Molecular Pathogenesis of Sporadic Desmoid Tumours and Its Implications for Novel Therapies: A Systematised Narrative Review

Thomas D. McLean1 · Serena Duchi2,4 · Claudia Di Bella2,3

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Abstract
Sporadic desmoid-type fibromatosis is a rare, fibroblastic soft-tissue neoplasm with local aggressiveness but no metastatic potential. Aberrant Wnt/β-catenin signalling has been extensively linked to desmoid pathogenesis, although little is known about other molecular drivers and no established treatment approach exists. We aimed to summarise the current literature regarding the molecular pathogenesis of sporadic desmoid-type fibromatosis and to discuss the effects of both current and emerging novel therapies targeting these mechanisms. A literature search was conducted of MEDLINE® ALL and EMBASE databases for published studies (2000–August 2021) using keywords related to ‘fibromatosis aggressive’, ‘immunohistochemistry’, ‘polymerase chain reaction’ and ‘mutation’. Articles were included if they examined the role of proteins in sporadic or extra-abdominal human desmoid-type fibromatosis pathogenesis. Searching identified 1684 articles. Following duplicate removal and eligibility screening, 36 were identified. After a full-text screen, 22 were included in the final review. At least 47% of desmoid-type fibromatosis cases displayed aberrant β-catenin immunoreactivity amongst ten studies. Cyclin D1 overexpression occurred in at least 40% of cases across five studies. Six studies reported oestrogen receptor-β expression with a range of 7.4–90%. Three studies implicated matrix metalloproteinases, with one study demonstrating vascular endothelial growth factor overexpression. One study explored the positive relationship between cyclooxygenase-2 and platelet-derived growth factor receptor-β. Aberrant Wnt/β-catenin signalling is a well-established pathogenic driver that may be targeted via downstream modulation. Growth factor signalling is best appreciated through the clinical trial effects of multi-targeted tyrosine kinase inhibitors, whilst oestrogen receptor expression data may only offer a superficial insight into oestrogen signalling. Finally, the tumour microenvironment presents multiple potential novel therapeutic targets.

Plain Language Summary
Sporadic desmoid tumours are rare soft-tissue neoplasms that arise from connective tissues in the chest wall, head, neck and limbs. Whilst lacking metastatic potential, uncertainty surrounding their locally aggressive growth and unpredictable recurrence complicates treatment approaches. At the molecular level, alterations in the Wnt/β-catenin signalling pathway, a fundamental coordinator of cell growth and development, have been strongly linked to desmoid tumour development. Beyond this, however, little is known about other molecular drivers. In the case of progressive or life-threatening disease, complex treatment decisions are made regarding the use of surgery, radiotherapy or systemic treatment modalities. Of the targeted systemic therapies, a lack of comparative clinical studies further complicates medical treatment decision making.

Thomas D. McLean
mcleant@student.unimelb.edu.au

1 Melbourne Medical School, The University of Melbourne, Melbourne, VIC, Australia
2 Department of Surgery, The University of Melbourne, Melbourne, VIC, Australia
3 Department of Orthopaedics, St Vincent’s Hospital Melbourne, VIC, Australia
4 Biofab 3D, Aikenhead Centre for Medical Discovery, Melbourne, VIC, Australia
as no definitive treatment approach exists. Therefore, this review aimed to summarise the literature regarding the molecular drivers of desmoid tumour pathogenesis and to discuss the current and emerging novel therapies targeting such mechanisms. Utilising findings from human desmoid tissue samples, we present the rationale for targeting downstream mediators of the central Wnt/β-catenin pathway and outline potential treatment targets in the tumour microenvironment. We also highlight the knowledge gained from clinical drug trials targeting desmoid growth factor signalling and present the potentially superficial insight provided by oestrogen receptor expression profiles on the role of oestrogen signalling in desmoid pathogenesis. In doing so, this work may assist in the eventual development of an evidence-based treatment approach for sporadic desmoid tumours.

### Key Points

| Aberrant Wnt/β-catenin signalling is a well-established driver of desmoid tumour pathogenesis that may be effectively targeted via downstream blockade. |
| The role of growth factors in desmoid tumour pathogenesis is best appreciated through the clinical trial success of tyrosine kinase inhibitor drugs targeting such factors. |
| Oestrogen receptor expression data may only offer a superficial insight into oestrogen signalling mechanisms with clinical findings opposing anti-hormonal therapy, although further treatment opportunities exist within the tumour microenvironment. |

### 1 Introduction

Desmoid-type fibromatosis (DTF), also known as desmoid tumour or aggressive fibromatosis, is a rare soft-tissue neoplasm defined histologically by a monoclonal fibroblastic proliferation. These tumours arise in musculoaponeurotic structures and are characterised by locally infiltrative growth and a tendency towards local recurrence with no metastatic potential [1]. The estimated incidence of DTF lies between two and five cases per million people per year [2, 3].

Aetiological characteristics define two main groups: sporadic and familial DTF. Sporadic DTF comprises 85–90% of total cases that arise predominantly in extra-abdominal (E-AD) locations and have a slightly higher incidence following trauma, surgery, oral contraceptive use or within female individuals of reproductive age [2, 4–9]. In contrast, familial DTF represents an inheritable form associated with familial adenomatous polyposis (FAP). These tumours differ both clinically and pathologically from their sporadic counterparts because of their prevailing abdominal (AD) wall or intra-abdominal (I-AD) mesenteric and visceral locations and underlying APC gene mutations [2, 4, 5].

Desmoid pathogenesis has been associated with a number of signalling pathway aberrations. Of these, Wnt/β-catenin signalling has been extensively linked to desmoid pathogenesis (Fig. 1) [10–14]. In sporadic DTF, this is demonstrated by the vast majority of cases harbouring activating β-catenin gene (CTNNB1) mutations [15–18]. Beyond this signalling cascade, however, little is known about other molecular drivers implicated in desmoid pathogenesis and their interactions with Wnt/β-catenin signalling.

Owing to disease rarity, unpredictable clinical course and spontaneous regression rates, the current evidence base supports an “active surveillance” approach with close radiological monitoring in patients with stable non-critical disease. In the case of persistent progression or involvement of life-threatening anatomical sites lies the complex decision to engage active treatment options such as surgery, radiotherapy, chemotherapy or novel therapeutics [9, 19–21]. Particularly in the latter group, a lack of comparative clinical studies has prevented the creation of a definitive treatment approach for the implementation of systemic targeted therapies such as anti-hormonal therapy or tyrosine kinase inhibitors (TKIs) [21].

Improving our understanding of DTF growth and development would add greater precision to novel therapeutic decisions and may improve desmoid treatment outcomes. Therefore, this review aimed to summarise the current literature regarding the molecular pathogenesis of sporadic DTF and to discuss the effects of both current and emerging novel therapies targeting these mechanisms.

### 2 Methods

#### 2.1 Search Strategy

A literature search was conducted on 7 August, 2021 using Ovid MEDLINE® ALL and EMBASE in consultation with a professional librarian. The search was limited to articles published after 1999 and an English language filter was applied. Keywords included ‘fibromatosis aggressive’, ‘immunohistochemistry’, ‘polymerase chain reaction’ and ‘mutation’ (see Tables 1, 2).
2.2 Article Eligibility and Study Selection

The titles and abstracts of records identified from database searching were assessed according to the eligibility criteria outlined in Table 3. Next, retrieved full-text articles were further assessed using the eligibility criteria listed in Table 3. Owing to the rare nature of desmoid tumours and the propensity for FAP-associated disease to occur in I-AD or AD locations [2, 4, 5], articles were excluded if they comprised > 15% of patients with FAP or included > 30% of AD or I-AD cases with no independent E-AD analysis (see Fig. 2).

