Priority Report

Kinase Domain Activation of FGFR2 Yields High-Grade Lung Adenocarcinoma Sensitive to a Pan-FGFR Inhibitor in a Mouse Model of NSCLC

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Abstract

Somatic mutations in FGFR2 are present in 4% to 5% of patients diagnosed with non–small cell lung cancer (NSCLC). Amplification and mutations in FGFR genes have been identified in patients with NSCLCs, and clinical trials are testing the efficacy of anti-FGFR therapies. FGFR2 and other FGFR kinase family gene alterations have been found in both lung squamous cell carcinoma and lung adenocarcinoma, although mouse models of FGFR-driven lung cancers have not been reported. Here, we generated a genetically engineered mouse model (GEMM) of NSCLC driven by a kinase domain mutation in FGFR2. Combined with p53 ablation, primary grade 3/4 adenocarcinoma was induced in the lung epithelial compartment exhibiting locally invasive and pleiotropic tendencies largely made up of multinucleated cells. Tumors were acutely sensitive to pan-FGFR inhibition. This is the first FGFR2-driven lung cancer GEMM, which can be applied across different cancer indications in a preclinical setting. Cancer Res; 74(17): 4676–84. ©2014 AACR.

Introduction

Non–small cell lung cancer (NSCLC) currently remains the leading cause of cancer-related deaths worldwide; more than 200,000 new cases are diagnosed annually, of which only 16% of patients survive longer than 5 years (1) NSCLC represents the most common subtype of lung cancer and is composed of large cell, squamous cell, and adenocarcinomas (2), all of which are being intensely researched to further delineate their respective oncogenic drivers and therapeutic targets. In turn, there is a significant preclinical need for the development of novel genetically engineered mouse models (GEMM) that exploit these potential “drivers” to further understand their underlying biology and relevance as therapeutic biomarkers. Upon successful recapitulation of the human disease in the mouse, researchers are able to test novel targeted therapeutics to improve therapies for specific patient genotypes in NSCLCs.

FGFs and their cognate cell surface receptors comprise a large signaling network, playing key roles in embryonic development and normal tissue homeostasis via ligand binding of the extracellular domains in FGFRs. Aberrant activation of these receptor tyrosine kinases (RTK) has been demonstrated in a variety of cancer types. To date, FGFR1 amplification and gene expression has been the most commonly observed, identified in 10% of patients with breast carcinomas (3), approximately 20% of patients with squamous cell lung cancers (4, 5), and 6% of patients with small cell lung cancer (6). FGFR2 mutations have been most highly represented in 12% of patients with endometrial carcinoma (7), both major subtypes of NSCLCs with the squamous cell population displaying a higher rate of mutation (8–10) and gastric tumors (11), as well. Somatic mutations in FGFR3 have been most commonly observed in bladder carcinomas (12) and a serine to cysteine amino acid change at amino acid 249 has been identified in 5% of invasive cervical carcinomas (13). Similar to the case of EML4-ALK, activating chromosomal translocations of FGFRs have begun to be identified in several different cancer types, including bladder cancer (14), multiple myeloma (15), lung squamous cell, thyroid, oral, head and neck squamous, breast and prostate cancers, as well as cholangiocarcinoma and glioblastoma (16). FGFR2/3/4 mutations were also identified in NSCLCs (8, 9) providing the rationale for the creation of GEMMs driven by FGFR-dependent activity.

To date, several mouse models of lung tumorigenesis have been generated that are driven by different FGFR subfamily members (FGF3/7/10). Each of these mouse models exhibited epithelial hyperplasia with some providing adenomas, but none of these models rendered an invasive cancer phenotype (17–19).
More recently, a group described an inducible mouse model driven by FGF9 expression in the adult mouse lung (20). This model was the first to develop papillary adenomas, which progressed to adenocarcinoma with the potential to metastasize and was dependent on a FGF9/FGFR3 signaling axis. Given that FGFR3/7/10 ligands predominantly signal through FGFR2 (21), the preclinical need for additional FGFR-driven models of invasive carcinoma is needed, as mutations in all FGFRs have been identified in various next-generation sequencing efforts in various cancer indications, including NSCLCs (8, 9). In addition, modes of resistance to tyrosine kinase inhibitors related to FGFR de-repression are also of interest. While there have been many FGFR mutations identified in NSCLCs, limited knowledge as to which are oncogenic drivers continues to be an obstacle.

