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Review Article

RET fusion gene: Translation to personalized lung cancer therapy

Takashi Kohno,[1,2,5] Koji Tsuta,[3] Katsuya Tsuchihara,[1] Takashi Nakaoku,[2] Kiyotaka Yoh[4] and Koichi Goto[4]

[1]Division of Translational Research, Exploratory Oncology Research & Clinical Trial Center (EPOC), National Cancer Center, Tokyo; [2]Division of Genome Biology, National Cancer Center Research Institute, Tokyo; [3]Division of Pathology and Clinical Laboratories, National Cancer Center Hospital, Tokyo; [4]Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

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Development of lung adenocarcinoma (LADC), the most frequent histological type of lung cancer, depends in many cases on the activation of "driver" oncogenes such as *KRAS*, epidermal growth factor receptor (*EGFR*), and anaplastic lymphoma kinase (*ALK*). Inhibitors that target the EGFR and ALK tyrosine kinases show therapeutic effects against LADCs containing *EGFR* gene mutations and *ALK* gene fusions, respectively. Recently, we and others identified the *RET* fusion gene as a new targetable driver gene in LADC. The RET fusions occur in 1–2% of LADCs. Existing US Food and Drug Administration-approved inhibitors of RET tyrosine kinase show promising therapeutic effects both *in vitro* and *in vivo*, as well as in a few patients. Clinical trials are underway to investigate the therapeutic effects of RET tyrosine kinase inhibitors, such as vandetanib (ZD6474) and cabozantinib (XL184), in patients with *RET* fusion-positive non-small-cell lung cancer. (*Cancer Sci* 2013; 104: 1396–1400)

Personalized Therapy of LADC

Lung cancer is the leading cause of cancer-related mortality worldwide. Lung adenocarcinoma (LADC) is the most frequent type of lung cancer. LADC occurs both in smokers and non-smokers, and its incidence is increasing.[1] Genome analyses of LADC show that these tumors contain distinct genetic alterations that activate oncogenes.[2,3] Genetic alterations that result in the activation of several oncogenes are detected in a mutually exclusive manner (Fig. 1); of the hundreds of genes mutated in each case of LADC, these oncogenes are considered to be "driver genes".[4] Remarkably, molecular targeted therapy using inhibitory drugs against activated oncogene products has begun to replace conventional chemotherapy using cytotoxic drugs, even for first-line use.[2]

The epidermal growth factor receptor (*EGFR*) gene is activated by single amino acid substitution mutations or in-frame amino acid deletion mutations in 10–20% of LADC cases in the USA and in 30–40% of cases in East Asia.[2] Tumors harboring these *EGFR* mutations respond to EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib, thereby improving progression-free survival and quality of life.[5,6] In addition, 3–5% of LADC harbor fusions that result in the activation of the anaplastic lymphoma kinase (*ALK*) gene; such mutations are mutually exclusive with *EGFR* mutations. Inhibitors, such as crizotinib, that target ALK tyrosine kinase show marked therapeutic effects against ALK fusion-positive LADCs.[7–9] These results indicate that personalized therapy for LADC using TKIs selected on the basis of somatic genetic alterations has been realized already; indeed, 20% of USA/European and 40% of Asian LADC patients benefit from such therapies.

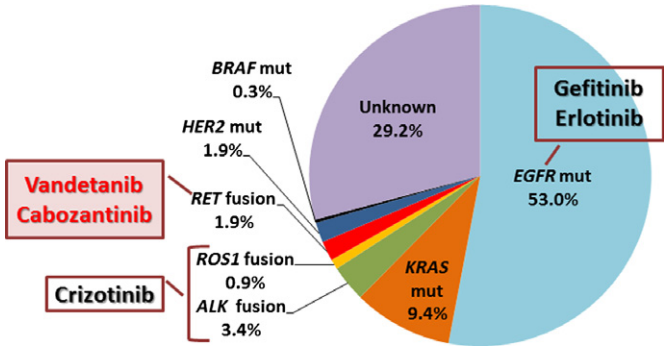

Fig. 1. Pie chart showing the fraction of Japanese lung adenocarcinoma patients that harbor "driver" gene mutations. Surgical specimens from 319 stage I–II lung adenocarcinomas deposited in the National Cancer Center Biobank (Japan) were subjected to analysis. The *EGFR*, *KRAS*, *BRAF*, and *HER2* mutations (mut) were examined using the high resolution melting method, whereas *ALK*, *ROS1* and *RET* fusions were examined by RT-PCR.[12,31] The protocol for this research project has been approved by the institutional review board of the National Cancer Center.

