

Review

Desmoid tumor: a disease opportune for molecular insights

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Summary. Desmoid tumors are monoclonal proliferations that fall within a broad histologic spectrum of fibrous mesenchymal tumors that ranges from benign proliferations of scar tissue to high-grade fibrosarcomas. These low-grade tumors are extremely infiltrative locally, but lack the ability to metastasize systemically. While they are only rarely a direct cause of mortality, using current therapeutic modalities, these tumors have a high rate of local recurrence that can result in significant treatment related morbidity. Sporadic desmoids are usually associated with somatic mutations in codons 41 or 45 of exon 3 of β -catenin (*CTNNB1*). Desmoid tumors occurring in the background of familial adenomatous polyposis (FAP) usually contain inactivating germline mutations in the adenomatous polyposis coli (*APC*) gene. *CTNNB1* and *APC* are part of the Wnt signaling pathway and mutations in either gene result in stabilization of the β -catenin protein and allow nuclear translocation and binding of β -catenin to the T-cell factor/lymphoid enhancer factor (TCF/Lef) family of transcription factors, resulting in activation of target genes which may underlie desmoid tumor biology and clinical behavior. In an era of molecularly targeted therapeutics there is a real need to better grasp the molecular mechanisms behind desmoid tumorigenesis and progression. This knowledge will eventually result in the development of patient and tumor tailored therapies and assist in the control and eradication of this disease.

Key words: Desmoid, β -catenin, APC, Estrogen receptors, c-Kit

Introduction

Desmoid tumors are mesenchymal fibroblastic/myofibroblastic proliferations occurring throughout the body, particularly in association with deep musculo-aponeurotic tissue planes. The contention that desmoid tumors, also called deep fibromatosis, arise in association with the deeper aponeurotic tissue, serves to distinguish them from the superficial fibromatoses that tend to arise in association with more superficial fascial planes in the distal extremities. The cell of origin of this tumor is not known and precursor lesions are not described.

Initial ambiguity over whether to consider desmoid as a reactive proliferation or neoplastic process was eventually resolved by non-random X chromosome inactivation methodologies that demonstrated the clonal nature of these tumors (Li et al., 1996; Alman et al., 1997). While clonality does not definitively establish neoplasia, combining the lack of self-limited growth and locally aggressive behavior indicates that this tumor is best regarded as a low-grade mesenchymal tumor or sarcoma. A unique feature of this intriguing malignancy is the highly local infiltrative character, but absolute lack of metastatic capacity. This fascinating pattern of growth while clinically and pathologically established, has not been extensively studied on the molecular level and thus is poorly understood.

Here we summarize the clinical and histopathological determinants of desmoid tumor, and discuss implicated molecular factors.

Materials and methods

Clinical features

Most desmoid tumors develop sporadically in young adults (peak age 25 to 35 years); however, some occur in the background of FAP, or the Gardner's variant of this

syndrome, where patients develop desmoid tumors in addition to epidermal inclusion cysts, osteomas, and multiple colonic adenomas and carcinoma. Trauma, such as a prior surgical incision, has also been found to be associated with occurrence of these tumors and is particularly pronounced in the setting of familial adenomatous polyposis (FAP) (Clark and Phillips, 1996). This association is of interest as desmoid tumors share many morphologic features in common with scar tissue, particularly hypertrophic scar.

Desmoid tumors usually present as a slowly growing solitary mass, but multifocal lesions confined to the same anatomical region can occasionally be encountered. While they can arise anywhere in the body, most desmoids develop in the extremities and superficial trunk wall. When arising from intraabdominal structures, desmoids can obstruct small bowel or ureters or compress neural or vascular structures causing digestive, motor or perfusion deficits. The histologic differential diagnoses for desmoid tumor include fibrosarcoma, solitary fibrous tumor, dermatofibrosarcoma protuberans, reactive fibrous proliferations such as scar, hypertrophic scar or keloid, and nodular fasciitis. A histological confirmation obtained via a core needle or incisional biopsy is necessary for accurate diagnosis. Correlation with the clinical presentation of the tumor is usually extremely helpful in narrowing the differential diagnosis, specifically the size and depth of the lesion.

Therapy usually consists of surgery, radiotherapy, and or/systemic approaches (i.e. chemotherapy, non-steroidal anti-inflammatory drugs, tamoxifen and imatinib mesylate) in various individualized combinations (Kinzbrunner et al., 1983; Wilcken and Tattersall, 1991; Hansmann et al., 2004; Picariello et al., 2004; Heinrich et al., 2006; Klein et al., 1987). Perhaps because of the relative rarity of these neoplasms and only sporadic reports of response to medical therapy, approaches to systemic therapy have yet to be

standardized. Complete surgical extirpation remains the standard of care when the tumor is tractable to such intervention.