As a result of data generated by TCGA analysis of lung squamous cell and adenocarcinoma, several potential key “drivers” were uncovered. Of those, FGFR2 was of particular interest as it is commonly mutated and/or amplified in patients with both lung squamous cell and adenocarcinoma (8, 9). Upon further evaluation of FGFR2, several key mutations in both the extracellular and kinase domains showed transforming capabilities in vitro and in xenograft studies with profound sensitivity to pan-FGFR inhibitors, such as BGJ-398 and AZD4547 (22). On the basis of these findings and the clear void of mouse models of human lung squamous cell carcinoma, here we report the generation and characterization of FGFR2 mutant GEMMs conditionally expressing an extracellular (W290C) or kinase (K660N) domain activating mutation.

Materials and Methods

**Generation and maintenance of transgenic mice**

Point mutations W290C and K660N within human FGFR2’s cDNA (isoform IIIb) were introduced as described elsewhere (22). In short, sequence-verified constructs were cloned into a modified transgenic targeting vector (23). Sequence-verified targeting vectors were co-electroporated with an FLPe recombinase plasmid into v6.5 C57BL/6J (female) x 129/sv (male) embryonic stem cells (Open Biosystems) as described elsewhere (23). Resulting hygromycin-resistant embryonic stem cells were transduced with a targeting vector (23). Sequence-verified constructs were cloned into a modified transgenic targeting vector (23). Sequence-verified targeting vectors were co-electroporated with an FLPe recombinase plasmid into v6.5 C57BL/6J (female) x 129/sv (male) embryonic stem cells (Open Biosystems) as described elsewhere (23). Resulting hygromycin-resistant embryonic stem clones were injected into black 6 blastocysts, and the resulting chimeras were mated with BALB/c WT mice to determine germline transmission of the Flx; C2107 pfu; University of Iowa) was administered per mouse and averaged with untreated).

**Western blotting and antibodies**

Tumor tissues were mechanically homogenized in RIPA buffer with EDTA (Boston BioProducts) with a protease/phosphatase inhibitor cocktail (Thermo Scientific). Twenty-five micrograms of total protein was separated by SDS-PAGE (Invitrogen) and transferred to polyvinylidene difluoride (PVDF; Millipore). Immunoblots were probed for various antibodies: TTF-1 (Epitomics, #58803-1), SFTPC (Chemicon, #AB378), CC-10 (Santa Cruz, #sc-9772), FGFR2 (Atlas Antibodies, #HPA035305), phospho-FRS2α (Abcam #10425), phospho-FRS2α (Cell Sign. #3861), total-Erk1/2 (Cell Sign. #4695), phospho-Erk1/2 (Cell Sign. #4370), total-Akt (Cell Sign. #9272), phospho-Akt (Cell Sign. #4060), and β-actin (Cell Sign. #4967).

**IHC and antibodies**

Mouse lungs were inflated and fixed with 10% buffered formalin overnight and embedded in paraffin (FFPE). Unstained sections were stained with the following antibodies: TTF-1 (Epitomics, #58803-1), SFTP C (Chemicon, #AB378), CC-10 (Santa Cruz, #sc-9772), FGFR2 (Atlas Antibodies #HPA035305), phospho-FRS2α (Abcam #78195), and phospho-Akt/Erk1/2 (see above). Staining kits for Ki67 (Vector #VP-K451) and TUNEL (Millipore #S7100) were performed per manufacturer’s instructions. Three representative images were quantified per mouse and averaged with a minimum sample size of 6 animals per cohort (treated vs. untreated).

**Statistical analysis**

Pvalues for all survival curves were assessed by log-rank test, whereas all other P values were assessed by the Student t test (GraphPad Prism).

**Results**

Next-generation sequencing of patient samples has been increasingly performed to uncover their oncogenic drivers and...
determine whether or not targeted therapy would be potentially more beneficial over cytotoxic therapy. We interrogated three publically available NSCLC datasets for mutation in FGFR2 (Supplementary Table S1; refs. 8, 9, 27). Mutations in FGFR2 are spread across the gene, primarily focused in the extracellular or kinase domains, in NSCLC (Fig. 1A). Mutations in these domains have been previously shown to lead to constitutive receptor dimerization or kinase activity, respectively, driving oncogenic intracellular signaling (22).