Discovery of the *RET* Fusion Gene as a New Targetable Driver Gene

In 2012, four studies, including one by our group, identified fusions of the *RET* (rearranged during transfection) oncogene[10–13] (Fig. 2). *RET* is a well-known driver oncogene kinase for thyroid cancer, and both activating mutations and fusions of this gene have been observed.[14,15] Germline gain-of-function mutations in *RET* predispose carriers to multiple endocrine neoplasia type 2, which is characterized by medullary thyroid cancer, pheochromocytoma, and hyperparathyroidism, and also to familial medullary thyroid carcinoma syndrome. Somatic gain-of-function *RET* mutations have been observed in 30–50% of sporadic medullary thyroid cancer, and somatic *RET* gene fusions have been observed in 30–50% of sporadic papillary thyroid cancer. The US Food and Drug Administration (FDA) have approved two inhibitory drugs, vandetanib (ZD6474) and cabozantinib (XL184), for the treatment of advanced medullary thyroid cancer. The molecular process for generating a *RET* fusion is similar to the mechanism underlying *ALK* fusion: the most frequent *RET*

[5]To whom correspondence should be addressed.
E-mail: tkkohno@ncc.go.jp

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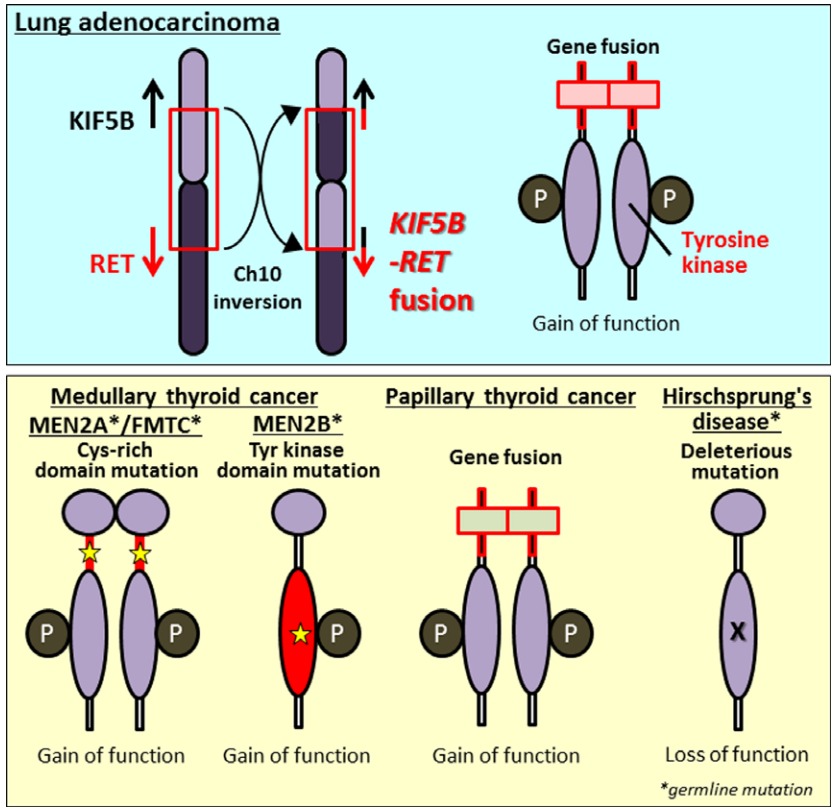