The major obstacle in the management of desmoid tumors is their high propensity for local recurrence even after what is considered complete ablation on both surgical and pathologic grounds. Recurrence rates ranging from 14% to 37% have been reported in major published series (Table 1).

Histopathology

On gross examination of resected specimen, desmoid tumor appears firm, smooth, and may initially thought to be well circumscribed. However, closer inspection often reveals thin wisps of tumor that extend radially, often along fibrous septae. On sectioning, the tumor has a glistening, coarse trabeculated surface resembling scar tissue lacking pools of hemorrhage or necrosis (Fig. 1a). On H&E section, the tumor consists of elongated spindle cells reminiscent of fibroblasts presenting uniform appearance with eosinophilic cytoplasm embedded within a collagenous matrix (Fig 1b,c). The nuclei are small, vesicular, pale staining, and sharply defined, and may contain one or two tiny nucleoli, but lack hyperchromasia. Intraabdominal desmoids can sometimes contain relatively scanty collagen and a pronounced myxoid matrix. Spindle cells and collagen fibrils are usually arranged in ill-defined fascicles and interlacing bundles. Occasionally extensive glassy hyalinization, which is also a feature of keloid, may also be encountered. The tumors can vary in cellularity and may assume a more storiform architecture as well. Special stains such as reticulin and mason trichrome have been traditionally used to highlight the collagen more clearly, but are currently rarely employed.

Immunohistochemistry studies also have a role in the diagnosis of desmoids. The spindle cells in the tumor usually stain positive for vimentin, show focal to patchy smooth muscle actin (SMA) reactivity, but are generally negative for desmin and other standard histogenic markers such as cytokeratins and S-100 – a pattern that is useful in narrowing the differential diagnosis. Immunohistochemistry for β -catenin (Fig. 1c, inset) has recently emerged as a helpful marker for desmoids. β -catenin is typically found in a membranous distribution in epithelial cells where it is involved in cell-cell

Table 1. Selected reports of desmoid tumor recurrence rate.

Study	%
Leibel et al., 1983	32
Bataini et al., 1988	12
McKinnon et al., 1989	18
McCullough et al., 1991	17
Acker et al., 1993	14
Catton et al., 1995	37
Plukker et al., 1995	31
Kamath et al., 1996	17
Spear et al., 1998	26
Ballo et al., 1999	30
Merchant et al., 1999	23
Jelinek et al., 2001	19
Gronchi et al., 2003	27
Abbas et al., 2004	38
Duggal et al., 2004	26
Phillips et al., 2004	19
Lev et al., 2007	20

Table 2. Prevalence of nuclear β -catenin staining in desmoid tumors.

Study	n/total	%
Tejpar et al., 1999	42/42	100
Abraham et al., 2002	27/33	82
Montgomery et al., 2002	9/10	90
Bhattacharya et al., 2005	21/21	100
Ng et al., 2005	14/17	82
Rakheja et al., 2005	4/12	33

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junctions (Fig 2a,b), but translocates, and accumulates in the nucleus when mutated or activated (Fig. 2c). A few studies have shown that nuclear reactivity is characteristic of desmoid in contrast to the more superficial fibromatoses (Table 2). While not entirely specific for desmoid fibromatosis, in the differential diagnosis of spindle cell lesions exhibiting fibrous differentiation, nuclear accumulation of β -catenin is highly suggestive of desmoid (Montgomery et al., 2002).

Electronic microscopy is no longer commonly utilized as a diagnostic tool for desmoid tumors. However, when performed, the spindle cells are frequently found to terminate in long and slender processes. Prominent and dilated endoplasmic reticulum, free ribosomes, Golgi apparatus and scattered mitochondria can be discerned. Dense bodies, which are

condensed intracytoplasmic actin-type microfilament bundles, can be seen inside the spindle cells. A fibronexus is sometimes encountered. The cell comprising the tumor can show various features of both myofibroblasts and fibroblasts (Feiner and Kaye, 1976). Deposition of mature collagen appears to increase over time in proportion to the fibroblast content of the tumor. Abundant stromal collagen and ground substance is usually encountered, and intranuclear collections or inclusions of collagen can be seen.

