revealed that MMR-deficient (MSI-high) colorectal cancers show up-

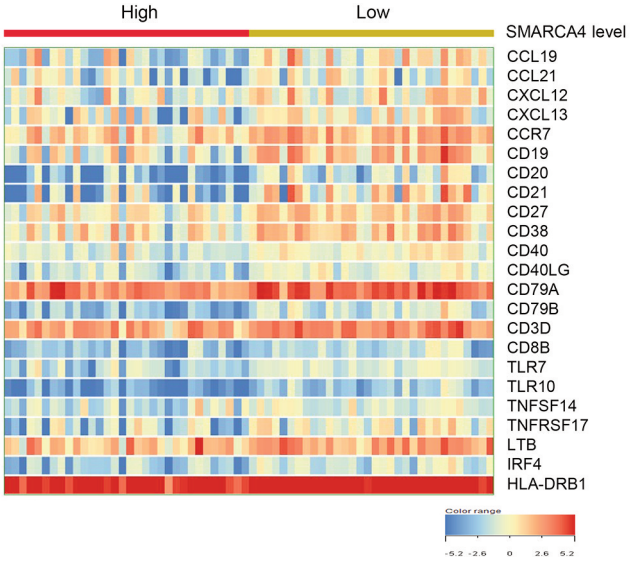

Figure 7. *Comparison of the expression levels of TLS-associated 23 genes between SMARCA4-high group and -low groups in SMARCA4-mutated stomach cancers. The data are presented in matrix format, where each row represents an individual case, and each column represents a gene. The red and green colors reflect the gene expression levels, as indicated in the color scale (log2-transformed scale) in the bottom right corner.*