Patients with FGFR2 mutations ranged in age from 42 to 81 years, averaging 66 years of age upon diagnosis. The combined data also suggested the 2:1 ratio of tumor histology (squamous cell carcinoma to adenocarcinoma) with no predilection for light to nonsmokers. Because of an overwhelming need for mouse models of novel oncogenic drivers in lung cancer, we set out to evaluate newly characterized FGFR2 mutations that were established to be transforming and oncogenic in vitro and in vivo (22).

We generated inducible models of human FGFR2-IIIb mutations found in the extracellular (W290C) or kinase domains (K660N; Supplementary Fig. S1). Patients with previously reported FGFR2 mutations were largely devoid of intact p53 activity (>85%; ref. 9); therefore, the FGFR2 GEMMs were crossed with the Trp53fl/fl model to obtain a bi-allelic mouse (Fig. 1B). The gain or loss of function of FGFR2 or p53, respectively, was conditional via cre-lox technology. At 6 weeks of age, bi-allelic mice were induced via intranasal delivery of adenovirus-cre (5 x 10^7 pfu), activating mutant FGFR2 activity while inactivating p53. Induced animals revealed a lung tumor latency of 28 to 32 weeks after adenovirus-cre administration (Fig. 1B). Sick animals presented with progressive dyspnea and weight loss. As expected, bi-allelic FGFR2K660N;p53fl/fl -/ tumor-
bearing animals displayed a significant decrease in overall survival as compared with uninduced littermate controls (Fig. 1C). Resulting tumors resembled poorly differentiated human grade 3/4 lung adenocarcinoma displaying high pleiotropy and heavily multinucleated tumor cells exhibiting strong characteristics of local invasion throughout the lung parenchyma (Fig. 1D). Indeed, these tumors expressed robust levels of the adenocarcinoma marker, thyroid transcription factor 1 (TTF-1; Fig. 1E). To further characterize the model, tumors were stained with surfactant protein C (SFTPC; Fig. 1E), suggesting a type II pneumocyte differentiation, similarly observed in another mouse model of lung adenocarcinoma driven by FGF9 (20). These tumors stained negative for the Clara cell antigen (CC10) marker at both early and late time points (20 and 32 weeks postinduction), whereas the Clara cells of the alveolar epithelium stained positive (Supplementary Fig. S2). FGFR2-mutant models displayed similar phenotypes, but the penetrance for the extracellular domain was less than the kinase domain (KD), 35% versus 92%, respectively. Furthermore, the extracellular domain (W290C) model’s tumor latency was substantially longer than that of the K660N (KD) animals. Thus, we chose to move forward with the kinase domain mutant for treatment studies because of its increased oncogenic activity (22) and recurrent mutation in patient samples (Supplementary Table S1). Loss of p53 activity yielded increased penetrance (40% vs. 92% for p53 wt and null, respectively) and decreased tumor latency (Supplementary Table S2).

Mutant mice developed distinct macroscopic nodules (Supplementary Fig. S3) that provided for isolation from normal adjacent lung to molecularly characterize them at both the RNA and the protein levels. Human FGFR2 mRNA in tumor nodules was 15- to 20-fold higher than what was found in normal uninduced lung (Fig. 2A). In general, FGFRs signal through a key intracellular binding partner, FGFR substrate 2 alpha (FRS2alpha) that leads to MAPK and PI3K/Akt activity (28). As a result of FGFR2 overexpression in our GEMM, elevated phosphorylation events in FRS2alpha demonstrated that the receptors increased tyrosine kinase activity, leading to increased levels of phosphorylated AKT and ERK1/2 (Fig. 2B).