Molecular insights

While desmoid clinical biology has been well characterized, the underlying tumor molecular biology is not as well understood. The global lack of suitable

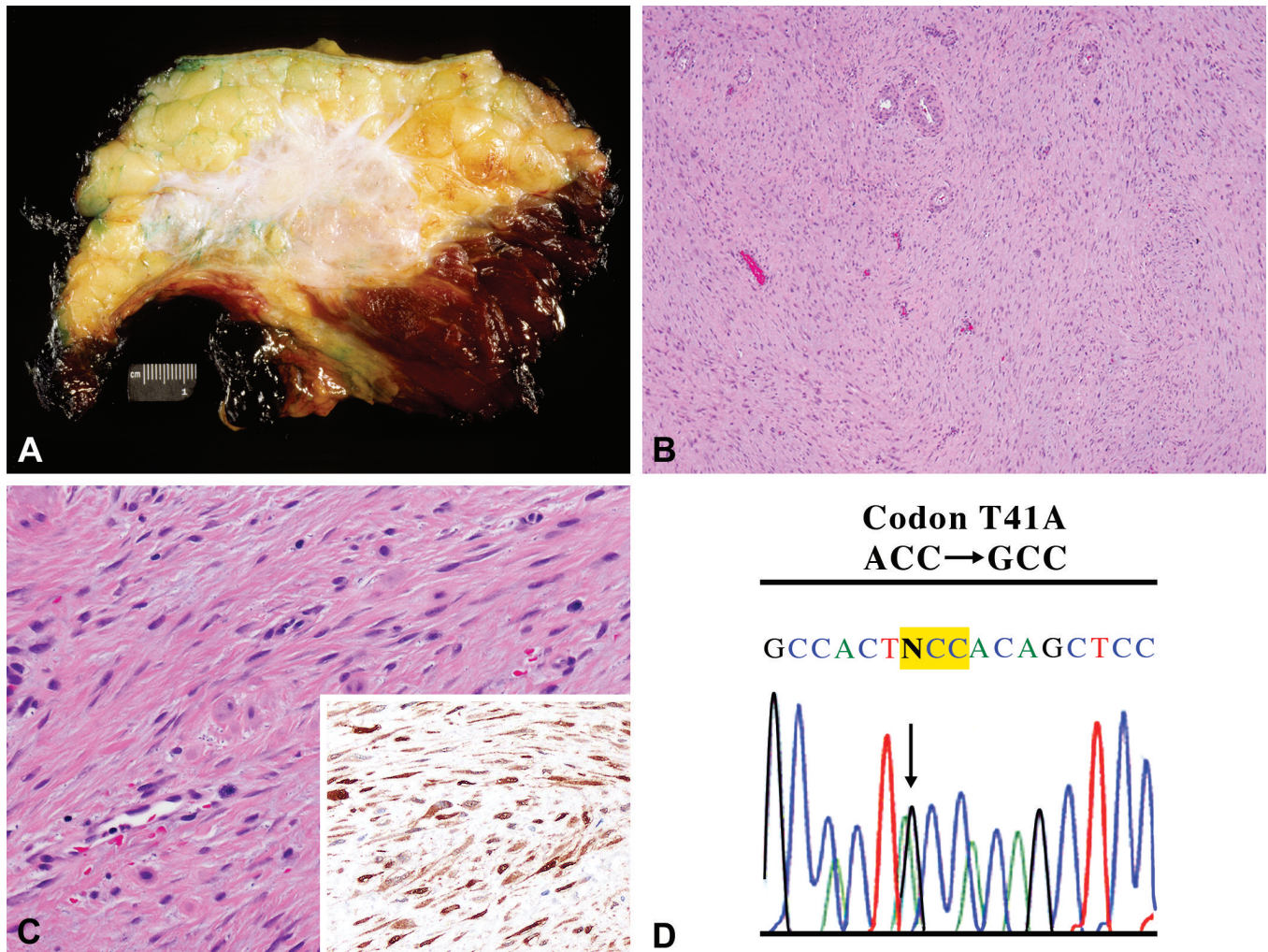


Fig. 1. Gross photograph of a desmoid tumor infiltrating adipose tissue (A). The tumor is composed of intersecting fascicles of slender, elongated fibroblasts (B, original magnification, x 40). The collagen matrix and scattered blood vessels are visualized at higher power (C, original magnification, x 200); the inset shows nuclear reactivity for β -catenin on immunohistochemistry. Mutations in exon 3 of *CTNNB1*, the gene encoding β -catenin, can often be demonstrated with PCR amplification of tumor DNA and Sanger sequencing (D).