Fig. 2. Involvement of the *RET* gene in lung and thyroid carcinogenesis and in a developmental disorder. Upper panel, somatic inversion in chromosome 10 results in *KIF5B–RET* fusions. The RET fusion protein has constitutive tyrosine (Tyr) kinase activity, representing a gain-of-function alteration. Lower panel, *RET* alterations in other diseases. A germline gain-of-function mutation of *RET* drives thyroid carcinogenesis in patients with multiple endocrine neoplasia type 2 (MEN2). Somatic gain-of-function mutation and translocation of *RET* cause medullary and papillary thyroid cancers, respectively. Germline loss-of-function *RET* mutations cause Hirschsprung's disease, a hereditary disorder characterized by the absence of enteric ganglia in variable segments of intestine. FMTC, familial medullary thyroid carcinoma; P, phosphorylation; X, inactivating mutation.

fusion, *KIF5B–RET*, is generated by a pericentric inversion in chromosome 10, whereas the most frequent *ALK* fusion, *EML4–ALK*, is generated by a paracentric inversion in chromosome 2 (Fig. 2).

Four different strategies resulted in the discovery of the same *RET* fusion gene (Table 1, Fig. 3). We carried out whole-transcriptome sequencing using RNA from 30 snap-frozen surgical LDAC specimens to identify novel fusion-gene transcripts.[12] Ju *et al.*[13] analyzed the whole genome and transcriptome of a single young (33-year-old) LADC patient. Lipson *et al.*[11] carried out targeted-capture sequencing of 145 cancer-relevant genes from genomic DNA obtained from 24 formalin-fixed paraffin-embedded tumor samples to identify genes mutated or fused in LADC. Takeuchi *et al.*[10] carried out a FISH-based screen against known fusion kinase and partner genes to detect rearrangement of oncogenes in >1500 LADC cases.

To date, *RET* fusions have been identified that involve four fusion partners comprising nine subtypes of fusion variants: *KIF5B*, *CCDC6/PTC/H4*, *NCO4/PTC3/ELE1*, and *TRIM33 /PTC7*.[16] The latter three partners are also fused to *RET* in thyroid cancer, whereas *KIF5B* is not. The deduced features of the proteins encoded by all types of *RET* fusion gene are similar to those of ALK: coiled-coil domains in the N-terminal fusion partners cause the RET domains to dimerize, resulting in activation of RET tyrosine kinase in the absence of ligands (Fig. 2). The ligand-independent dimerization and constitutive activation of RET protein are also caused by gain-of-function mutations and translocations of *RET,* which have been detected in sporadic and hereditary thyroid cancers.[15] In fact, autophosphorylation of the KIF5B–RET fusion protein, representing RET protein activation, was observed in LADC tissues harboring the corresponding *RET* fusion gene,[12] as well as in cells cultured in the absence of serum. The transforming and signal-addictive activities of KIF5B–RET fusion proteins are suppressed by FDA-approved drugs (e.g., vandetanib, sorafenib, and sunitinib), which themselves suppress RET kinase.[10–12] In addition, the LADC cell line, LC-2/ad, which harbors a *CCDC6–RET* fusion, is sensitive to these drugs both *in vitro* and *in vivo*.[17,18] Unfortunately, these drugs are not approved for use as treatments for lung cancer; however, the existing data led us to investigate their therapeutic effects in clinical trials, as described below.

Prevalence and Characteristics of *RET* Fusion-Positive LADC

Several studies have validated the presence of *RET* fusion in a small subset of non-small-cell lung cancers (NSCLCs).[16,19–24] The total number of examined cases has reached approximately 5000 (Table 1). Most of the positive cases are LADC, but several cases involve other histological types of NSCLC, such as adenosquamous carcinoma.[19,20] The *RET* fusions are present in 1–2% of NSCLC/ADC of patients of both Asian and European descent. Several studies indicate that *RET* fusion occurs preferentially in young, never-smoker, and light-smoker patients.[10,12,20]

The LADCs harboring *KIF5B–RET* fusions are well or moderately differentiated, similar to LADCs harboring *EGFR* mutations. This is in contrast to *EML4–ALK* fusion-positive LADCs, which tend to show signet-ring and mucinous cribriform patterns.[10] Those LADCs harboring *CCDC6–RET* fusions show such histological features.[10,18]

In our previous study, we did not detect *RET* fusions in a screen of 234 squamous cell, 17 large cell, and 20 small-cell lung cancers.[12] Adenocarcinomas of other organs, such as colon (n = 200) and ovary (n = 100), were also negative for *RET* fusion. To date, whole-transcriptome analysis of other organs has not identified *RET* fusions in cancers outside the lung. Therefore, *RET* fusion may occur mainly in LADC and papillary thyroid cancer.