2.3 Data Extraction

The first author, publication year, study type and methodological techniques were collected from all included papers. Clinical characteristics included the number of participants, number of primary and recurrent tumour samples, age, sex, sporadic status, tumour location and size. Tumour location

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**Fig. 1** Wnt/β-catenin signalling pathway. The Wnt/β-catenin pathway coordinates cell proliferation, differentiation and fate during both embryogenesis and in normal adult tissues. **a** In the absence of a Wnt signal, cytoplasmic β-catenin that is not involved in cell-cell adhesion interacts with a degradation complex comprising axin, APC, GSK3 and CK1. Here, the sequential phosphorylation of β-catenin by CK1 and GSK3 marks it for ubiquitylation and degradation. This constant degradation prevents β-catenin from entering the nucleus and promoting the transcription of Wnt target genes. **b** The binding of Wnt to its frizzled receptor and LRP co-receptor leads to the recruitment of dishevelled. Together, this complex recruits the degradation complex to the cell membrane where LRP becomes phosphorylated by GSK3 then CK1. Axin then binds to the phosphorylated LRP, resulting in the disassembly of the degradation complex. Consequently, the stabilisation of β-catenin allows it to accumulate and translocate into the nucleus. Here, it binds to the TCF/LEF promotor region to stimulate the transcription of Wnt target genes including **CCND1** (cyclin D1), **MYC**, **PTGS2** (cyclooxygenase-2), **MMP7**, **VEGF** and **WISP1**. With deregulated, constitutive activation, the resultant protein products may drive tumorigenesis by enhancing proliferation, angiogenesis and invasiveness [10–14]. Created with BioRender.com
Table 1  Ovid MEDLINE® ALL search strategy, 1946 to 5 August, 2021

| Search Term                                                                 | Logic   |
|----------------------------------------------------------------------------|---------|
| Fibromatosis, Aggressive/                                                 | 1       |
| (Desmoid tumo* or Aggressive fibromatosis or Desmoid-type fibromatosis or Deep fibromatosis or musculoaponeurotic fibromatosis).tw. | 2       |
| 1 or 2                                                                     | 3       |
| Polymerase Chain Reaction/or Signal Transduction/or Immunohistochemistry/or tissue microarray/ | 4       |
| (Signal transduct* or signalling pathway* or signal pathway* or transcription factor* or polymerase chain reaction or RT-PCR or RNA sequenc* or messenger RNA expression or mRNA expression or protein expression or molecular).tw. | 5       |
| (Immunohistochem* or Immunoreact* or tissue array or tissue microarray or biomarker* or biochem*).tw. | 6       |
| Mutation/ or mutagenesis/ or Genes, Neoplasms/                           | 7       |
| (Pathogenesis or mutation* or microvessel densit* or angiogenesis or Proto-oncogen* or oncogene* or Tumor suppressor or Tumour suppressor).tw. | 8       |
| 4 or 5 or 6 or 7 or 8                                                    | 9       |
| 3 and 9                                                                   | 10      |
| exp animals/ not humans/                                                  | 11      |
| 10 not 11                                                                 | 12      |
| Limit 12 to (english language and yr=“2000 -Current”)                    | 13      |

Table 2  EMBASE Classic + EMBASE search strategy, 1947–5 August, 2021

| Search Term                                                                 | Logic   |
|----------------------------------------------------------------------------|---------|
| Aggressive fibromatosis/or desmoid/                                       | 1       |
| (Desmoid tumo* or Aggressive fibromatosis or Desmoid-type fibromatosis or Deep fibromatosis or musculoaponeurotic fibromatosis).tw. | 2       |
| 1 or 2                                                                     | 3       |
| Polymerase Chain Reaction/or Signal Transduction/or Immunohistochemistry/or tissue microarray/ | 4       |
| (Signal transduct* or signalling pathway* or signal pathway* or transcription factor* or polymerase chain reaction or RT-PCR or RNA sequenc* or messenger RNA expression or mRNA expression or protein expression or molecular).tw. | 5       |
| (Immunohistochem* or Immunoreact* or tissue array or tissue microarray or biomarker* or biochem*).tw. | 6       |
| Mutation/ or mutagenesis/ or tumor gene/                                  | 7       |
| (Pathogenesis or mutation* or microvessel densit* or angiogenesis or Proto-oncogen* or oncogene* or Tumor suppressor or Tumour suppressor).tw. | 8       |
| 4 or 5 or 6 or 7 or 8                                                    | 9       |
| 3 and 9                                                                   | 10      |
| exp animal/not human/                                                    | 11      |
| 10 not 11                                                                 | 12      |
| Limit 12 to (english language and yr=“2000 -Current”)                    | 13      |

Table 3  Inclusion and exclusion criteria for study selection

| Inclusion criteria                                                                 | Exclusion criteria                                                                 |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Human DTF samples                                                                 | Case reports or review articles                                                   |
| Positive sporadic or E-AD tumour status                                           | Animal models                                                                     |
| Analysed specific genes and/or proteins for their role in tumour pathogenesis    | In vitro cell cultures                                                            |
| Full-text article                                                                 | Genome sequencing techniques                                                      |
| Published after 1999                                                              | Prognostic or diagnostic studies                                                   |
| English language                                                                  | Treatment outcomes                                                               |
|                                                                                  | Inadequate statistical analysis                                                   |
|                                                                                  | Exclusive paediatric population (age <18 years)                                   |
|                                                                                  | Patients with FAP-associated disease                                              |

DTF desmoid-type fibromatosis, E-AD extra-abdominal, FAP familial adenomatous polyposis

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was grouped into three broad categories. E-AD comprised the head and neck, pectoral and pelvic girdle, chest, upper and lower extremities, AD comprised the abdominal wall and I-AD comprised the abdominal cavity. Immunohistochemistry, DNA and mRNA sequencing data were retrieved for each studied protein.

### 3 Results

#### 3.1 Systematic Literature Search

The search strategy yielded 1684 articles. Duplicates were then removed via computational software, leaving 1183 articles. The title and abstract were then screened, and a further 1147 articles were excluded. Of the 36 articles sought for retrieval, 22 articles were included in the final review (Fig. 3).

#### 3.2 Study Design and Quality Assessment

All included studies were retrospective case series. Although some studies included control groups to assist with their deductions, these were not considered case-control studies as the features of these groups remained implicit and unclear [22]. The Joanna Briggs Institute critical appraisal tool for case series was utilised to determine each study’s risk of bias across nine domains (Fig. 4) [23]. ‘Overall’ judgement is described in Table 4. The domain concerning follow-up results was omitted as this was outside the scope of the review.

### 3.3 Study Findings

Multiple proteins and associated signalling pathways have been linked to DTF pathogenesis (Table 5) with each pathway possessing potential therapeutic targets. Figure 5 outlines the key molecular drivers and associated pathophysiological domains identified by this review.

#### 3.3.1 Proliferation

##### 3.3.1.1 β-Catenin

β-Catenin primarily coordinates cell proliferation, differentiation and fate, with its deregulated signalling being intrinsically linked to the development of several human cancers, such as skin, colon and breast cancer [13, 14]. β-Catenin demonstrated aberrant nuclear immunoreactivity in at least 47% of DTF cases [24–33]. DTF cases with a mutated CTNNB1 gene also demonstrated more frequent β-catenin nuclear expression (39/43, 90.7%) compared with cases with wild-type CTNNB1 (Fisher’s exact test, 17/27, 63.0%, \( p = 0.012 \)) [28]. Saito et al. also dem-
onstrated this difference with the mutated CTNNB1 group showing significantly higher β-catenin mRNA expression compared with the wild-type group (Mann–Whitney U test, \( p = 0.0036 \)) [31]. DTF cases with abnormal β-catenin accumulation demonstrated a significantly higher proliferating cell nuclear antigen-labelling index than those with normal staining patterns (Fisher’s exact test, \( p = 0.007 \)) [27]. Nuclear β-catenin immunoreactivity was significantly higher in desmoid tumours compared with both hypertrophic scar and normal fibrous tissue (Kruskal–Wallis test, \( p = 0.0003 \); Dunn’s post-tests, \( p < 0.01 \)) [32]. These results are consistent with the current knowledge of Wnt/β-catenin’s role in DTF pathogenesis.