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assembled desmoid bioresources, including lack of banked desmoid tumor tissue, lack of desmoid tumor cell lines, and lack of small animal *in vivo* desmoid

tumor models has hampered desmoid tumor research to date, and has been a major impediment to conducting the needed systematic molecular mechanism-oriented

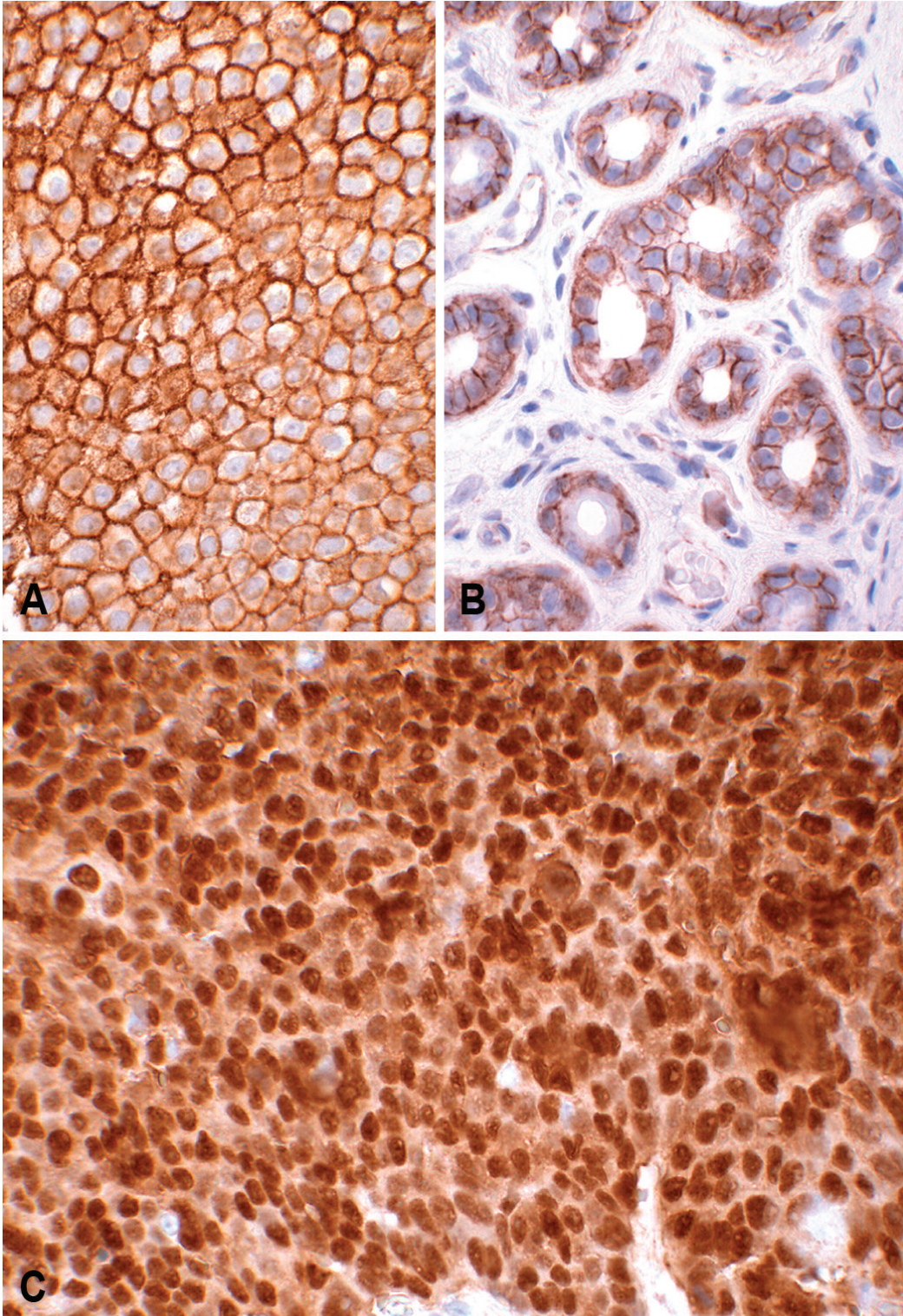


Fig. 2. Immunohistochemistry for β -catenin in cutaneous squamous epithelium and sweat ducts shows a distinct membranous distribution (A and B, respectively), while cytoplasmic and distinct nuclear accumulation is noted with activating mutations in exon 3 of *CTTNB1* as seen in a cutaneous pilomatixoma (C). β -catenin is also present in cell adhesion foci with E-cadherin and other catenins (Fig. 3). The complex relationship between the signaling and cell adhesion pools of β -catenin is not fully appreciated. x 400

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experimentation. Some initial clues to the molecular driving forces will be discussed below.

