New Directions in
Desmoid Fibromatosis

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CTNNB1 mutational status correlates with desmoid recurrence

Tumorigenesis and Neoplastic Progression

Specific Mutations in the β-Catenin Gene (CTNNB1) Correlate with Local Recurrence in Sporadic Desmoid Tumors

Alexander J.F. Lazar,† Daniel Tuvin,‡ Shohrae Hajibashi,§ Sultan Habeeb,¶ Svetlana Bolshakov,∥ Empar Mayordomo-Aranda,¶ Carla L. Warneke,∥ Dolores Lopez-Terrada,¶ Raphael E. Pollock,‡ and Dina Lev§

common in desmoid tumors. Furthermore, patients harboring CTNNB1 (45F) mutations are at particular risk for recurrence and therefore may especially benefit from adjuvant therapeutic approaches. (Am J Pathol 2008, 173:1518–1527; DOI: 10.2353/ajpath.2008.080475)
The prognostic role of\textit{CTNNB1 S45F} mutations

High frequency of $\beta$-catenin heterozygous mutations in extra-abdominal fibromatosis: a potential molecular tool for disease management

\textbf{CTNNB1 45F Mutation Is a Molecular Prognosticator of Increased Postoperative Primary Desmoid Tumor Recurrence}

\textit{An Independent, Multicenter Validation Study}

\textbf{Prognostic Value of CTNNB1 Gene Mutation in Primary Sporadic Aggressive Fibromatosis}

\textbf{Ann Surg Onc, 22:1464; 2015}
Why study doxorubicin or sorafenib in the context of desmoid tumor S45F mutations?

- “…anthracycline-based regimen is another option and is expected to achieve more rapid tumor responses”

- “Sorafenib currently looks to be the most active drug…”

*The Management of Desmoid Tumors: a Joint Global Evidence based Approach (draft); Desmoid Tumor Working Group, 2018*
Therapeutic impact: no significant induction of apoptosis in S45F mut after doxirubicin
CTNNB1 mut T41A vs S45F apoptosis differences not due to differing β-catenin protein levels
Decreased S45F apoptosis not due to inhibited p21 induction
We transfected mutated β-catenin genes into normal 293T embryonic cells to recapitulate the biology observed in desmoid cell strains.
S45F transfected 293T cells have decreased doxorubicin-induced apoptosis
β-catenin is more highly expressed in S45F vs T41A mutated desmoid cell nuclei.
Pro-apoptotic gene decreased expression in S45F mut; anti-apoptotic gene increased expression in S45F mut

** = P > 0.001
RUNX3 interacts with β-catenin; direct binding and/or pathway cross talk?
RUNX3 mRNA and protein; downregulated in 293T cells transfected with S45F vs T41A mut CTNNB1
Decreased RUNX3 binding to β-catenin in S45F mut desmoid cells
(coimmunoprecipitation assay)
RUNX3 transfection overcomes dox apoptotic resistance in S45F transfected 293T cells
RUNX3 transfection overcomes dox apoptotic resistance in S45F transfected 293T cells: sustained over time
S45F mut desmoid cells, even at 1mM (low dose), show marked resistance to Sorafenib
Sorafenib induces apoptosis in T41A but less so in S45F mut desmoid cells

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<tr>
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<th>T41A</th>
<th>S45F</th>
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<tbody>
<tr>
<td>DMSO</td>
<td>6.3%</td>
<td>10%</td>
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<tr>
<td>D76</td>
<td>Sorafenib (1μM): 38.4%</td>
<td>Sorafenib (10μM): 85.9%</td>
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<tr>
<td>D168</td>
<td>Sorafenib (1μM): 4%</td>
<td>Sorafenib (10μM): 73.2%</td>
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<tr>
<td>D23</td>
<td>Sorafenib (1μM): 10.1%</td>
<td>Sorafenib (10μM): 12.3%</td>
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<tr>
<td>D157</td>
<td>Sorafenib (1μM): 13.1%</td>
<td>Sorafenib (10μM): 26.6%</td>
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ATG5 KO (autophagy blockade) inhibits S45F (but not T41A) desmoid cell growth
Autophagy blockade (HCQ) enhances Sorafenib cytotoxicity in S45 F but not T41A desmoid cells.

Currently examining underlying genetic mechanisms of control.
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For all the football fans here today...

OSU vs UM; Nov. 24, 2018--very tasty!
Thank you for your attention!

The Ohio State University
Wexner Medical Center