3.3.1.2 Cyclin D1 and c-Myc Cyclin D1 and c-Myc signalling is commonly deregulated in tumourigenesis due to their promotional effects on cell proliferation by enhancing the G1 to S-phase transition of the cell cycle [34, 35]. Cyclin D1 was overexpressed in at least 40% of DTF cases [26, 27, 29, 36]. Two studies found a significant correlation between β-catenin nuclear expression and cyclin D1 overexpression (Fisher’s exact test, \( p = 0.029 \); Fisher’s exact test, \( p = 0.034 \), respectively) [27, 29]. Similarly, Jilong et al. found a significantly higher c-Myc expression in cases with abnormal β-catenin staining compared with normal cytomembrane staining (\( \chi^2 = 15.68, p = 0.0001 \)) [26]. Furthermore, three studies demonstrated significantly higher CCND1 gene expression in the mutated CTNNB1 group compared with the wild-type group (\( \chi^2 \) test, \( p = 0.038 \); Mann–Whitney U test, \( p = 0.019 \); Mann–Whitney U test, \( p = 0.0120 \), respectively) [26, 29, 31]. Saito et al. and Santti et al. demonstrated significant cellular proliferative activity in DTF cases with cyclin D1 overexpression via a proliferating cell nuclear antigen-labelling index (Fisher’s exact test, \( p = 0.004 \)) and Ki-67 (\( r = 0.40, p = 0.001 \), respectively [27, 36]. These findings suggest aberrant Wnt/β-catenin signalling may exert its proliferative effects through the overexpression of positive cell-cycle regulatory proteins.
**Fig. 4 Joanna Briggs Institute critical appraisal for case-series via ROBINS-I [54]**

| Study                        | Risk of bias | D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8 | D9 | Overall |
|------------------------------|--------------|----|----|----|----|----|----|----|----|----|---------|
| Matono et al., 2011          |              | X  | +  | X  | +  | -  | +  | X  | -  | +  | -       |
| Ferenc et al., 2009          |              | X  | +  | X  | X  | +  | +  | -  | +  | -  | -       |
| Jilong et al., 2007          |              | X  | +  | X  | X  | +  | +  | -  | +  | -  | -       |
| Stalinska et al., 2009       |              | X  | +  | X  | X  | X  | +  | X  | -  | +  | X       |
| Saito et al., 2001           |              | -  | +  | X  | -  | X  | X  | X  | +  | X  | -       |
| An et al., 2021              |              | +  | +  | +  | +  | X  | +  | +  | +  | +  | -       |
| Matono et al., 2008          |              | -  | +  | +  | +  | +  | X  | -  | +  | -  | -       |
| Signoroni et al., 2007       |              | X  | -  | -  | -  | -  | +  | X  | -  | X  | -       |
| Santi et al., 2019           |              | +  | +  | +  | +  | -  | +  | +  | +  | +  | +       |
| Deyrup et al., 2006          |              | X  | +  | +  | -  | -  | +  | X  | X  | -  | X       |
| Santos et al., 2010          |              | -  | +  | +  | -  | -  | +  | X  | X  | +  | -       |
| Gebert et al., 2007          |              | X  | +  | +  | +  | X  | +  | +  | -  | +  | -       |
| Misemer et al., 2014         |              | X  | +  | +  | -  | -  | +  | +  | -  | +  | -       |
| Ishizuka et al., 2006        |              | +  | +  | +  | +  | X  | X  | X  | -  | X  | -       |
| Leithner et al., 2005        |              | -  | -  | -  | -  | -  | +  | X  | -  | -  | X       |
| Colombo et al., 2011         |              | -  | +  | +  | -  | X  | X  | X  | +  | X  | X       |
| Ahlen et al., 2001           |              | +  | +  | +  | +  | -  | X  | +  | +  | +  | -       |
| Brautigam et al., 2020       |              | +  | +  | +  | +  | -  | +  | +  | +  | +  | +       |
| Saito et al., 2002           |              | +  | -  | +  | X  | X  | +  | X  | -  | +  | -       |
| Mignemi et al., 2012         |              | +  | +  | +  | +  | +  | +  | -  | +  | +  | +       |
| Cates et al., 2012           |              | +  | +  | +  | +  | -  | -  | -  | +  | -  | -       |
| Varghese et al., 2017        |              | +  | X  | -  | X  | -  | +  | X  | -  | +  | X       |

**Legend:**
- **D1:** Inclusion criteria
- **D2:** Standardisation and reliability of measurements
- **D3:** Valid identification methods
- **D4:** Consecutive inclusion of participants
- **D5:** Complete inclusion of participants
- **D6:** Reporting of patient demographics
- **D7:** Reporting of patient clinical information
- **D8:** Reporting of the site(s) demographic information
- **D9:** Statistical analysis

**Judgement:**
- **High**
- **Unclear**
- **Low**

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Akt expression was detected in 56% of samples, (EGFR) expression, which was detected in 11% of cases. Two studies evaluated epidermal growth factor receptor (HER2) [30, 43]. TGFβ and related growth factors appeared to demonstrate aberrant expression in DTF, although the direct pathological consequence of this finding remains unclear.

### 3.3.2 Growth Factor Regulatory Signalling

#### 3.3.2.1 Cyclooxygenase-2 (COX2) and Platelet-Derived Growth Factor Receptor (PDGFR)

COX2 is an inducible member of the cyclooxygenase family involved in multiple physiological purposes. In colorectal cancer, COX2 has been extensively implicated in promoting angiogenesis, invasion and proliferation through the upregulation of growth factors such as platelet-derived growth factor [37, 38]. Nuclear β-catenin did not correlate with COX2 expression ($p = 0.034$, $p = 0.873$) [32]. However, COX2 immunoreactivity was significantly higher in desmoid tumours compared with both hypertrophic scar and normal fibrous tissue (Kruskal–Wallis test, $p < 0.0001$; Dunn’s post-hoc test, $p < 0.01$) [32]. Signoroni et al. demonstrated 100% COX2, PDGFRα and PDGFRβ immunoreactivity and phosphorylation in their cohort of eight sporadic patients [39]. Cates et al. found 100% PDGFRβ expression in DTF samples (27/27) with a significantly higher immunoreactivity compared with normal fibrous tissue [40]. Albeit in a small cohort, COX2 induction may be responsible for the PDGFR expression validated by desmoid TKI trials, although this appeared to occur independently of β-catenin signalling.

#### 3.3.2.2 Transforming Growth Factor-β (TGFβ) Superfamily and Other Growth Factors

The multifunctional TGFβ superfamily and related growth factors play complex and often opposing roles in cell proliferation, differentiation, regeneration and morphogenesis [41]. Two studies examined TGFβ signalling. Varghese et al. illustrated moderate- strong TGFβ and connective tissue growth factor (CTGF) immunoreactivity in 100% and 66.7% of DTF cases, respectively [33]. Mignemi et al. demonstrated phosphorylated SMAD2/3 immunoreactivity in 96% of their DTF cohort, which was significantly greater than both hypertrophic scar and normal fibrous tissue (Kruskal–Wallis test, $p = 0.0001$; Dunn’s post-hoc test, $p < 0.001$) [32]. Cates et al. found weak MET expression in 89% of DTF cases that differed significantly from normal fibrous tissue (Kruskal–Wallis test, $p = 0.0005$; Dunn’s post-hoc test, $p < 0.001$) [40]. Two studies evaluated epidermal growth factor receptor (EGFR) expression, which was detected in 11% of cases [30, 40]. Akt expression was detected in 56% of samples, which was significantly lower than the levels observed in hypertrophic scars (Kruskal–Wallis test, $p = 0.0002$; Dunn’s post-hoc test, $p < 0.01$). No study demonstrated positive expression for c-Kit [30, 42, 43] or human epidermal growth factor receptor 2 (HER2) [30, 43]. TGFβ and related growth factors appeared to demonstrate aberrant expression in DTF, although the direct pathological consequence of this finding remains unclear.

