Molecular Characterization of Desmoid Tumors: Decryption of the Enigma

Trenton L. Place  James J. Mezhir

Department of Surgery, Division of Surgical Oncology, University of Iowa Hospitals and Clinics, Iowa City, IA, USA

Desmoid tumors have long been known as an ‘enigma’ due to their unusual biology and aggressive clinical behavior [1–3]. These tumors may arise from the extremities, abdominal wall, intestinal wall and mesentery, head and neck, and breast and can be sporadic or associated with familial adenomatous polyposis [4–9]. Despite being histologically benign tumors, desmoids are locally aggressive and can cause debilitating symptoms and death [10]. It has been reported that aggressive measures to surgically extirpate desmoid tumors can result in significant morbidity and mortality, which has resulted in changes in management of these lesions [4]. Alternatives such as observation, radiation, and chemo/hormonal therapy have been explored, but with unproven durable success [11, 12]. Molecular and genetic characterization of desmoid tumors must be done in order to ultimately develop novel, effective targets for therapy.

Several studies have been performed to begin to ‘decrypt’ these enigmatic tumors in an effort to better understand the etiology and genetic machinery behind this disease. A sample of studies is shown in table 1. Many of the studies to date have found signaling changes in the β-catenin pathway, and in addition, chromosomal alterations. From these studies, it is reasonable to conclude that desmoid tumors are highly heterogeneous and require further investigation.

In this issue of Onkologie, Erben and colleagues comprehensively evaluated 9 patients with desmoid tumors of the abdomen (n = 7) and extremity (n = 2); 8/9 were sporadic desmoids while 1 patient had familial adenomatous polyposis [13]. Resection only was the treatment for 4 patients while 5 patients had radiation therapy, 1 patient chemotherapy, and 2 patients hormonal therapy. 3 patients recurred during the follow-up period. Despite this being a small sample size, it is a snapshot representation of patients with desmoid tumors who are often treated with multimodality therapy.

The authors aimed to expand the existing knowledge of the chromosomal abnormalities associated with desmoid tumors by utilizing single-nucleotide polymorphism array (SNP-A) karyotyping. This technology allows for the high resolution characterization of chromosomal abnormalities down to the kilobase level, whereas previous studies on desmoid tumors have largely employed techniques suited for the detection of megabase or larger chromosomal alterations [14]. In conjunction with SNP-A, the authors performed traditional DNA sequencing on a number of genes known to be mutated in desmoid tumors, including β-catenin (CTNNB1) and APC.

Using these combined methodologies, the authors validated existing data on the presence of mutations in CTNNB1, and losses in chromosome 8q, which contains the APC locus. In addition, they detected numerous other small deletions and insertions that have previously not been reported in desmoid tumors. The most significant of these novel lesions was a heterozygous, somatic deletion affecting a small region of chromosome 8p23, which was observed in 44% of the tumors tested. This deletion falls within the CUB and Sushi multiple domains1 (CSMD1) gene, a putative tumor suppressor that is also mutated or deleted in tumors of the head and neck, colon, breast, and prostate [15, 16]. Furthermore, the authors noted a correlation between CSMD1 deletion and relapse, as 3 of the 9 patients with disease recurrence at the time of publication had exhibited a CSMD1 deletion. The small sample size and short follow-up time limit the authors’ ability to make firm conclusions regarding the prognostic significance of these otherwise exceptional and novel data.

The management of desmoid tumors remains a challenge to the patient and the clinician. However, studies such as this by Erben and colleagues add to the arsenal of data that will eventually lead to novel therapies for this disease. As for all patients presenting with complex malignancies such as desmoid tumors, continued efforts for tissue collection and multi-institution and protocol-based regimens are justified.

Disclosure Statement

The authors have no conflict of interest.
Table 1. Select recent studies evaluating the biology of desmoid tumors

<table>
<thead>
<tr>
<th>Author, year [ref.]</th>
<th>n</th>
<th>Sites included</th>
<th>Analysis technique</th>
<th>Controls</th>
<th>Pertinent findings</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mignemi et al., 2012 [17]</td>
<td>27</td>
<td>extremity</td>
<td>IHC of TMA</td>
<td>scar, normal fibrous tissue</td>
<td>increases in p-B-catenin, SMAD2/3, COX2</td>
<td>TGFB signaling is activated in desmoid tumors</td>
</tr>
<tr>
<td>Huss et al., 2012 [18]</td>
<td>56</td>
<td>mesenteric, abdominal wall, extremity</td>
<td>IHC, mutational analysis</td>
<td>fibrosis</td>
<td>mesenteric tumors more often had mutations in B-catenin gene than non-mesenteric tumors</td>
<td>mesenteric desmoids may have genetic differences compared to non-mesenteric tumors</td>
</tr>
<tr>
<td>Cho et al., 2012 [19]</td>
<td>6</td>
<td>abdominal, extremity</td>
<td>IHC, WB</td>
<td>matched normal tissue</td>
<td>Increased B-catenin expression in tumors</td>
<td>variable response to different targeted agents in desmoid tumors</td>
</tr>
<tr>
<td>Salas et al., 2010 [20]</td>
<td>194</td>
<td>abdominal, abdominal wall, extremity</td>
<td>comparative genomic hybridization</td>
<td>sex-matched DNA</td>
<td>76% of tumors had no genomic changes loss of 6q and 5q, gain of 20q and Chr 8 in 40/46 tumors with alterations</td>
<td>mutations in APC and CTNNB1 did not account for tumorogenicity in all cases further study of the novel genetic alterations is warranted</td>
</tr>
<tr>
<td>Domont et al., 2010 [21]</td>
<td>155</td>
<td>abdominal, extremity, trunk, head/neck</td>
<td>B-catenin gene sequencing</td>
<td>NA</td>
<td>B-catenin mutations were present in 83% of cases DFS was worse in B-catenin mutated tumors</td>
<td>B-catenin mutations are present in the majority of extra-abdominal desmoid tumors and is a potential prognostic marker</td>
</tr>
</tbody>
</table>

IHC, immunohistochemistry; TMA, tissue microarray; WB, western blot; NA, not available; DFS, disease free survival.

References