Table 1. Prevalence of *RET* gene fusion in non-small-cell lung cancer (NSCLC)

Institution	No. of cases examined	No. of *RET* fusion (+) cases	*RET* fusion%	Fusion type	Ref.
	NSCLC/lung adenocarcinoma				
National Cancer Center, Japan	704/433	7/7	1.0/1.6	*KIF5B–RET*: 7	12
Japan Foundation for Cancer Research, Japan	1482/1119	13/13	0.9/1.2	*KIF5B–RET*: 12 *CCDC6–RET*: 1	10
Foundation Med, USA	643/561	12/12	1.8/2.1	*KIF5B–RET*: 12	11
Seoul National University, Korea	21/21 (Driver mutation −)	3/3	14/14	*KIF5B–RET*: 3	13
Chinese Academy of Sciences, China	202/202 (Driver mutation −)	2/2	1.0/1.0	*CCDC6–RET*: 2	24
Nagoya City University, Japan	371/270	3/3	0.8/1.1	*KIF5B–RET*: 3	23
Memorial Sloan-Kettering Cancer Center, USA	69/69 (Driver mutation −)	1/1	1.4/1.4	*KIF5B–RET*: 1	21
Fudan University Shanghai Cancer Center, China	936/633	13/11	1.4/1.7	*KIF5B–RET*: 9 *CCDC6–RET*: 3 *NCOA4–RET*: 1	20
Tongji University School of Medicine, China	392/231	6/4	1.5/1.7	*KIF5B–RET*: 6	19
Korea Research Institute of Bioscience and Biotechnology, Korea	6/6 (Female non-smoker)	1/1	17/17	*CCDC6–RET*: 1	22
Memorial Sloan-Kettering Cancer Center, USA	31/31 (Driver mutation −)	5/5	16/16	*KIF5B–RET*: 2 *TRIM33–RET*: 1 (Unknown: 2)	16
Total	4857/3576	66/62	1.4/1.8	*KIF5B–RET*: 55 *CCDC6–RET*: 7 *NCOA4–RET*: 1 *TRIM33–RET*: 1	

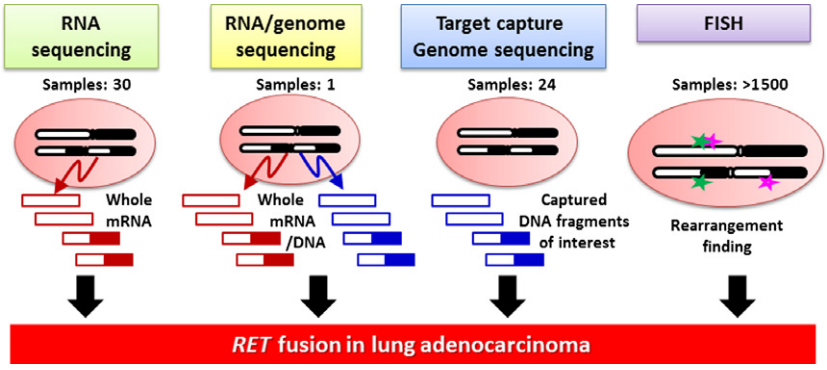

Fig. 3. Strategies used to identify *RET* fusion in lung adenocarcinoma. Four different methods were used to identify novel oncogenic fusions in lung adenocarcinomas.[10–13]

Therapeutic Effects of RET TKIs in Patients with *RET* Fusion-Positive NSCLC

In clinical trials, the ALK TKI, crizotinib, showed a dramatic therapeutic effect against NSCLCs harboring *ALK* gene fusions. Crizotinib was approved for use in the USA in August 2011 and for use in Japan in March 2012.[8] Considering that the *ALK* gene fusion was first identified in NSCLC in 2007, approval has been achieved extremely rapidly. Consequently, the discovery of the *RET* fusion has raised expectations that patients with NSCLCs harboring *RET* fusions will soon benefit from targeted therapy using existing RET TKIs.