#### 3.3.3 Oestrogen-Related Pathway

Oestrogens are steroid hormones that promote growth, differentiation and reproduction throughout a range of human tissues. Their role in tumourigenesis has been extensively studied in breast cancer, where aberrant signalling drives proliferation, invasion and metastasis [44]. Six studies evaluated the role of sex steroids in desmoid tumour pathogenesis [36, 42, 43, 45–47]. Oestrogen receptor-β (ERβ) expression was demonstrated in all studies and ranged from 7.4% to 90% [36, 42, 43, 45–47], whilst only Ishizuka et al. demonstrated oestrogen receptor-α (ERα) expression in two patients [46]. ERβ significantly correlated with the expression of cyclin A ($r = 0.34$, $p = 0.004$), cyclin D1 ($r = 0.34$, $p = 0.004$) and Ki-67 ($r = 0.35$, $p = 0.003$) [36]. Ishizuka et al. also demonstrated positive progesterone receptor A and B expression in 25.9% and 33.3% of DTF cases respectively [46], whilst the remaining studies were negative for progesterone receptor expression [42, 43, 47]. In addition to sex steroid receptor analysis, Brautigam et al. found poly(ADP-ribose) polymerase 1 (PARP1) expression in 98.3% of DTF cases, which negatively correlated with Ki-67 expression (Spearman–Rho test, $−0.375$, $p = 0.041$) [47]. In the context of widespread ERβ expression and its positive correlation with proliferation markers, these findings support a proliferative role for oestrogen in desmoid pathogenesis.

#### 3.3.4 Tumour Microenvironment

#### 3.3.4.1 Invasion

Matrix metalloproteinases (MMPs) and related proteases play a pivotal role in cancer pathogenesis through their modulation of the extracellular matrix, angiogenesis, cell migration and growth [48]. Four studies evaluated the expression of MMPs [29, 49–51]. β-Catenin nuclear expression significantly correlated with MMP7 overexpression (Fisher’s exact test, $p < 0.01$), and mutated CTNNB1 which negatively correlated with Ki-67 expression (Spearman–Rho test, $−0.375$, $p = 0.041$) [47]. In the context of widespread ERβ expression and its positive correlation with proliferation markers, these findings support a proliferative role for oestrogen in desmoid pathogenesis.
## Table 5  Molecular aberrations in desmoid tumours: retrospective case-series

| Author                  | Patients and samples (recurrence) | Mean age, range (years) | Sex (F/M) (%) | Sporadic status (%) | Tumour location (%) | Mean tumour size, range (cm) | Molecular target                  | Results | Significance |
|-------------------------|-----------------------------------|-------------------------|---------------|---------------------|---------------------|-------------------------------|-----------------------------------|---------|--------------|
| Matono et al. [24]      | 63 patients 74 samples (11)       | 34.2, 0–76              | 65/35         | 100                 | E-AD: 67 AD: 19 I-AD: 14 | NS                            | β-catenin (n > 50%)                | 35/74 (56)| *p = 0.04*   |
|                         |                                   |                         |               |                     |                     |                               | VEGF > 10%                         | 47/74 (73)|             |
|                         |                                   |                         |               |                     |                     |                               | **MVD:** mean ± SD                |         |              |
|                         |                                   |                         |               |                     |                     |                               | VEGF (+)                           | 10.62 ± 4.41| *p = 0.84*   |
|                         |                                   |                         |               |                     |                     |                               | VEGF (−)                           | 9.55 ± 3.96 |             |
|                         |                                   |                         |               |                     |                     |                               | Recurrent tumour                  | 13.97 ± 5.32 | *p = 0.02*   |
|                         |                                   |                         |               |                     |                     |                               | Primary tumour                    | 9.56 ± 3.72 |             |
| Ferenc et al. [25]      | 33 patients 35 samples (2)        | 33.5, 15–68             | 86/14         | 100                 | E-AD: 43 AD: 57      | 5, 2–12 3 missing             | **IHC:** n (%)                     |         |              |
|                         |                                   |                         |               |                     |                     |                               | α-catenin (c) ≥ 10%               | E-AD: 10/15 (67) | –      |
|                         |                                   |                         |               |                     |                     |                               | AD: 13/20 (65)                 |         |              |
|                         |                                   |                         |               |                     |                     |                               | α-catenin (c) (−)                 | E-AD: 5/15 (33) | –      |
|                         |                                   |                         |               |                     |                     |                               | AD: 7/20 (35)                  |         |              |
|                         |                                   |                         |               |                     |                     |                               | β-catenin (c) ≥ 10%               | E-AD: 14/15 (93) | –      |
|                         |                                   |                         |               |                     |                     |                               | AD: 17/20 (85)                 |         |              |
|                         |                                   |                         |               |                     |                     |                               | β-catenin (n ≥ 10%)               | E-AD: 8/15 (53) | –      |
|                         |                                   |                         |               |                     |                     |                               | AD: 15/20 (75)                 |         |              |
|                         |                                   |                         |               |                     |                     |                               | β-catenin (c + n) ≥ 10%           | E-AD: 7/15 (47) | –      |
|                         |                                   |                         |               |                     |                     |                               | AD: 12/20 (60)                 |         |              |
|                         |                                   |                         |               |                     |                     |                               | N-Cadherin (c) ≥ 10%             | E-AD: 4/15 (27) | –      |
|                         |                                   |                         |               |                     |                     |                               | AD: 4/20 (20)                  |         |              |
|                         |                                   |                         |               |                     |                     |                               | **IHC:** % mean immunoreactive cells |         |              |
|                         |                                   |                         |               |                     |                     |                               | α-catenin (c)                    | E-AD: 61.5 | *p = 0.0165* |
|                         |                                   |                         |               |                     |                     |                               | AD: 42.3                       |         |              |
|                         |                                   |                         |               |                     |                     |                               | β-catenin (c)                    | E-AD: 51.3 | *p > 0.05*   |
|                         |                                   |                         |               |                     |                     |                               | AD: 35.5                       |         |              |
|                         |                                   |                         |               |                     |                     |                               | β-catenin (n)                    | E-AD: 24.7 | *p > 0.05*   |
|                         |                                   |                         |               |                     |                     |                               | AD: 32.5                       |         |              |
|                         |                                   |                         |               |                     |                     |                               | β-catenin (c + n)                | E-AD: 24.0 | *p > 0.05*   |
|                         |                                   |                         |               |                     |                     |                               | AD: 26.0                       |         |              |
|                         |                                   |                         |               |                     |                     |                               | N-cadherin (c)                   | E-AD: 55.0 | *p > 0.05*   |
|                         |                                   |                         |               |                     |                     |                               | AD: 42.5                       |         |              |
|                         |                                   |                         |               |                     |                     |                               | **Correlation:** r               | −0.0363 | *p = 0.9207* |
|                         |                                   |                         |               |                     |                     |                               | β-catenin (n) and α-catenin      | −0.7510 | *p = 0.2490* |
|                         |                                   |                         |               |                     |                     |                               | β-catenin (n) and N-cadherin     |         |              |