Desmoid tumors can be divided into sporadic and familial etiologies. When underlying molecular mechanisms are considered, both categories are generally initiated by different, albeit related cellular events. Most sporadic desmoids have been found to harbor activating mutations in exon 3 of the gene *CTNNB1* that encodes the cell adhesion co-factor and nuclear signaling factor, β -catenin (Miyoshi et al., 1998; Tejpar et al., 1999; Abraham et al., 2002). Chromosomal abnormalities such as trisomy 8, 20, and deletion of 5q which includes the *APC* locus have also been described (Bridge et al., 1996, 1999; Qi et al., 1996; Rohen et al., 1996). Desmoids arising in the setting of FAP display germline inactivating mutations in *APC*. Similar mutations in *APC* have also noted in a small subset of sporadic desmoid tumors (Alman et al., 1997; Giarola et al., 1998). Both *APC* and β -catenin proteins are part of the Wnt signaling pathway (Fig. 3), dysregulation of this pathway is known to be involved in the tumorigenic process of an array of human malignancies (Polakis, 2000; Miller, 2002)

β -catenin

β -catenin, the protein product of the *CTNNB1* gene, is a proto-oncogene involved in at least two recognized developmental processes: (1) specific cell-cell interactions through adherens junctions and (2) regulation of gene expression through Wnt signaling pathway (Fig. 2). The β -catenin gene consists of 3 domains: (1) a 150 amino acid N-terminal domain which contains the binding site for α -catenin and the phosphorylation sites for CK1 (casein kinase 1) and GSK3 β , (2) a 550 amino acid central armadillo repeat domain containing binding sites for TCF/LEF, APC, Axin and E-cadherin, and (3) a 100 amino acid C-terminus that plays a major role in transcriptional co-activation with the TCF/LEF transcription factor family.

The Wnt/ β -catenin signaling pathway is activated by the binding of secreted Wnt to the cell membrane receptor frizzled that in turn phosphorylates dishevelled (dvl) protein. Phosphorylated dvl prevents phosphorylation of β -catenin by the APC/axin/CK1/GSK3 complex. Normally phosphorylation of β -catenin is primed by CK1 with phosphorylation of serine 45 (S45) and is continued sequentially by GSK3 at T41, S37 and S33 (Fig. 4). Phosphorylation at all four sites allows recognition by ubiquitin ligase, ultimately targeting the protein for destruction by the proteasome. Unphosphorylated or partially phosphorylated β -catenin is stable and can translocate to the nucleus to interact with the TCF family of transcription factors to activate downstream genes. Mutations in exon 3 of *CTNNB1* encoding the phosphorylation domain of β -catenin prevent phosphorylation and allow the nuclear accumulation of β -catenin. β -catenin signaling is also important in the tumorigenesis of various neoplasms

through activation by upstream components of the Wnt pathway in the absence of direct activating mutations of exon 3.

Desmoids are one of multiple tumors with demonstrated mutations in exon 3 of the β -catenin gene (Miyoshi et al., 1998; Tejpar et al., 1999; Abraham et al., 2002); others include colorectal carcinoma, endometrial carcinoma, gastric fundic gland polyps, Wilms tumor, pilomatricomas and pilomatrical carcinomas, hepatocellular carcinoma, and hepatoblastoma (Clevers, 2006). In desmoids, these β -catenin exon 3 mutations occur most commonly in codons S45 and T41 (Fig. 4 and Table 3). These two residues are phosphorylation

Table 3. Incidence and site of β -catenin (CTNNB1) mutations in desmoid tumors.

Study	n/total	T41	S45	Others	%
Miyoshi et al., 1998	7/13	7	7	-	53
Tejpar et al., 1999	22/42	10	12	-	53
Abraham et al., 2002	15/33	11	3	1	46
Amary et al, 2007	60/69	24	36	-	87