Several commercially available multikinase inhibitors, such as vandetanib (ZD6474), cabozantinib (XL184), sorafenib, sunitinib, lenvatinib (E7080), and ponatinib (AP24534), have activity against the RET kinase; however, no selective RET inhibitors have yet been developed for clinical use. Several phase II clinical trials have been initiated to investigate the therapeutic effects of such multikinase inhibitors in patients with advanced *RET* fusion-positive NSCLC (Table 2). As for previous clinical trials of ALK TKIs, all of these trials have open-label and single-arm designs, with response rate as the primary endpoint. One study, carried out by Drilon *et al.* at the Memorial Sloan-Kettering Cancer Center (NCT01639508),

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Table 2. Ongoing phase II clinical trials of RET tyrosine kinase inhibitors in patients with *RET* fusion-positive non-small-cell lung carcinoma

Trial number†	Drug (pharmaceutical company)	Study design	Primary end-point	Enrolment no.	Study start
NCT01639508	Cabozantinib/XL184 (Exelixis)			25	July 2012
UMIN000010095	Vandetanib/ZD6474 (AstraZeneca)			17	Feb 2013
NCT01823068	Vandetanib/ZD6474 (AstraZeneca)	Open-label, single arm	Response rate	17	April 2013
NCT01877083	Lenvatinib/E7080 (Eisai)			20	April 2013
NCT01813734	Ponatinib/AP24534 (ARIAD)			20	June 2013

†Detailed information is available at http://clinicaltrials.gov/ or https://upload.umin.ac.jp.

Table 3. Response of lung adenocarcinoma patients to RET tyrosine kinase inhibitors

Patient	*RET* fusion gene	Inhibitor	Ethnicity	Sex	Age, years	Pathological diagnosis	Smoking history (pack-year)	Response (% decrease)	Reference
1	*TRIM33–RET*	Cabozantinib	Caucasian	Female	41	Papillary adenocarcinoma	Never-smoker	Partial response (66)	16
2	*KIF5B–RET*	Cabozantinib	African-American	Female	75	Poorly differentiated adenocarcinoma	Never-smoker	Partial response (32)	16
3	*KIF5B–RET*	Cabozantinib	Caucasian	Female	68	Mixed subtype adenocarcinoma	Never-smoker	Stable disease	16
4	*KIF5B–RET*	Vandetanib	Caucasian	Male	58	Poorly differentiated adenocarcinoma	Former smoker (5)	Decrease in size	26

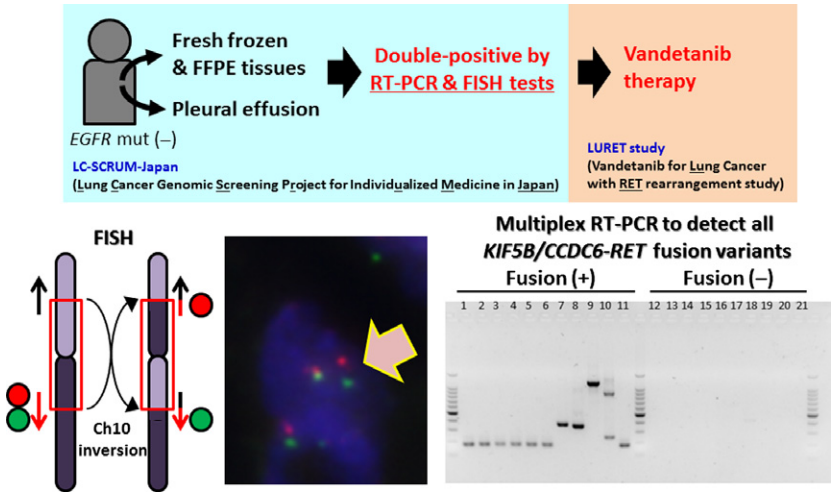

Fig. 4. Consolidated Standards of Reporting Trials diagram of the Lung Cancer Genomic Screening Project for Individualized Medicine in Japan (LC-SCRUM) and the Lung Cancer with *RET* rearrangement (LURET) study in Japan. The LC-SCRUM screen identified 17 *RET* fusion-positive cases from non-squamous non-small-cell lung carcinoma cases without epidermal growth factor receptor (*EGFR*) mutations (mut). The *RET* fusion-positive cases are defined as being positive in both RT-PCR and subsequent FISH tests. Representative pictures of these tests are shown. Fusion-positive cases were treated with vandetanib in the LURET study. Ch10, chromosome 10; FFPE, formalin-fixed paraffin-embedded.