*Note: E-AD: Extra-Aponeurotic, AD: Aponeurotic, I-AD: Intramuscular, VEGF: Vascular Endothelial Growth Factor, MVD: Microvessel Density, IHC: Immunohistochemistry.*
| Author       | Patients and samples (recurrence) | Mean age, range (years) | Sex (F/M) (%) | Sporadic status (%) | Tumour location (%) | Mean tumour size, range (cm) | Molecular target | Results | Significance |
|--------------|-----------------------------------|-------------------------|---------------|---------------------|---------------------|---------------------------|------------------|---------|--------------|
| Jilong et al. [26] | 99 patients (14) 69 samples | 30.5†, 8–86 | 77/23 | 100 | E-AD: 45 AD: 35 I-AD: 20 | NS | Gene sequencing: n (%) |
|               |                                   |                         |               |                     |                     |                           | CTNNB1 T41A     | 13/69 (18.8) | –            |
|               |                                   |                         |               |                     |                     |                           | CTNNB1 WT       | 56/69 (81.2) | –            |
|               |                                   |                         |               |                     |                     |                           | CTNNB1 T41A and CCND1 > 10% | 9/13 (69.2) | $\chi^2 = 4.323$ |
|               |                                   |                         |               |                     |                     |                           | CTNNB1 WT and CCND1 > 10% | 21/56 (37.5) | $p = 0.038^d$ |
|               |                                   |                         |               |                     |                     | IHC: $n (\%)$             | β-catenin (c +n) > 10% | 33/69 (47.8) | –            |
|               |                                   |                         |               |                     |                     |                            | c-myc > 10%     | 31/69 (44.9) | –            |
|               |                                   |                         |               |                     |                     |                            | Cyclin D1 > 10% | 30/69 (43.5) | –            |
|               |                                   |                         |               |                     |                     |                            | β-catenin ( +) and c-myc > 10% | 23/33 (69.7) | $\chi^2 = 15.68$ |
|               |                                   |                         |               |                     |                     |                            | β-catenin (−) and c-myc > 10% | 8/36 (22.2) | $p = 0.001^d$ |
|               |                                   |                         |               |                     |                     | AI: $n, mean \pm SD$        | β-catenin (c +n) > 10% | 33, 0.019 ± 0.008 | $t = 1.72$ |
|               |                                   |                         |               |                     |                     |                            | β-catenin (c +n) (−) | 36, 0.023 ± 0.009 | $p = 0.09^e$ |
|               |                                   |                         |               |                     |                     |                            | c-myc > 10%     | 31, 0.019 ± 0.007 | $t = 2.78$ |
|               |                                   |                         |               |                     |                     |                            | c-myc (−)       | 38, 0.024 ± 0.010 | $p = 0.007^c$ |
|               |                                   |                         |               |                     |                     |                            | Cyclin D1 > 10% | 30, 0.018 ± 0.009 | $t = 2.495$ |
|               |                                   |                         |               |                     |                     |                            | Cyclin D1 (−)   | 39, 0.024 ± 0.010 | $p = 0.015^c$ |
### Table 5 (continued)

| Author         | Patients and samples (recurrence) | Mean age, range (years) | Sex (F/M) (%) | Sporadic status (%) | Tumour location (%) | Mean tumour size, range (cm) | Molecular target | Results | Significance |
|----------------|-----------------------------------|-------------------------|---------------|---------------------|---------------------|----------------------------|------------------|---------|--------------|
| Stalinska et al. [56] | 18 samples                        | NS                      | NS            | NS                  | **E-AD**: 100        | NS                         | IHC: n (%)      |         |              |
|                |                                   |                         |               |                     |                     |                            | pRb > 50%        | 17/18 (94.4) | –            |
|                |                                   |                         |               |                     |                     |                            | pRb 10–50%       | 1/18 (5.56)  | –            |
|                |                                   |                         |               |                     |                     |                            | p16 > 50%        | 9/18 (50)    | –            |
|                |                                   |                         |               |                     |                     |                            | p16 10-50%       | 9/18 (50)    | –            |
|                |                                   |                         |               |                     |                     |                            | PCNA > 50%       | 18/18 (100)  | –            |
|                |                                   |                         |               |                     |                     |                            | Ki-67 > 50%      | 0/18 (0)     | –            |
|                |                                   |                         |               |                     |                     |                            | Ki-67 (−)        | 15/18 (83.33) | –            |
|                |                                   |                         |               |                     |                     |                            | MCMS > 50%       | 0/18 (0)     | –            |
|                |                                   |                         |               |                     |                     |                            | MCMS (−)         | 18/18 (100)  | –            |
|                |                                   |                         |               |                     |                     |                            | **IHC**: % mean immunoreactive cells |
|                |                                   |                         |               |                     |                     |                            | pRb               | 73.87    | –            |
|                |                                   |                         |               |                     |                     |                            | P16               | 46.32    | –            |
|                |                                   |                         |               |                     |                     |                            | PCNA              | 79.26    | –            |
|                |                                   |                         |               |                     |                     |                            | Ki-67             | 7.54     | –            |
|                |                                   |                         |               |                     |                     |                            | MCMS              | 0.00     | –            |
Table 5 (continued)

| Author          | Patients and samples (recurrence) | Mean age, range (years) | Sex (F/M) (%) | Sporadic status (%) | Tumour location (%) | Mean tumour size, range (cm) | Molecular target | Results | Significance |
|-----------------|-----------------------------------|-------------------------|---------------|---------------------|---------------------|-----------------------------|------------------|---------|--------------|
| Saito et al. [27] | 38 samples                        | NS                      | NS            | 100                 | E-AD: 74           | AD: 26                      | IHC: n (%)       |         |              |
|                 |                                   |                         |               |                     |                     |                             | β-catenin (n) > 75% | 19/38 (50) | –            |
|                 |                                   |                         |               |                     |                     |                             | Cyclin D1 > 5%     | 27/38 (71.1) | –            |
|                 |                                   |                         |               |                     |                     |                             | β-catenin (n) and cyclin D1 | 17/19 (89.5) | p = 0.029a |
|                 |                                   |                         |               |                     |                     |                             | β-catenin (−) and cyclin D1 | 10/19 (52.6) |              |
|                 |                                   |                         |               |                     |                     |                             | IHC: mean (range)  |         |              |
|                 |                                   |                         |               |                     |                     |                             | MIB-1-LI          | 3.0 (0–28.6) | –            |
|                 |                                   |                         |               |                     |                     |                             | PCNA-LI           | 31.8 (2.5–67.4) | –            |
|                 |                                   |                         |               |                     |                     |                             | IHC: n, mean (SD)  |         |              |
|                 |                                   |                         |               |                     |                     |                             | MIB-1-LI and β-catenin (n) | –         | p > 0.05a  |
|                 |                                   |                         |               |                     |                     |                             | MIB-1-LI and cyclin D1 | –         | p > 0.05a  |
|                 |                                   |                         |               |                     |                     |                             | PCNA-LI and β-catenin (n) | 19, 37.9 (14.1) | p = 0.007a |
|                 |                                   |                         |               |                     |                     |                             | PCNA-LI and cyclin-D1 (+) | 27, 35.9 (13.6) | p = 0.004a |
|                 |                                   |                         |               |                     |                     |                             | Gene amplification: n (%) |         |              |
|                 |                                   |                         |               |                     |                     |                             | CCND1 amplification | 13/22 (59.1%) | –            |
Table 5 (continued)

