Re: The Wnt Signaling Pathway in Non-Small Cell Lung Cancer

We read with great interest the article by Stewart (1) in the December issue of the Journal. The author gives a useful update of genomic alterations affecting Wnt signaling components that are frequently observed in non-small cell lung cancer (NSCLC) and reminds us that Wnt component mutations seen in other cancers such as colon are uncommon in NSCLC. We believe it is necessary to bring further attention to the fact that Wnt pathway disruption in lung cancer differs greatly from what is observed in other malignancies.

As described by Stewart, numerous Wnt pathway components are disrupted in lung adenocarcinoma (LUAD). The alterations summarized in Table 1 from Stewart (1) are also prominent in our own LUAD cohort (n = 77; Figure 1). Further investigation of our tumor set revealed that when considering gene expression signatures associated with canonical Wnt pathway transcription, up to 30% of tumors showed signatures consistent with active Wnt signaling (TCF1 13–30%, TCF4 4%, LEF1 2%; gene set enrichment analysis [GSEA], \( P < .01 \)). These results agree with other studies assessing Wnt pathway activation in lung cancer, indicating Wnt/TCF is active in a significant fraction of lung tumors. For example, a recent study demonstrated that 45% of 309 NSCLCs stained positive for nuclear \( \beta \)-catenin, which is often associated with Wnt/TCF activity (2). However, despite the occurrence of component disruption and the apparent Wnt activity across lung tumor datasets, we found no correlation between Wnt/TCF activity (defined using GSEA) and disruption status of the Wnt pathway component genes (Table 1 from Stewart [1]). The frequencies of component alteration do not differ between tumors classified as Wnt/TCF active vs inactive for

![Figure 1](broadinstitute.org/gsea/index.jsp). The figure shows results for the gene set with the highest percentage of Wnt/TCF active tumors, for which 30% of tumors were deemed Wnt active (GSEA Kolmogorov-Smirnov permutation test \( P < .01 \)). Concurrent mRNA expression and DNA alterations within individual samples are highlighted in darker color. Fisher’s exact tests have been performed for each gene to compare the proportions of samples with and without alterations between TCF1 active and inactive samples. Statistical tests were performed on expression data only, as well as on data for concurrent DNA and mRNA alterations. The \( P \) values indicated are those for comparisons of samples with and without alterations between TCF1 active and inactive samples. The data is non-statistically significant when considering mRNA expression data only. A Fisher’s exact test also showed no difference in tumor stage based on TCF activation status.
any of the Wnt pathway expression signatures we assessed (Fisher’s exact test, \( P > .05 \) for all; Figure 1). This was also evident in a panel of LUAD cell lines (\( n = 8 \)) that harbor Wnt pathway component gene alterations, as we did not see any difference in Wnt/TCF activity between altered and nonaltered lines (measured by the standard TOPflash TCF/LEF reporter assay). This may suggest a limited role for these recurrent gene alterations in Wnt/TCF activation, implying that their disruption affects signaling outside of the canonical Wnt pathway. The possibility of a limited role for the canonical pathway in lung cancer is also evident in studies of lung squamous-cell carcinoma where downregulation of the canonical and upregulation of the noncanonical pathways have been associated with tumorigenesis (3,4).

In conclusion, at least in our tumor cohort, frequent genomic disruption of Wnt pathway component genes is not associated with Wnt transcriptional activity. We are not questioning the involvement of the Wnt/TCF pathway in lung tumorigenesis; in fact, there has been evidence of its involvement in tumor recurrence and metastasis (5,6). Our findings suggest the need for investigating the potential roles of Wnt components outside of the canonical Wnt/TCF pathway.

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References


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