Figure 2. Conditional activation of FGFR2K660N and inactivation of p53 in the lung compartment drives expression of FGFR2 and its intracellular signaling counterparts. A, 15- to 20-fold higher FGFR2 mRNA levels were observed in tumors driven by conditional activation of the bi-allelic GEMM as compared with normal lung controls (normalized to mouse GAPDH). B, expression of FGFR2, FRS2, pFRS2 (Y436), AKT, pAKT (S473), ERK, and pERK1/2 (T202/Y204) by Western blotting. Tumor nodules from four different mice and a control mouse lung are shown. β-Actin was run as a loading control. C, representative images from hematoxylin and eosin (H&E) staining and immunohistochemistry for Ki67, FGFR2, and phosphorylated forms of FRS2alpha, AKT, and ERK on FFPE sections of the same tumor nodule shown at low and high magnifications (inset image scale bar, 100 μm; high magnification scale bar, 50 μm).
Next, we validated our immunoblot results via IHC for the same downstream signaling mediators resulting from increased FGFR2 activity (Fig. 2C and Supplementary Fig. S4). Tumor nodules from both mutant FGFR2 models displayed robust specific cell surface staining of FGFR2. A tumor driven by mutant Kras activity showed no staining (Supplementary Fig. S5A). Expected phosphorylation of various downstream signaling molecules, including AKT, ERK1/2, and FRS2α, was present in tumor nodules from both the kinase domain mutant (Fig. 2C) and the extracellular domain mutant (Supplementary Fig. S4). Both models were deemed proliferative and actively growing as a result of positive Ki67 IHC.

Until relatively recently, the standard of care for patients with advanced NSCLC has been limited to cytotoxic chemotherapy when surgery and radiotherapy were otherwise ineffective (29). With the boom of targeted therapy driving patient stratification, we wanted to evaluate the effect of a pan-FGFR inhibitor in our FGFR2-driven lung cancer model. In a tumor efficacy study, we treated FGFR2K660N;p53C0/C0/C0 lung tumor–bearing animals with BGJ-398 (n = 10), a pan-FGFR inhibitor, or vehicle (n = 5). Tumors were confirmed via MRI and served as baseline tumor volume. After 1 week of treatment with daily, orally delivered 15 mg/kg BGJ-398, 8 of 10 animals displayed greater than 50% tumor regression and 3 of 10 animals had regressed 80% (Fig. 3A and B). This phenomenon is very similar to the efficacy of erlotinib in our mutant EGFR-driven lung cancer mouse model (30). Efficacy of BGJ-398 continued to significantly improve at 2 and 4 weeks as

Figure 3. Pan-FGFR inhibitor, BGJ-398, is effective against FGFR2-driven lung adenocarcinoma in a GEMM. A, representative serial MR images of two FGFR2K660N;p53C0/C0/C0 lung tumor–bearing mice treated once daily for 4 weeks with either BGJ-398 (15 mg/kg) or vehicle (PEG300). Images represent baseline, 1, 2, and 4 weeks after start of treatment (white H, the heart). B, quantification of tumor burden from the MR images in BGJ-398 (top waterfall plot)– or vehicle (bottom waterfall plot)–treated mice at 1, 2, and 4 weeks after the start of treatment. C, comparison of tumor volume changes in BGJ-398– or vehicle–treated mice at 4 weeks after the start of treatment (P < 0.0001; n = 10 and 4, respectively).
compared with vehicle-treated animals (Fig. 3C), where animals showed near remission with 8 of 10 animals showing greater than 75% tumor regression (Supplementary Fig. S5B). Long-term sustained tumor remission is being evaluated with no acquired resistance seen at 6 months ($n = 4$; data not shown).

Next, we investigated the changes in downstream signaling pathways as a result of BGJ-398 treatment. Lung tumor-bearing mice were treated for 2 days with either vehicle or BGJ-398 (15 mg/kg) and sacrificed 2 hours after the second dose to evaluate the drug’s pharmacodynamics. Isolated tumor nodules from both vehicle and drug treatment arms were evaluated for phosphorylated FRS2α, AKT, and ERK proteins (31). Overall, inhibition of FGFR2-dependent tyrosine kinase activity reduced MAPK and PI3K signaling (Fig. 4A) with obvious phosphorylation depletion in key signaling proteins FRS2α, AKT, and ERK1/2. As a result of short term dosing, BGJ-398–treated tumors displayed signs of decreased proliferation (Ki67) and increased apoptosis (TUNEL) via IHC (Fig. 4B). Moreover, there was a significant overall survival benefit of animals undergoing BGJ-398 treatment ($n = 12$) compared with an untreated, induced group ($n = 30$; Fig. 4C). Animals died on treatment due to issues unrelated to lung tumor or drug toxicity, most commonly due to improper oral dosing ($n = 2$) or a secondary tumor arising in the nasal airway epithelia that commonly metastasized to the brain (Supplementary Fig. S6). Unlike the tumors originating in the lungs, these FGFR2-positive nasal tumors were negative for the type II pneumocyte marker SFTPC (Supplementary Fig. S6). After review, a veterinary