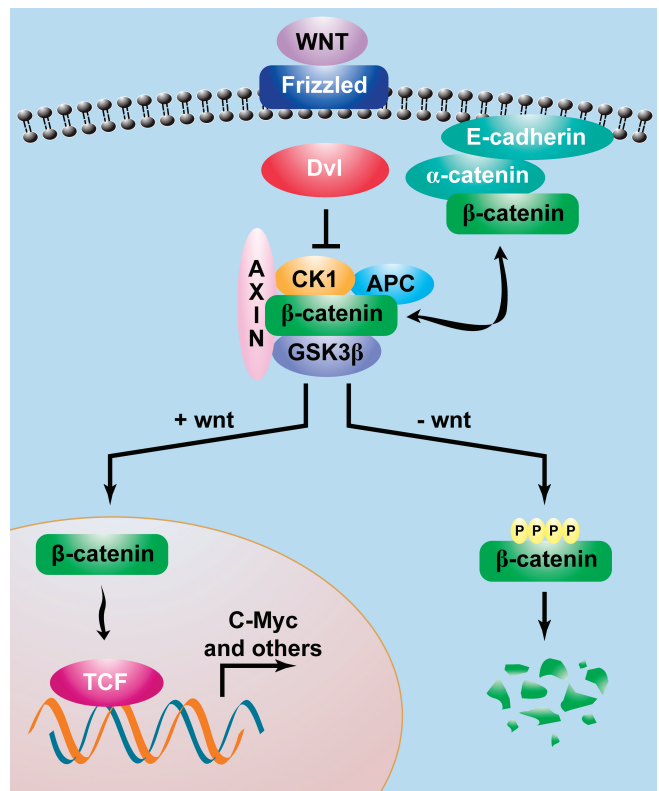


Fig. 3. The fate of β -catenin is determined by the activity of Wnt signaling pathway. When activated, β -catenin is not phosphorylated and thus can accumulate in the nucleus and help induce transcription of target genes.

sites by CK1, and GSK-3, respectively (Fig. 4). Other tumor types show predominantly mutations in S33 and S37 (Mirabelli-Primdahl et al., 1999). The significance of these differences in mutational pattern is not known. The mutations in this region prevent proper, sequential phosphorylation of β -catenin, thus making it refractory to regulation by the axin-APC complex, and eventually leading to stabilization and nuclear accumulation of β -catenin enabling its binding to TCF. Other tumors such as hepatocellular carcinomas having activating mutations in β -catenin or inactivation of APC have also been shown to have inactivating mutations in axin (Zucman-Rossi et al., 2007), but this has not been described in desmoids. There may be differences in the consequences of these two events.

The T-cell factor/lymphoid enhancing factor (TCF/lef) family of transcription factors includes TCF-1, TCF-3, TCF-4 and lef-1 that belong to the broader family of HMG transcription factors. In concert with additional factors, these proteins bind and bend DNA, acting as adaptors to allow other factors to bind and activate or repress the transcription of target genes. It is thought that while in colorectal cancers and pilomatricomas nuclear β -catenin acts primarily through binding TCF-4 (Morin et al., 1997) and lef-1 (Chan et al., 1999) respectively, in desmoids β -catenin specifically binds to TCF-3 (Tejpar et al., 2001) to convey downstream effects. This binding pattern has not been extensively studied and it is possible that it is cell lineage dependent in that the TCF family of transcription factors appears to be differentially expressed in various tissues and cell types. Selectivity of β -catenin for a certain member of the TCF family is also possible, but the mechanisms for such selectivity are not known yet could involve additional proteins in the nuclear transcription factor complex. Thus, while β -catenin mutations occur in a variety of malignancies, the downstream effects may not be identical secondary to the specific TCF family member involved.

It is the nuclear signaling functions of β -catenin rather than its roles in the E-cadherin, α -catenin adhesion complex that appear important in tumorigenesis, though disruption of these adhesions complexes could serve to provide additional β -catenin for nuclear signaling. The control and targeting mechanisms that regulate β -catenin translocation to the nucleus or cell junctions is poorly understood, but Wnt signaling appears to shunt β -catenin to the nucleus. Partial phosphorylation of β -catenin may disrupt interactions with the TCF transcription factor family, but this issue requires further study.

APC

The adenosis polyposis coli (APC) tumor suppressor gene is located on chromosome 5q. It is involved in cell adhesion and binds to cytoskeletal proteins and cell growth regulatory factors. It was first detected in patients with FAP, who have numerous colorectal polyps

and a marked propensity for developing colonic carcinoma and desmoid tumors. Desmoids occurring in the setting of FAP (sometimes called Gardner's fibromas) harbor germline mutations in APC, with most mutations clustered between codons 1250-1500 (mutation cluster region). The mutations at these spots lead to an early stop codon and a truncated protein that can no longer facilitate the phosphorylation and degradation of β -catenin. Analysis of the mutational spectra of the APC gene clearly points to selection for abrogation of the β -catenin regulatory domain (Polakis, 2000). The site of the mutation may also be a factor in determining the severity of desmoids; a germline mutation at the extreme 3' end of the APC gene (codons 2643-2644) was found in a very aggressive desmoid phenotype in a French-Canadian kindred (Couture et al., 2000).

