Letter to the Editor

Molecular Cancer Therapeutics

Wnt Signaling Inhibition Promotes Apoptosis in Sarcomas—Letter

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In a recent issue of *Molecular Cancer Therapeutics* (1), Martinez-Font and colleagues reported that the WNT/β-catenin signaling pathway represents a potential therapeutic target in soft tissue sarcomas (STS). Analysis of cell lines representing different pathologic subtypes showed frequent pathway activation and *in vitro* antitumor activity of PKF118-310, a disruptor of TCF/β-catenin binding. STSs are rare and heterogeneous cancers of mesenchymal origin (2), with poor prognosis: approximately 50% of nonmetastatic operated patients die from metastatic relapse, and in this metastatic setting, the median survival is inferior to 18 months. The development of new systemic therapies is crucial, and the Martinez-Font's study represents a promising new avenue of research. However, the frequency and clinical relevance of WNT/β-catenin signaling pathway activation in STS clinical samples are not documented (3).

We examined the activation probability of the β-catenin pathway based on a transcriptional signature (4) in 1,439 clinical soft tissue samples gathered from 15 public datasets (Supplementary Table S1), including 1,379 primaries and 32 relapses of STS, and 28 normal tissues. Expression profiles, generated using DNA microarrays and RNA-seq, were normalized before analysis (5). The β-catenin activation probability, assessed as a continuous variable, was higher in primary tumors than in normal samples ($P = 1.68E{-}15$; Supplementary Fig. S1A), and heterogeneous but similar in primary tumors and relapses ($P = 0.12$). In the 1,379 nonmetastatic, operated patients, the activation probability was associated with patients' gender (higher in women; $P = 2.39E{-}02$), tumor site (higher in extremities; $P = 4.24E{-}05$), pathologic subtypes (higher in leiomyosarcomas, $P = 2.33E{-}17$), tumor grade (higher in grade 2–3; $P = 1.84E{-}16$), genetic profile (higher in complex profile; $P = 3.77E{-}27$), and CINSARC class (higher in high-risk; $P = 3.28E{-}77$). Positive correlation existed with *CDC25A* mRNA expression, a known WNT target gene, as reported in cell lines (1).

Metastasis-free survival (MFS) was available for 610 nonmetastatic, operated patients. With a median 36-month follow-up, the 5-year MFS was 64% [95% confidence interval (CI), 59–69]. In univariate analysis, high β-catenin activation probability (HR = 6.6; 3.88–11.20; $P = 3.19E{-}12$), leiomyosarcoma subtype ($P = 3.37E{-}05$), grade 2–3 ($P = 1.32E{-}02$), complex genetic profile ($P = 8.33E{-}03$), and CINSARC high-risk ($P = 1.66E{-}11$) were associated with shorter MFS. High and low activation probabilities were associated with respective 5-year MFS of 53% (95% CI, 47–60) and 75% (95% CI, 69–82; $P = 2.53E{-}09$; Supplementary Fig. S1B). In multivariate analysis, pathologic subtype ($P = 2.46E{-}02$), genetic profile ($P = 4.93E{-}02$), and β-catenin activation probability ($P = 4.16E{-}02$) remained associated with MFS, suggesting independent prognostic value.

This analysis of β-catenin activation in STS in a large series of clinical samples nicely complements the Martinez-Font's study and reinforces the potential therapeutic value of this new target in STS.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Note: Supplementary data for this article are available at Molecular Cancer Therapeutics Online (http://mct.aacrjournals.org/).

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