is testing cabozantinib, a drug recently approved by the FDA for the treatment of thyroid cancer. The therapeutic responses of the first three patients to be treated with cabozantinib were reported to be promising (Table 3).[16]

The other phase II clinical trial was initiated by our own group in Japan (UMIN00001009). This trial, designated LURET (Lung Cancer with *RET* rearrangement study), is investigating the therapeutic effects of vandetanib in 17 patients with *RET* fusion-positive NSCLC (Table 2). Because vandetanib is a multikinase inhibitor that is effective against EGFR and vascular endothelial growth factor, this drug was previously examined for its therapeutic efficacy in advanced NSCLC patients in several "all-comer" clinical trials.[25] Those trials were carried out without considering gene alterations in determining eligibility, and the trials did not show significantly greater therapeutic effects than pre-existing therapeutic regimens. Therefore, only *RET* fusion-positive cases, which represent 1–2% of all NSCLCs, are eligible for the LURET study.

To evaluate eligibility for this study, we established a diagnostic method for detecting *RET* fusions using a combination of RT-PCR and FISH (Fig. 4). In this study, RNAs from frozen biopsy tissue or pleural effusion from patients with non-squamous NSCLCs without *EGFR* mutations are subjected to RT-PCR; this method enables us to detect all seven *KIF5B–RET* and *CCDC6–RET* variants identified to date.[16] The positive cases are then subjected to break-apart and fusion FISH to validate the RT-PCR results. Cases positive by both RT-PCR and FISH are eligible for the LURET study. The RT-PCR screening is being carried out in >100 hospitals throughout Japan by a consortium designated LC-SCRUM (Lung Cancer Genomic Screening Project for Individualized Medicine in Japan). The therapeutic results will be obtained within 2 years.

Notably, a recent study reported that one patient with LADC harboring a *KIF5B–RET* fusion responded to vandetanib (Table 3). The patient was Caucasian male and a former smoker. Tumor shrinkage was observed starting in the first week, and continued for 4 weeks.[26]

Perspective

The *RET* gene is predicted to be an additional therapeutic target for therapy against LADC. Three other oncogene kinases,

HER2 (activated by inflame insertion mutations), BRAF (activated by point mutation), and ROS1 (activated by gene fusion) are also promising targets for personalized therapy in addition to EGFR and ALK (Fig. 1). In fact, inhibition of these kinases has yielded therapeutic effects in several lung cancer patients. The LADCs harboring *HER2* mutations responded to therapy with anti-HER2 antibodies and HER2 TKIs.[27] One LADC case harboring a *BRAF* mutation responded to therapy with vemurafenib, an FDA-approved drug for the treatment of melanoma.[28] The ALK TKI, crizotinib, suppresses the activity of the ROS1 tyrosine kinase due to the high structural similarity between the ALK and ROS1 tyrosine kinase domains. Consistent with this, a significant portion of the LADC patients with *ROS1* fusions that were enrolled in a clinical trial responded to crizotinib.[29] Therefore, developing therapies that target RET and other kinases means that increasing numbers of LADC patients will benefit from personalized therapy (Fig. 1). Thus, LADC represents a type of cancer in which "precision cancer medicine"[30] based on somatic gene alterations will be realized.

Acquisition of drug resistance is a serious problem for therapies based on TKIs. The LADCs harboring ALK fusions become resistant to crizotinib by acquiring second-site mutations in the gatekeeper region of ALK tyrosine kinase.[7] Those LADCs harboring *ROS1* fusions also become resistant to crizotinib, in this case through second-site mutations in the gatekeeper region of ROS1.[29] Therefore, *RET* fusion-positive LADCs might also acquire resistance to RET TKIs through the same mechanism. Clinical trials of RET TKIs as a treatment for fusion-positive NSCLCs should be carried out carefully, and focus both on efficacy and the acquisition of resistance.

Acknowledgments

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Disclosure Statement

The authors have no conflict of interest.

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