Thus, desmoid tumors may be initiated by APC mutations through loss of β -catenin regulatory function (Li et al., 1998). When desmoid cell lines isolated from desmoid tumors developing in APC mutated mice are transfected transiently or stably with full-length wild type APC gene, the β -catenin protein levels and cell proliferation are decreased (Li et al., 1998).

Somatic APC mutations can be seen in sporadic desmoids (Alman et al., 1997; Giarola et al., 1998); biallelic inactivation of the APC gene has been demonstrated in desmoid tumors occurring in individuals lacking a germline mutation. The mere absence of a complete APC protein or the gain of function/dominant negative function of the truncated mutated APC protein in the initiation of desmoid tumors merits further study and could shed light on the role of APC in this tumor.

β -catenin downstream effectors

A variety of studies identified several proteins physiologically involved in cell cycle control, motility

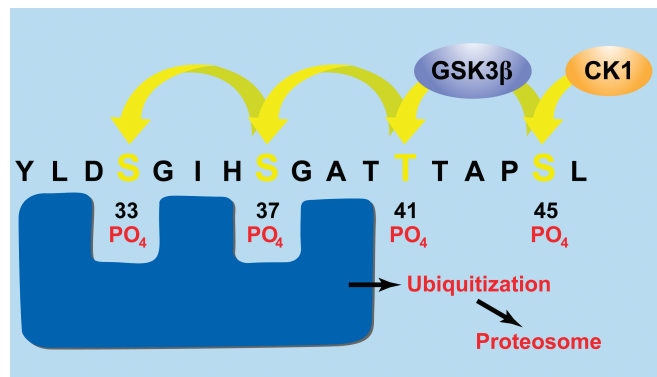


Fig. 4. Sequential phosphorylation of amino acid residues S45, T41, S37 and S33 encoded by exon 3 of β -catenin (*CTNNB1*) by CK1 and GSK3 β leads to ubiquitination and destruction by the proteosome. This steady-state destruction is the basal state for the signaling pool of β -catenin

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and invasion, tissue remodeling, thrombolysis, wound healing and other biological processes, to possibly play a role in desmoid tumorigenesis and progression (Table 4), a few examples will be further given below. Most of these investigated molecules have been shown to be regulated by the β -catenin /TCF-3 pathway in keeping with the hypothesis that β -catenin dysregulation is the key factor in desmoid tumor pathogenesis. The attempt to identify additional potential desmoid related effectors has been further aided with the advent of high throughput techniques such as cDNA expression microarrays (Denys et al., 2004b; Bacac et al., 2006). Results of such assays will hopefully result in better understanding of the desmoid cellular milieu and enable the identification of desmoid-associated therapeutic targets.

Matrix metalloproteinases (MMP) are a family of proteases separable by substrate specificity, inhibitor and extracellular membrane binding efficiency, and are implicated in invasion and angiogenesis. They have been extensively studied for their possible role in a variety of human cancers. MMP 1, 3, 7, 11, 12 and 13 have been shown to be highly expressed by desmoid cells in comparison to normal human fibroblasts. Inhibition of MMPs by either synthetic or physiological inhibitors drastically reversed the invasive capacity of desmoid cells (Denys et al., 2004a). While to the best of our knowledge MMP inhibitors have not been clinically employed for desmoid patients, it is possible that such therapeutic agents might show efficacy in this subset of cancer.

Initial anecdotal reports of desmoid response to imatinib mesylate, a tyrosine kinase inhibitor targeting c-kit, platelet derived growth factor receptor (PDGFR) and bcr/abl culminating in a recently published clinical trial (Heinrich et al., 2006), has prompted immunohistochemical assessment of desmoid tumors for c-kit (CD117) reactivity (Hornick and Fletcher, 2002; Montgomery et al., 2002; Leithner et al., 2005). While a variable staining intensity was reported with initial reports suggesting high c-kit expression (60-90%) depending on series, antibody used, and type of antigen

retrieval, in more recent studies utilizing standardized IHC techniques the rates of reactivity are relatively low (<5%). However, it is possible that imatinib efficacy is secondary to the expression of activated PDGF receptors by desmoid tumor cells or desmoid-associated normal stromal cells. A few studies have shown an increased expression of PDGF receptors and their ligands in desmoid tumors (Alman et al., 1995; Liegl et al., 2006), although no activating mutations in these receptors were found.