| Author          | Patients and samples (recurrence) | Mean age, range (years) | Sex (F/M) (%) | Sporadic status (%) | Tumour location (%) | Mean tumour size, range (cm) | Molecular target | Results | Significance |
|-----------------|-----------------------------------|------------------------|---------------|---------------------|---------------------|-----------------------------|------------------|---------|--------------|
| An et al. [28]  | 70 samples                        | 36.01, 0.17–84         | 59/41         | NS                  | E-AD: 74            | 6.7, 0.9–17                 | IHC: n (%)       | β-catenin (n) > 1% |             |
|                 |                                   |                        |               |                     | AD: 13              |                            |                  | 56/70 (80) |             |
|                 |                                   |                        |               |                     | I-AD: 13            |                            |                  | MT and β-catenin (n) | \( p = 0.012^a \) |
|                 |                                   |                        |               |                     |                     |                            |                  | WT and β-catenin (n) | \( p = 0.020^b \) |
|                 |                                   |                        |               |                     |                     |                            |                  | MT and β-catenin (n) |             |
|                 |                                   |                        |               |                     |                     |                            |                  | WT and size (cm; mean ± SD) | 4.973 ± 0.952, \( n = 22 \) |
|                 |                                   |                        |               |                     |                     |                            |                  | MT and size (cm; mean ± SD) | 7.655 ± 0.642, \( n = 42 \) |
| Author                  | Patients and samples (recurrence) | Mean age, range (years) | Sex (F/M) (%) | Sporadic status (%) | Tumour location (%) | Mean tumour size, range (cm) | Molecular target | Results | Significance |
|-------------------------|-----------------------------------|-------------------------|---------------|---------------------|---------------------|-------------------------------|------------------|---------|--------------|
| Matono et al. [29]      | 63 patients 74 samples (9)        | 34.2, NS                | 65/35         | 100                 | E-AD: 72 AD: 16 I-AD: 12 | NS                           | IHC: n (%)       |         |              |
|                         |                                   |                         |               |                     |                     |                               | β-catenin (n) > 50% | 35/63 (56) | –            |
|                         |                                   |                         |               |                     |                     |                               | MMP7 > 50%       | 39/63 (62) | –            |
|                         |                                   |                         |               |                     |                     |                               | Cyclin D1 > 5%    | 40/63 (63) | –            |
|                         |                                   |                         |               |                     |                     |                               | β-catenin (n) and MMP7 | 32/63 (51) | \( p < 0.1 \) |
|                         |                                   |                         |               |                     |                     |                               | β-catenin (−) and MMP7 | 7/63 (11)   | \( p = 0.034 \) |
|                         |                                   |                         |               |                     |                     |                               | β-catenin (n) and cyclin D1 | 27/63 (43) | \( p = 0.034 \) |
|                         |                                   |                         |               |                     |                     |                               | β-catenin (−) and cyclin D1 | 13/63 (21) | \( p = 0.034 \) |

