To the editor:

The *RHOA* G17V gene mutation occurs frequently in peripheral T-cell lymphoma and is associated with a characteristic molecular signature

Peripheral T-cell lymphomas (PTCLs) are a group with poor outcome and nonspecific therapeutic regimens. Recently, Palomero et al[1] and Sakata-Yanagimoto et al[2] identified a recurrent heterozygous mutation in the *RHOA* small GTPase gene encoding a p.Gly17Val alteration (G17V) that leads to inhibition of the ρ-signaling pathway. Because the RHOA/ρ-kinase pathway plays a pivotal role in many cellular functions, we wanted to establish whether the G17V mutation of the *RHOA* gene (*RHOA-G17V*) has any biological relevance in nodal PTCL (n-PTCL).

Twenty-six frozen n-PTCL-samples (13 peripheral T-cell lymphomas not specified [PTCL-NOSs], 11 angioimmunoblastic T-cell lymphomas [AITLs], and 2 anaplastic large cell lymphomas) were hybridized on a whole-human-genome oligo microarray and analyzed for the presence of the *RHOA-G17V* using a specific qBiomarker somatic-mutation PCR assay (SABiosciences). Expression profile data were analyzed with gene set enrichment analysis software. *RHOA-G17V* was found in 6 AITLs and 3 PTCL-NOSs (34.6% of cases). Thirty-two gene sets were overrepresented in the mutated subgroup of tumors. Of particular significance were the pathways related to the follicular helper CD4 T-cell and AITL signature. Moreover, other pathways of great relevance to PTCL pathogenesis, such as p38 mitogen-activated protein kinase, phosphatidylinositol 3-kinase, KRAS, the alternative nuclear factor κB (NF-κB) pathway, and the RAC1 pathway, were significantly associated with the presence of the *RHOA-G17V* (see supplemental Table 1 available at the *Blood* Web site).

The presence of *RHOA-G17V* was further analyzed by the previously described method in an independent consecutive series of 136 paraffin-embedded n-PTCL samples. Positive results were confirmed by Sanger sequencing of the mutated region. A total of 26.4% (32/121) of the cases carried *RHOA-G17V*. A total of 34.2% (25/73) of cases were AITL; 14.6% (7/48) were PTCL-NOS ($P = .016$), 3 of which had AITL-like features. The lower percentage of mutated cases than previously reported,[1,2] especially in AITLs, may have been due to the lower sensitivity of our assay and the paucity of tumoral cells in some AITL cases.

Immunohistochemical studies using tissue microarrays revealed a positivity for programmed cell death 1 (PD-1),[3] phospho-extracellular signal-regulated kinase (p-ERK), p50, and p52 in 48.5% (66/136), 32.1% (41/136), 72.1% (98/136), and 59.6% (81/136) of patients, respectively. The presence of PD-1, nuclear p-ERK, or p52 expression was significantly positively correlated with the presence of *RHOA-G17V* ($P = .024$, 0.002, and 0.042, respectively).

There is a relationship between *RHOA* and Rac1 in which a high level of Rac activity leads to a reduction in that of ρ, and vice versa.[4] Rac1 activity also activates multiple downstream effectors, including the NF-κB, p38 mitogen-activated protein kinase, and mitogen-activated protein kinase kinase/extracellular signal-regulated kinase pathways.[5,6] These findings are consistent with gene set enrichment analysis results, and some of them were validated by immunohistochemistry in an independent series of patients. However, explanations involving other biological mechanisms cannot be ruled out.[7]

Although standard prognostic indices for this series (International Prognostic Index and Prognostic Index for PTCL-u) identified prognostic subgroup of patients (both indices, $P < .001$), the mutational status of the *RHOA* gene did not, either in the total group of all patients or after histologic subclassification (AITL vs PTCL-NOS) (Table 1 and supplemental Tables 2-3 available on the *Blood* Web site.).

We and other researchers have previously reported the usefulness of NF-κB, phosphatidylinositol 3-kinase/AKT, and extracellular signal-regulated kinase pathway inhibitors for treating PTCL patients.[8,9] The findings presented here suggest that *RHOA-G17V* could identify patients who are sensitive to some of these inhibitors. Further clinical and biological studies are needed to validate these results.

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Table 1. Univariate analysis of the clinical and molecular parameters and the mutational status of the *RHOA* gene in the cohort of 121 patients with PTCLs

RHOA	Total cases	WT	MUT	*P*
DX	121/121			.016
AITL		48/73 (65.8%)	25/73 (34.2%)	
PTCL-NOS		41/48 (85.4%)	7/48 (14.6%)	
p-ERK	121/121			.002
Negative		70/86 (81.4%)	16/86 (18.6%)	
Positive		19/35 (54.3%)	16/35 (45.7%)	
p50	118/121			.166
Negative		25/30 (83.8%)	5/30 (16.7%)	
Positive		62/88 (70.5%)	26/88 (29.5%)	
p52	117/121			.042
Negative		34/40 (85%)	6/40 (15%)	
Positive		52/77 (67.5%)	25/77 (32.5%)	
NF-κB	119/121			.068
None		16/18 (88.9%)	2/18 (11.1%)	
p50 or p52		30/37 (81.1%)	7/37 (18.9%)	
Both		42/64 (65.6%)	22/64 (34.4%)	
PD-1	88/121			.024
Negative		24/27 (88.9%)	3/27 (11.1%)	
Positive		40/61 (65.6%)	21/61 (34.4%)	
Sex	117/121			.064
Male		47/69 (68.1%)	22/69 (31.9%)	
Female		40/48 (83.3%)	4/48 (16.7%)	
Age at diagnosis	114/121			.453
<60 y		33/42 (78.6%)	9/42 (21.4%)	
≥60 y		52/72 (72.2%)	20/72 (27.8%)	
IPI	106/121			.560
Low risk		26/32 (81.2%)	6/32 (18.8%)	
Low-intermediate risk		18/27 (66.7%)	9/27 (33.3%)	
High-intermediate risk		19/26 (73.1%)	7/26 (26.9%)	
High risk		14/21 (66.7%)	7/21 (33.3%)	
PIT	94/121			.962
Low risk		10/14 (71.4%)	4/14 (28.6%)	
Low-intermediate risk		26/35 (74.3%)	9/35 (25.7%)	
High-intermediate risk		15/22 (68.2%)	7/22 (31.8%)	
High risk		16/23 (69.6%)	7/23 (30.4%)	
ECOG	102/121			.479
<1		53/72 (73.6%)	19/72 (26.4%)	
≥1		20/30 (66.7%)	10/30 (33.3%)	
Treatment	106/121			.068
CHOP/CHOP-like		61/76 (80.3%)	15/76 (19.7%)	
Others		19/30 (63.3%)	11/30 (36.7%)	
Response	96/121			.446
CR		44/61 (72.1%)	17/61 (27.9%)	
PR		13/15 (86.7%)	2/15 (13.3%)	
No response		16/20 (80%)	4/20 (20%)	
Recurrence	94/121			.660
No		50/66 (75.8%)	16/66 (24.2%)	
Yes		20/28 (71.4%)	8/28 (28.6%)	
State of the patient	112/121			.615
Dead		50/69 (72.5%)	19/69 (27.5%)	
Alive		33/43 (76.7%)	10/43 (23.3%)	

CHOP, cyclophosphamide, vincristine, doxorubicin, prednisone; CR, total response; DX, diagnosis; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; MUT, mutated; PIT, Prognostic Index for PTCL-u; PR, partial response; WT, wild type.

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