Editorial

Dividing and conquering the variation among variants in *EML4-ALK* lung cancer

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Activating gene rearrangements in the anaplastic lymphoma kinase are present in approximately 2–7% of lung adenocarcinomas (ALK + cancers) (1,2). Patients with ALK + lung adenocarcinoma often benefit from treatment with an ALK tyrosine kinase inhibitor (TKI), such as crizotinib, ceritinib, and alectinib (2). However, acquired ALK TKI resistance remains an obstacle to long-term patient survival in patients who do respond to initial therapy and a distinct subset of ALK + patients fails to experience an initial tumor regression, exhibiting intrinsic resistance (2). Identifying the basis of both innate and acquired resistance is essential to improve clinical outcomes.

The *ALK* gene rearrangements present in lung adenocarcinoma typically involve a 5' fusion of the echinoderm microtubule-associated protein-like 4 (EML4) gene to the ALK kinase domain (2). Several variants of the *EML4-ALK* fusion have been observed in lung adenocarcinoma patients. These different variants result from translocations at different points within the *EML4* gene: variant 1, variant 2, and variant 3a/b are the most common fusion variants (2). EML4 contains several protein domains that may be critical to protein folding, stability, and function (3,4): N-terminal coiled-coil region, a basic region, a hydrophobic echinoderm microtubule-associated protein-like protein (HELP) region, and tryptophan-aspartic acid repeats (WD). The HELP-WD region forms a tandem atypical β-propeller (TAPE) structure (3). The EML4 TAPE domain is variably present in the different *EML4-ALK* fusion proteins. The absence of the full TAPE domain in *EML4-ALK* variants 1, 2, 7 may render the protein less stable than *EML4-ALK* variants 3a/b and 5a/b, which contain the full TAPE domain (3,4). Whether the different variants of *EML4-ALK* as they relate to the presence or absence of the full TAPE domain impact clinical response to ALK TKI treatment has remained an important unresolved question.

A new study now begins to address this question (5). The authors conducted a retrospective analysis of *EML4-ALK* lung adenocarcinoma patients treated with an ALK TKI to determine whether the different variants that either contained or lacked the full TAPE domain were associated with differential treatment response. They report that patients with variants 3a/b showed decrease response to ALK TKI treatment, compared to patients with variants 1 and 2. *In vitro* studies further showed that cells expressing variant 1 or 2 were more sensitive to ALK TKI treatment and showed lower kinase activity than cells expressing variant 3a or 5a.

Together, these findings provide important evidence suggesting that the degree of kinase activity and/or stability of the EML4-ALK fusion protein, as dictated by determinants within EML4, influence ALK TKI response in patients. The data, if further confirmed in additional clinical cohorts, could establish *EML4-ALK* variant status as a novel biomarker by which to stratify patients for treatment with an ALK TKI and/or additional treatment strategies [such as combination therapies (6,7)]. On the basis of these intriguing findings, additional retrospective analyses and, more importantly, prospective studies are warranted to confirm these new findings.

Overall, we are just beginning to understand the role of non-kinase fusion partners in oncogenesis in kinase fusion driven cancers, such as EML4-ALK lung adenocarcinoma. This study is an important step forward. Another recent study by our group revealed an important role for the HELP domain within EML4 in the EML4-ALK fusion protein in downstream signaling pathway activation and RAS-mitogen activated protein kinase (MAPK) pathway signaling (7). More detailed studies are necessary to determine how the different domains within kinase fusion partners such as EML4 influence the signaling, oncogenic, and biomarker roles of this class of oncogene driver. Studies such as this recent report (5) are essential to fuel both basic and translational research efforts that hold promise to improve the molecular precision with which we diagnose and treat patients with ALK + lung adenocarcinoma, and potentially other malignancies driven by kinase gene fusions in the future.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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