**mRNA expression:** mean ± SD

|                          |                      |                      |                             |                         |                       | MT CTNNB1 and MMP7 RNA     | 129.1 ± 111.8 | \( p = 0.0018 \) |
|-------------------------|----------------------|----------------------|-----------------------------|-------------------------|-------------------------|-----------------------------|----------------|----------|--------------|
|                          |                      |                      |                             |                         |                       | WT CTNNB1 and MMP7 RNA     | 33.9 ± 23.6    | \( p = 0.0019 \) |
|                          |                      |                      |                             |                         |                       | MT CTNNB1 and CCND1 RNA     | 29.7 ± 8.86    | \( p = 0.019 \) |
|                          |                      |                      |                             |                         |                       | WT CTNNB1 and CCND1 RNA     | 6.8 ± 8.01     | \( p = 0.019 \) |
| Author         | Patients and samples (recurrence) | Mean age, range (years) | Sex (F/M) (%) | Sporadic status (%) | Tumour location (%) | Mean tumour size, range (cm) | Molecular target | Results | Significance |
|----------------|----------------------------------|-------------------------|---------------|---------------------|---------------------|--------------------------|-----------------|---------|--------------|
| Signoroni et al. [39] | 8 patients                      | 43, 25–70                | 37/63         | 100                 | E-AD: 50            | AD: 50                   | IHC: n (%)     |         |              |
|                |                                  |                         |               |                     |                     |                          | COX-2 (c)       | 8/8 (100) | –            |
|                |                                  |                         |               |                     |                     |                          | PDGFRA (c)      | 8/8 (100) | –            |
|                |                                  |                         |               |                     |                     |                          | PDGFRB (c)      | 8/8 (100) | –            |
| mRNA expression: n (%) |                                  |                         |               |                     |                     |                          |                 |         |              |
| PTGS2 (COX-2)  |                                  |                         |               |                     |                     |                          | 8/8 (100)       |         | –            |
| Gene expression: real-time PCR (mean $2^{-ΔΔC}_T$) |                                  |                         |               |                     |                     |                          |                 |         |              |
| PDGFRA         |                                  |                         |               |                     |                     |                          | 3.4             |         |              |
| PDGFRB         |                                  |                         |               |                     |                     |                          | 31.8            |         |              |
| Immunoprecipitation and phosphorylation: n (%) |                                  |                         |               |                     |                     |                          |                 |         |              |
| PDGFRA expression |                                  |                         |               |                     |                     |                          | 8/8 (100)       |         | –            |
| PDGFRA high expression |                                  |                         |               |                     |                     |                          | 0/8 (100)       |         | –            |
| PDGFRB expression |                                  |                         |               |                     |                     |                          | 8/8 (62.5)      |         | –            |
| PDGFRB high expression |                                  |                         |               |                     |                     |                          | 3/8 (37.5)      |         | –            |
| Author                  | Patients and samples (recurrence) | Mean age, range (years) | Sex (F/M) (%) | Sporadic status (%) | Tumour location (%) | Mean tumour size, range (cm) | Molecular target | Results | Significance |
|-------------------------|----------------------------------|------------------------|---------------|---------------------|---------------------|-----------------------------|----------------|---------|--------------|
| Santti et al. [36]      | ERβ                              |                        |               |                     |                     |                             | IHC: n (%)      |         |              |
|                         | 83 patients < 35: 43             | 71/29                  | 87            | E-AD and AD: 88     | < 6: 26             |                             | ERβ expression (median, IQR) | 10.8, 31.1 | –           |
|                         | 83 samples > 35: 40              |                        |               | I-AD: 11            | > 6: 43             |                             | ERβ > 1%        | 68/83 (82) | –           |
|                         |                                  |                        |               | Multifocal: 1       | 14 missing          |                             | Cyclin D1 expression (median, IQR) | 15.6, 21.0 | –           |
|                         | Cyclin D1                        |                        |               |                     |                     |                             | Correlation: r  |         |              |
|                         | 77 patients < 35: 38             | 69/31                  | 87            | E-AD and AD: 88     | < 6: 23             |                             | ERβ and cyclin D1 | 0.34     | p = 0.004⁴ |
|                         | 77 samples > 35: 39              |                        |               | I-AD: 10            | > 6: 42             |                             | ERβ and Ki67   | 0.35     | p = 0.003⁵ |
|                         |                                  |                        |               | Multifocal: 2       | 12 missing          |                             | ERβ and cyclin A | 0.40     | p < 0.001⁴ |
|                         | Santos et al. [42]               |                        |               |                     |                     |                             | Cyclin D1 and Ki67 | 0.40     | p = 0.001⁴ |
|                         |                                  |                        |               |                     |                     |                             | Cyclin D1 and cyclin A | 0.34     | p = 0.004⁴ |
|                         | Deyrup et al. [45]               |                        |               |                     |                     |                             | IHC: n (%)       |         |              |
|                         | 40 patients 33.4, 5–74           | 73/27                  | 100           | E-AD: 100           | NS                  |                             | ERβ > 50%       | 33/40 (83) | –           |
|                         | 40 samples                       |                        |               |                     |                     |                             | ERβ 11–50%      | 5/40 (12) | –           |
|                         |                                  |                        |               |                     |                     |                             | ERβ < 10%       | 2/40 (5)  | –           |
|                         |                                  |                        |               |                     |                     |                             | ERα             | 0/40 (0)  | –           |
|                         | Santos et al. [42]               |                        |               |                     |                     |                             | IHC: n (%)       |         |              |
|                         | 59 patients < 50: 30             | 61/39                  | 100           | E-AD: 61 AD: 39     | NS                  |                             | ERα ≥ 1%        | 0/59 (0)   | –           |
|                         | 59 samples > 50: 29              |                        |               |                     |                     |                             | ERβ ≥ 1%        | 53/59 (90) | –           |
|                         |                                  |                        |               |                     |                     |                             | PR ≥ 1%         | 0/59 (0)   | –           |
|                         |                                  |                        |               |                     |                     |                             | c-KIT ≥ 1%      | 0/59 (0)   | –           |
| Author                  | Patients and samples (recurrence) | Mean age, range (years) | Sex (F/M) (%) | Sporadic status (%) | Tumour location (%) | Mean tumour size, range (cm) | Molecular target | Results | Significance |
|------------------------|-----------------------------------|------------------------|---------------|---------------------|---------------------|---------------------------|-----------------|---------|--------------|
| Gebert et al. [30]     | 37 patients 37 samples            | 32.7, 0.9–64.7         | 74/26         | 100                 | E-AD and AD: 100    | < 5: 10                   | β-catenin (n) > 20% | 8/37 (22) | –            |
|                        |                                   |                        |               |                     |                     | > 5: 8                    | β-catenin (n) 1–19% | 17/37 (46) | –            |
|                        |                                   |                        |               |                     |                     | 19 missing               | p53 ≥ 2%         | 12/37 (32) | –            |
|                        |                                   |                        |               |                     |                     |                          | β-catenin (n) and p53 | –         | \( p < 0.05^d \) |
|                        |                                   |                        |               |                     |                     |                          | MIB1 ≥ 2%        | 1/37 (3)  | –            |
|                        |                                   |                        |               |                     |                     |                          | EGFR ≥ 5%         | 0/37 (0)   | –            |
|                        |                                   |                        |               |                     |                     |                          | HER2 ≥ 5%         | 0/37 (0)   | –            |
|                        |                                   |                        |               |                     |                     |                          | c-Kit ≥ 5%        | 0/37 (0)   | –            |
| Misemer et al. [51]    | 29 patients 29 samples            | 32, 10–80              | 48/52         | 93                  | E-AD: 79 AD: 14 I-AD: 7 | NS                        | ADAM12 and log[CDR] | 0.30 (0.25, 0.39) | \( p < 0.001^c \) |
|                        |                                   |                        |               |                     |                     |                          | FAP-alpha and log[CDR] | 0.44 (0.27, 0.60) | \( p < 0.001^f \) |
|                        |                                   |                        |               |                     |                     |                          | WISP1 and log[CDR]   | 0.27 (0.10, 0.42) | \( p < 0.001^f \) |
|                        |                                   |                        |               |                     |                     |                          | SOX11 and log[CDR]   | 0.14 (−0.09, 0.30) | \( p = 0.24^c \) |
| Ishizuka et al. [46]   | 27 patients 27 samples            | 37, 13–72              | 70/30         | 100                 | E-AD: 78 AD: 22      | NS                        | ERα > 10%         | 2/27 (7.4) | –            |
|                        |                                   |                        |               |                     |                     |                          | ERβ > 10%         | 2/27 (7.4) | –            |
|                        |                                   |                        |               |                     |                     |                          | PR-A > 10%         | 7/27 (25.9) | –            |
|                        |                                   |                        |               |                     |                     |                          | PR-B > 10%         | 9/27 (33.3) | –            |
|                        |                                   |                        |               |                     |                     |                          | AR > 10%           | 14/27 (52.9) | –            |
| Leithner et al. [43]   | 80 patients 116 samples (26)      | 34, 0–83               | 61/39         | NS                  | E-AD: 58 AD: 26 I-AD: 13 | NS                        | ERα ≥ 10%         | 0/46 (0)    | –            |
|                        |                                   |                        |               |                     |                     |                          | ERβ ≥ 10%         | 4/46 (8.7)   | –            |
|                        |                                   |                        |               |                     |                     |                          | PR ≥ 10%           | 0/46 (0)     | –            |
|                        |                                   |                        |               |                     |                     |                          | AR ≥ 5%            | 6/46 (13.0)  | –            |
|                        |                                   |                        |               |                     |                     |                          | Cathepsin D ≥ 10%   | 46/46 (100)  | –            |
|                        |                                   |                        |               |                     |                     |                          | c-Kit ≥ 10%        | 0/46 (0)     | –            |
|                        |                                   |                        |               |                     |                     |                          | Ki-67 > 5%         | 14/46 (30.4) | –            |
|                        |                                   |                        |               |                     |                     |                          | HER2 > 1%          | 0/46 (0)     | –            |
| Author             | Patients and samples (recurrence) | Mean age, range (years) | Sex (F/M) (%) | Sporadic status (%) | Tumour location (%) | Mean tumour size, range (cm) | Molecular target | Results | Significance |
|--------------------|----------------------------------|-------------------------|----------------|---------------------|---------------------|--------------------------|------------------|---------|--------------|
| Colombo et al.     | 152 patients 195 samples (54)     | NS                      | NS             | 100                 | E-AD: 87            | I-AD: 13                 | ADAM12           | 195/195 (100) | –            |
|                    |                                  |                         |                |                     |                     |                          | Midkine           | 90/195 (46) | –            |
|                    |                                  |                         |                |                     |                     |                          | MMP2             | 189/195 (97) | –            |
| Ahlen et al.       | DTF                              | 40.1, 26–52             | 71/29          | NS                  | E-AD: 100           | NS                      | DTF              | –       | \( p = 0.0438 \) |
|                    | BFT                              | 34, 27–65               | 50/50          | NA                  | E-AD: 100           | NS                      | EMMPRIN          | 2/7 (28.6) | –            |
|                    |                                  |                         |                |                     |                     |                          | MMP14 <10%       | 1/7 (14.2) | –            |
|                    |                                  |                         |                |                     |                     |                          | MMP2             | 3/7 (42.9) | –            |
|                    |                                  |                         |                |                     |                     |                          | <10%             | 2/7 (28.6) | –            |
|                    |                                  |                         |                |                     |                     |                          | 10–70%            | 1/7 (14.2) | –            |
|                    |                                  |                         |                |                     |                     |                          | > 70%             | 3/7 (42.9) | –            |
|                    |                                  |                         |                |                     |                      |                          | MMP14 >70%       | 4/7 (57.1) | –            |
|                    |                                  |                         |                |                     |                      |                          | EMMPRIN >70%     | 1/6 (17)   | –            |
|                    |                                  |                         |                |                     |                      |                          | MMP2 >70%        | 0/6 (0)    | –            |
|                    |                                  |                         |                |                     |                      |                          | MMP14 >70%       | 0/6 (0)    | –            |
|                    | DTF and BFT                      |                         |                |                     |                      |                          | \( p > 0.05 \)    | –        | \( p > 0.05 \) |
|                    | EMMPRIN                          |                         |                |                     |                      |                          | \( p > 0.05 \)    | –        | \( p > 0.05 \) |
|                    | MMP2                             |                         |                |                     |                      |                          | \( p > 0.05 \)    | –        | \( p > 0.05 \) |
|                    | MMP14                            |                         |                |                     |                      |                          | \( p > 0.05 \)    | –        | \( p > 0.05 \) |