![Figure 4](https://cancerres.aacrjournals.org/content/74/17/4681/F4.large.jpg)
pathologist termed these esthesioneuroblastomas (n = 2, Supplementary Fig. S6), arising from the neuroepithelium. These tumors developed well beyond the normal lung tumor latency (>50 weeks), likely as a direct result of nasally delivered adenovirus cre and resulted in lethality due to obstruction of the nasal cavity, affecting the animal’s normal respiration. BGJ-398 caused a significant decrease in proliferation (Fig. 4D) and a significant increase in apoptosis of the lung tumor cells (Fig. 4E) after a short-term (2-day) treatment, resulting in near-complete tumor regression at 4 weeks.

Discussion

FGF ligands and their cognate receptors have become significant clinical targets of interest in the oncology field. Recently, a group reported an inducible mouse model driving FGFR9 expression in the adult airway epithelia leading to the formation of papillary adenomas, which were shown to progress into primary adenocarcinomas with a metastatic potential (20). The FGFR9 expression signaled through the FGFR3 receptor, and once the tumors were established, they were shown to be FGFR9-independent. Furthermore, while widespread expression of FGFR3 and FGFR7 in the adult mouse lung was shown to produce type II cell hyperplasia (18, 19), FGFR9 or FGFR10 expression led to the development of cancer or adenomas, respectively (17, 20). Interestingly, the FGF7 subfamily of ligands (FGF3, 7, 10) is known to preferentially bind FGFR2 receptors, whereas FGFR9 has been shown to signal through FGFR3 (21), suggesting both receptors are important in lung tumor development.

Activating mutations in FGFR2 have recently been unveiled as novel targets in NSCLC, both in lung squamous cell and in adenocarcinoma (8, 9). Inherent in their clinical relevance, models driven by FGFR2-activating mutations have the potential to help researchers explore the biology of the RTK and to evaluate novel targeted therapies for patients that fall into this clinical relevant subset of cancers. A multitude of FGFR2 mutations have been identified in NSCLC, although it has been unclear as to which are, in fact, oncogenic drivers up until recently (22). In addition, with the recent success of targeted therapies in patients with lung adenocarcinoma, it would be advantageous to develop novel models of FGFR2-driven lung squamous cell carcinoma given the prevalence of FGFR alterations in this disease.

Described herein, we have developed the first FGFR2-driven GEMM of NSCLC. We developed conditional bi-allelic mice that upon exposure to nasally delivered adenovirus cre led to activated FGFR2 signaling while also abrogating p53 function concurrently. Both mutant models that were developed yielded primary grade 3/4 lung adenocarcinoma that led to a significant decrease in overall survival as compared with uninduced control littermates. While p53 loss of function was not required for tumor formation (Supplementary Table S2), it was necessary to provide reasonable tumor latency for long-term efficacy studies to be completed. Combining loss of p53 with constitutive FGFR2 signaling led to a marked reduction in tumor latency, also observed in a KRAS-driven mouse model of lung cancer (32). Furthermore, combining loss of p53 in our model is clinically relevant given the high frequency of p53 loss in lung cancers (8, 9).

Unlike the FGFR9 model where the oncogene is broadly expressed in all cells expressing SFTPC throughout the lung, our system targets a smaller number of epithelial cells of diverse lineages via expression of Cre recombinase by nasal inhalation of adenovirus. This difference in technique may explain the shorter latency in previously described models (17, 20). Differences in latency are possibly also due to over-expression of FGF ligands in previous models versus expression of the mutant receptor in this model. Ligands can have non–cell-autonomous effects on the other cells in the tumor microenvironment such as endothelial cells (33) or cancer-associated fibroblasts (34, 35), likely supporting the growth of these tumors. In contrast to the previously described FGFR9 model, early or late lesions in our FGFR2 model lack CC-10 staining, potentially indicating a non-clara cell origin, although additional work is required to discover the cell of origin in these tumors (Supplementary Fig. S2).