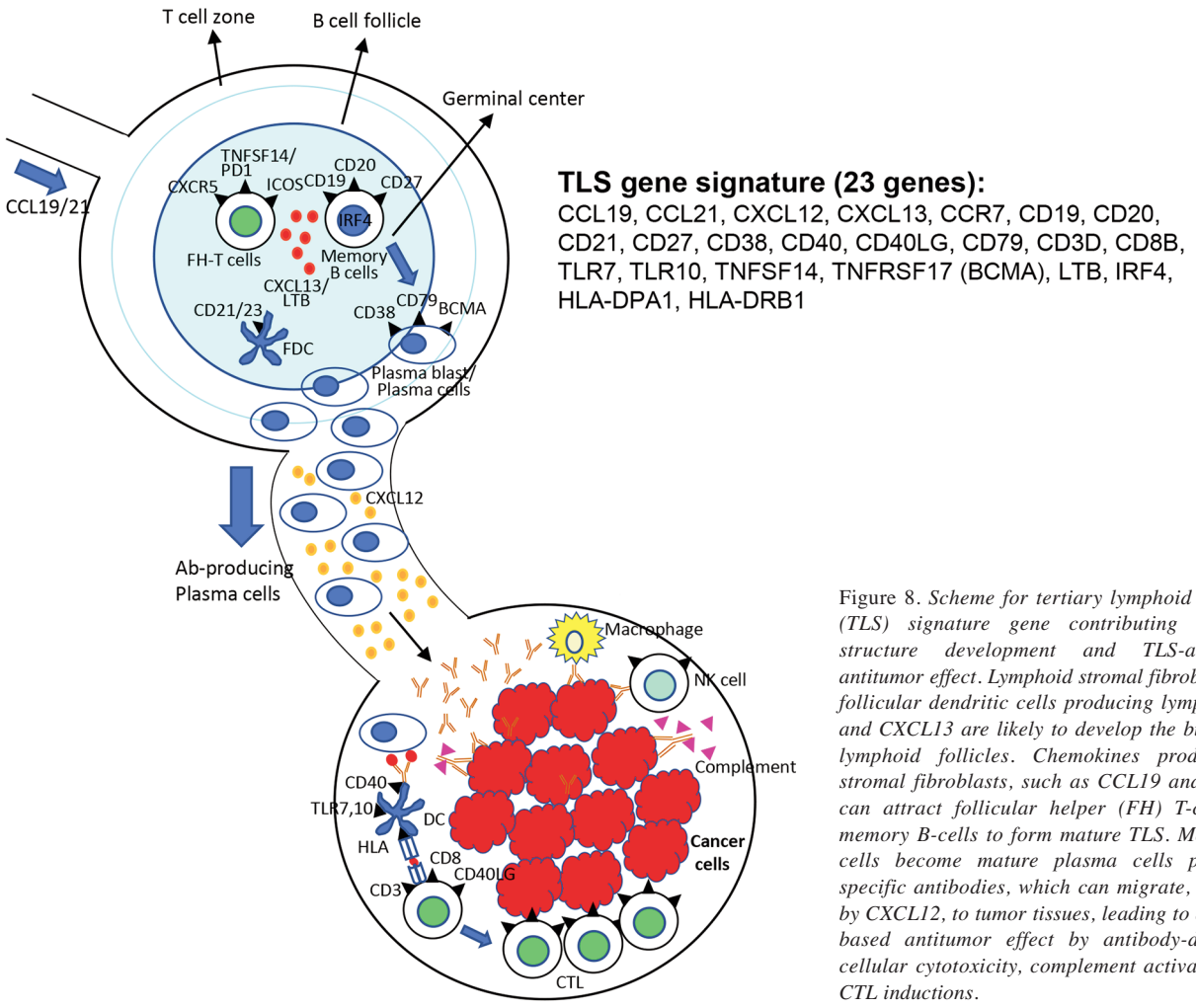

Figure 8. *Scheme for tertiary lymphoid structure (TLS) signature gene contributing lymphoid structure development and TLS-associated antitumor effect. Lymphoid stromal fibroblasts and follicular dendritic cells producing lymphotoxins and CXCL13 are likely to develop the budding of lymphoid follicles. Chemokines produced by stromal fibroblasts, such as CCL19 and CCL21, can attract follicular helper (FH) T-cells and memory B-cells to form mature TLS. Memory B-cells become mature plasma cells producing specific antibodies, which can migrate, mediated by CXCL12, to tumor tissues, leading to antibody-based antitumor effect by antibody-dependent cellular cytotoxicity, complement activation, and CTL inductions.*

regulation of *cGAS-STING* mRNAs, resulting in functional type-I interferon production (unpublished data).

Remarkably, a few studies have demonstrated that immune checkpoint blockade (ICB) therapy leads to positive antitumor responses in *PBRM1*-deficient clear cell renal cell cancer (33) and *ARID1A*-deficient ovarian cancers (19). Furthermore, Alessi *et al*. reported the response to ICB therapy against *SMARCA4*-mutated non-small cell lung cancer and demonstrated no difference in the objective clinical response rate between *SMARCA4*-wild type and *SMARCA4*-mutated non-small cell lung cancer (NSCLC) groups; however, the concurrent *SMARCA4* and *KRAS*-mutated NSCLC group showed a significantly lower overall response rate (ORR) and shorter median overall survival than the *SMARCA4*-mutant alone group (34). Other clinical researchers have reported similar observations except one case report, which showed a responder to the combination of chemotherapy and ICB (35-37).

Despite previous reports regarding the clinical response of ICB therapy in *SMARCA4*-mutated cancers, few studies have investigated the immune TME derived from SWI/SNF chromatin remodeling complex gene-mutated tumors (38, 39). Ganzer *et al*. characterized nine cases of thoracic *SMARCA4*-deficient undifferentiated tumors and found that all specimens had an immune-desert TME phenotype; four patients were given ICB therapy, but only one responded (38).

In the current study, T-cell (*CD3*, *CD8* and *PD-1*) and mature B-cell marker (*CD19*, *CD20*, and *CD38*) genes were up-regulated inside the tumor in *SMARCA4*-mutant solid tumors with low SMARCA4 expression (below median). To the best of our knowledge, this is the first report of *SMARCA4*-mutant tumors. With regard to the association of TMB with TIL accumulation, considering that TMB levels were higher in the SMARCA4 expression-high group of SMARCA4-mutated stomach cancers, TMB is unlikely to be involved in TIL accumulation.

Our hypothesis scheme shown in Figure 6 suggests that immune-activating events inducing T- and B-cell attraction derived from *MYC*, *AURKB* and *IL20RA* gene down-regulation (40, 41) involved in *SMARCA4*-inactivating mutation might be triggered. These results may suggest that the immune TME signature, such as TIL recruitment and immune activation, could contribute to classification of SWI/SNF chromatin remodeling complex gene-mutated tumors as immune checkpoint blockade therapy-sensitive target tumors.

Conclusion

The tertiary lymphoid structure (TLS)-associated gene signature has been proposed in the present study; 23 genes, such as mature B cell marker genes (CD19, CD20, CD27, CD38, CD40, TNFRSF17, IRF4), follicular DC marker genes (CD21, CCR7) and chemokine genes (CCL19, CCL21, CXCL13), were up-regulated in SMARCA4-mutated stomach cancers. Previous research has demonstrated that TLS signature genes are closely involved in budding of lymphoid tissue, development, and maturation of lymphoid follicles with germinal center inside the tumor (42, 43).

At the moment specific reasons or mechanisms that induced TLS development and mature B cell accumulation in SMARCA4-mutated stomach cancers have not been elucidated. In the future, TLS gene signature could become a possible biomarker for immune checkpoint-based immunotherapy promoting functional antibody production against cancers. Thus, TLS might be a novel source for cancer neoantigen-specific antibodies and a promising target for single-cell RNAseq-based analysis.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

CH and YA participated in the design of the study and drafting of the manuscript and were responsible for supervising the study. TN, KO, YS, and KU performed the genetic analysis using NGS and gene microarray. AI, HM, CM, and TA mainly performed the immunological *in vitro* experiments. TI performed the statistical analysis. KM and TS contributed to the preparation and staining of pathological specimens. AS, YO, EB, KF, Teiichi Sugiura, TM, SN, YH, Koichi Mitsuya, SY, YT, HK, and MN were involved in collecting the clinical samples and clinical data. Hirotsugu Kenmotsu and KY reviewed the manuscript. All the authors have read and approved the final draft.

Acknowledgements

We thank the staff of the Shizuoka Cancer Center Hospital for assistance in sample preparation and the members of the Shizuoka Cancer Center Research Institute for discussions. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Received August 25, 2023
Revised October 18, 2023
Accepted October 24, 2023