The comparatively high incidence of desmoid tumors in young women and their known growth during pregnancy suggest a possible regulatory role for sex hormones, particularly estrogen. Furthermore, use of anti-estrogens has been modestly beneficial in some patients (Kinzbrunner et al., 1983; Wilcken and Tattersall, 1991; Hansmann et al., 2004; Picariello et al., 2004). A few studies have shown increased expression especially of estrogen receptor- β (but not the α -form) in some desmoid tumor specimens (Table 5). In a recent series, more than 80% of 40 desmoid specimens exhibited an intense staining for estrogen receptor- β (Deyrup et al., 2006). Interestingly, expression of neither the α - or β -form of the receptor demonstrated correlation with clinical response to tamoxifen. Inconclusive evidence for interaction between the estrogen receptor pathway and the β -catenin pathway does exist, however the specific molecular mechanisms are not known.

The interaction of Wnt signaling pathway with Wilms tumor gene 1 (WT1) has prompted investigation of the role of WT1 in β -catenin mutation positive desmoid tumor (Amini Nik et al., 2005). Increased WT1 protein and mRNA expression levels, without WT1 gene mutation, were found in desmoid cells compared to surrounding normal fibroblasts. It is possible that WT1 overexpression plays a role in initiation and progression of desmoid tumors and further investigation is necessary.

Insulin like growth factor binding protein 6 (IGFBP-6) is a member of the IGF-binding protein family, regulating the activity of IGF-1 and IGF-2 by directly binding to them and preventing their association with the IGF receptors. This factor has been found to be downregulated in desmoid tumors (Denys et al., 2004b). Two functional β -catenin/TCF responsive elements were identified in the human IGFBP-6 promoter, indicating a transcriptional regulatory role for nuclear β -catenin.

Table 4. Molecular markers possibly contributing to desmoid tumorigenicity and progression.

Molecular markers	Reference
TGF- β 1	Locci et al., 2001
PDGF (a & b)	Alman et al., 1995; Liegl et al., 2006
PDGF Receptor (a & b)	Alman et al., 1995; Liegl et al., 2006
Cyclin D1	Saito et al., 2001
Receptor for hyaluronan-mediated motility (RHAMM)	Tolg et al., 2003
Wilms tumor gene 1(WT1)	Amini Nik et al., 2005
Plasminogen activator inhibitor-1(PAI-1)	Fen Li et al., 2005
MMP-1, 3, 7, 11, 12, 13	Denys et al., 2004a
IGFBP-6	Denys et al., 2004b

Table 5. Estrogen and progesterone receptor status in desmoid tumors.

Study	ER- α	ER- β	PR
Fong et al., 1993	0/6	0/6	0/6
Serpell et al., 1999	0/24	-	0/24
Sorensen et al., 2002	0/72	0/72	-
Picariello et al., 2004	0/7	3/7 (42%)	-
Leithner et al., 2005	0/116	7/116 (6%)	0/116
Ishizuka et al., 2006	2/27 (7.4%)	2/27 (7.4%)	7/27 (25.9%)
Deyrup et al., 2006	0/40	40/40	-

Additional studies have identified other molecular markers such as the receptor for hyaluronan-mediated motility (rhmm), TGF- β 1 (Locci et al., 2001) and plasminogen activator inhibitor-1(PAI-1) (Fen Li et al., 2005) to be overexpressed in desmoid tumors and these should be further investigated for their role and adequacy as potential therapeutic targets in this disease.

Conclusion

Desmoid tumors, although lacking metastatic capability, can be debilitating and at times require multiple surgeries with attendant severe morbidity. While surgery remains the mainstay of treatment, outcomes are not uniformly favorable and recurrence remains a significant obstacle. Activation of the Wnt/ β -catenin pathway is a hallmark of these tumors, and inhibition of this pathway may have clinical utility as this appears to be the critical molecular event underlying desmoid tumor biology. Therapeutic efficacy using small molecule inhibitors that disrupt the formation of the β -catenin/TCF transcriptional machinery have recently been demonstrated in multiple myeloma, although β -catenin in this neoplasm is apparently activated by upstream components of the Wnt pathway rather than by activating mutations in exon 3 of *CTNNB1* (Sukhdeo et al., 2007). Nonetheless, this finding indicates that such an approach may have therapeutic efficacy. There is a crucial need to develop novel therapies inhibiting this pathway, especially in the setting of activating mutations, hopefully leading to useful interventions for desmoid patients.

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