This FGFR2-driven GEMM of NSCLC was created to study the development and clinical aspects of lung cancer; however, previously established mouse models overexpressing different FGFs in the lung show similar but also distinct phenotypes to the current model. The proliferative phenotypes in the FGF7 subfamily models are dependent on sustained FGF signaling (17–19), whereas the FGFR9 model develops ligand independence upon tumor formation via FGFR3 signaling (20).

As expected, lung tumors driven via constitutive FGFR2 signaling displayed increased AKT and ERK activity correlating with FRS2α phosphorylation. As the extracellular domain model had longer tumor latency, we chose to test BGJ-398, a pan-FGFR inhibitor, in our kinase mutant model. This model displayed exquisite sensitivity to BGJ-398 just after 1 week of dosing. By 4 weeks after dose commencement, a large majority of lung-bearing animals had undergone nearly full tumor remission leading to significantly longer overall survival than in untreated lung tumor–bearing animals. This sustained response was durable and strikingly resembled our study of EGFR tyrosine kinase inhibitors in mutant EGFR-driven mouse lung cancers (30). There was a small group of BGJ-treated animals that died of improper oral dosing or tumors arising in the nasal epithelia. The animals showing near-complete lung tumor remission developed SFTPC-negative nasal tumors that protruded into the brain while also impeding upon the animal’s breathing capacity. The lack of type II alveolar marker staining (SFTPc) in these tumors confirms that they are not a result of lung metastasis. We have adapted an intratracheal delivery method to circumvent this issue in the future. While we cannot unequivocally suggest why the BGJ-398 had no therapeutic effect on these tumors, a proper drug pharmacokinetic and pharmacodynamic study would be beneficial to assess the drug’s capability to penetrate the blood–brain barrier.

Although the mutations in FGFR2 were identified in a squamous cell carcinoma patient population, elevated FGFR2-related activity is seen across both the major subtypes of NSCLC. While we set out to develop a mouse model that recapitulates human FGFR2-driven NSCLC, we were not...
surprised by the adenocarcinoma phenotype as the preclinical space is largely devoid of a lung squamous cell carcinoma mouse model for many potential reasons. First, when inducing oncogene expression in the mouse lung, targeting is largely directed to type II pneumocytes (alveolar type II cells), which have a predilection to lead to bronchioalveolar adenomas leading to lung adenocarcinoma (36). Furthermore, the naïve mouse lung epithelium has no squamous cell differentiation until an inflammatory event occurs driving metaplasia, which is often initiated in patients with squamous cell carcinoma by smoking (37). Recently, a group has shown the necessity for chronic inflammation to drive spontaneous squamous cell carcinoma formation within the mouse lung. They reported that inactivation of IKKε (kinase-dead IKKε knock-in) drives the upregulation of squamous cell carcinoma–associated markers including p63, Trim29, and keratin 5, leading to downregulation of LKB1 (STK11) activity (38). Second, there are likely several features of the microenvironment that play a role in squamous cell differentiation, which would be difficult to recapitulate without an initial inflammatory insult in the transgenic environment. Third, there is also a strong possibility that those patients with FGFR2 mutations may require another collaborating oncogene to drive the differentiation into the squamous cell histology or perhaps the loss of another tumor suppressor.

In summary, we have developed a mouse model of lung adenocarcinoma driven by FGFR2 constitutive kinase activation originally identified in patients with NSCLC. With the exquisite sensitivity of the lung tumor model to a pan-FGFR inhibitor, researchers gain a powerful tool to further bolster their understanding of FGFR-related cancer biology and targeted therapy discovery within the lung and across various cancer indications. In addition, with the inevitability of acquired resistance, this model could be of significant value for evaluation of response to targeted therapies, chemotherapy as well as novel immunotherapies in an immunocompetent environment. Together, these data validate a role for FGFR2 in lung adenocarcinoma providing a model to further make an impact in the decisions made by an oncologist treating this genetically defined population in the clinic.

Disclosure of Potential Conflicts of Interest
M. Meyerson reports receiving a commercial research grant from Bayer, has ownership interest (including patents) in Foundation Medicine, and is a consultant/advisory board member for Foundation Medicine. P.S. Hammerman is a consultant/advisory board member for ARIAD. ImClone, and Janssen. No potential conflicts of interest were disclosed by the other authors.

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References


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