**MCP1**

**EMMPRIN**

**MMP2**

**MMP14**

**CTNNB1**

**MT**

**Intensity score** (%): 0 = none, 1 = low, 2 = moderate/strong

**Molecular target**

**Significance**

\( \text{NS} \) = Not significant; \( \text{NA} \) = Not applicable

\( \text{EMMPRIN} \) = Expression matrix protein 1

\( \text{MMP2} \) = Matrix metalloproteinase 2

\( \text{MMP14} \) = Matrix metalloproteinase 14

\( \text{CTNNB1} \) = Cadherin 11

\( \text{MT} \) = Microtubule
| Author            | Patients and samples (recurrence) | Mean age, range (years) | Sex (F/M) (%) | Sporadic status (%) | Tumour location (%) | Mean tumour size, range (cm) | Molecular target | Results | Significance |
|-------------------|----------------------------------|-------------------------|---------------|---------------------|---------------------|-----------------------------|-----------------|---------|--------------|
| Brautigam et al. [47] | 69 patients, 69 samples (19) | 40, 0–73                | 39/61         | 90                  | E-AD and AD: 67      | 5.5, 0.7–30                | IHC (IRS > 0): n (%) |         |              |
|                   |                                  |                         |               |                     | I-AD: 13             |                            | ERα (n)          | 0/42 (0) | –            |
|                   |                                  |                         |               |                     | Unknown: 20          |                            | ERβ (n)          | 1/37 (2.7) | –            |
|                   |                                  |                         |               |                     |                     |                            | ERβ (c)          | 18/33 (54.5) | –            |
|                   |                                  |                         |               |                     |                     |                            | PR (n)           | 0/41 (0)  | –            |
|                   |                                  |                         |               |                     |                     |                            | AR (n)           | 1/33 (3.0) | –            |
|                   |                                  |                         |               |                     |                     |                            | PARP1 (n)        | 57/58 (98.3) | –            |
|                   |                                  |                         |               |                     |                     |                            | PARP1 (c)        | 0/58 (0)   | –            |
|                   |                                  |                         |               |                     |                     |                            | PARP1 (n) IRS 2-3 | 47/58 (81) | –            |
|                   |                                  |                         |               |                     |                     |                            | Correlation: r   |         |              |
|                   |                                  |                         |               |                     |                     |                            | Ki-67 positivity and PARP-1 IRS | −0.375 | p = 0.041f |
|                   |                                  |                         |               |                     |                     |                            | Gene sequencing: n (%) |         |               |
|                   |                                  |                         |               |                     |                     |                            | CTNNB1            | S45F     | 5/17         |              |
|                   |                                  |                         |               |                     |                     |                            | T42R              | 1/17     | –            |              |
|                   |                                  |                         |               |                     |                     |                            | mRNA expression: V |         |              |
|                   |                                  |                         |               |                     |                     |                            | CTNNB1 and CCND1 | 4259.60  | p = 0.0120b |              |
|                   |                                  |                         |               |                     |                     |                            | CTNNB1 and β-catenin | 141.02   | p = 0.0036c |              |
|                   |                                  |                         |               |                     |                     |                            | IHC: n (%)        | β-catenin (n) ≥ 80% | 12/17 (70.6) | – |
|                   |                                  |                         |               |                     |                     |                            | β-catenin (n) 50–70% | 5/17 (29.4) | – |
| Author          | Patients and samples (recurrence) | Mean age, range (years) | Sex (F/M) (%) | Sporadic status (%) | Tumour location (%) | Mean tumour size, range (cm) | Molecular target | Results | Significance |
|-----------------|----------------------------------|-------------------------|---------------|---------------------|---------------------|-----------------------------|-----------------|---------|--------------|
| Mignemi et al.  | DTF                               | 27 patients 27 samples  | 26.6, 1–73    | 52/48               | 100                 | E-AD: 78, AD: 11, Unknown: 11 | β-catenin (n) > 5% | DTF 19/27 (70 *) | \(p = 0.0003^{\alpha}\) |
|                 |                                  |                         |               |                     |                     |                             |                  | HS 2/14 (14 *) | \(*p < 0.01^{\alpha}\) |
|                 |                                  |                         |               |                     |                     |                             |                  | FT 0/6 (0) |               |
|                 | HS                               | 14 samples 17–58        | 43.3, 71/29   | NA                  | E-AD: 71            | NS                          | p-SMAD2/3 > 5%   | DTF 26/27 (96 *) | \(p < 0.0001^{\alpha}\) |
|                 |                                  |                         |               |                     |                     |                             |                  | HS 4/14 (29 *) | \(*p < 0.001^{\alpha}\) |
|                 |                                  |                         |               |                     |                     |                             |                  | FT 0/6 (0) |               |
|                 | FT                               | 6 samples 34–57         | 48.3, 50/50   | NA                  | E-AD: 33, AD: 67    | NS                          | p-SMAD1/5/8 > 5% | DTF 5/27 (17) | \(p > 0.005^{\alpha}\) |
|                 |                                  |                         |               |                     |                     |                             |                  | HS 2/14 (14) |               |
|                 |                                  |                         |               |                     |                     |                             |                  | FT 0/6 (0) |               |
|                 |                                  |                         |               |                     |                     |                             |                  | COX2     |               |
|                 |                                  |                         |               |                     |                     |                             |                  | DTF 22/27 (83 *) | \(p < 0.0001^{\alpha}\) |
|                 |                                  |                         |               |                     |                     |                             |                  | HS 3/14 (21 *) | \(*p < 0.01^{\alpha}\) |
|                 |                                  |                         |               |                     |                     |                             |                  | FT 0/6 (0) |               |
|                 |                                  |                         |               |                     |                     |                             |                  | Correlation: | β-catenin and COX2: 0.034 | \(p = 0.873^{\alpha}\) |
|                 |                                  |                         |               |                     |                     |                             |                  | TGFR1 and p-SMAD2/3: 0.651 | \(p = 0.0006^{\alpha}\) |
|                 |                                  |                         |               |                     |                     |                             |                  | COX2 and p-SMAD2/3: 0.760 | \(p < 0.0001^{\alpha}\) |
|                 |                                  |                         |               |                     |                     |                             |                  | COX2 and TGFR1: 0.714 | \(p = 0.0001^{\alpha}\) |
### Table 5 (continued)

| Author          | Patients and samples (recurrence) | Mean age, range (years) | Sex (F/M) (%) | Sporadic status (%) | Tumour location (%) | Mean tumour size, range (cm) | Molecular target | Results | Significance |
|-----------------|-----------------------------------|-------------------------|---------------|---------------------|---------------------|-----------------------------|------------------|---------|--------------|
| Cates et al. [40] | **DTF**                           |                         |               |                     |                     |                             |                  |         |              |
|                 | 27 patients 27 samples            | 26.6, 1–73             | 52/48         | 100                 | E-AD: 78 AD: 11     | 5.5‡, 1–15                 | PDGFRβ expression | DTF 27/27 (100), 3 +* | \( p < 0.001 \) § |
|                 |                                   |                         |               |                     | Unknown: 11         |                             |                  | HS 14/14 (100), 2 + | \( p < 0.01 \) § |
|                 |                                   |                         |               |                     | FT 5/6 (80)         |                             |                  | FT 5/6 (80) 2 +* |              |
| Varghese et al. [33] | **HS**                           |                         |               |                     |                     |                             |                  |                     |              |
|                 | 14 samples                           | NS NS NA NS NS NS      |               |                     |                     |                             |                  |                     |              |
|                 |                                   |                         |               |                     |                     |                             |                  |                     |              |
|                 | **FT**                             |                         |               |                     |                     |                             |                  |                     |              |
|                 | 6 samples                            | NS NS NA NS NS NS      |               |                     |                     |                             |                  |                     |              |
|                 |                                   |                         |               |                     |                     |                             |                  |                     |              |
|                 | **STDC**                           |                         |               |                     |                     |                             |                  |                     |              |
|                 | 10 samples                          | NS NS NA NS NS NS      |               |                     |                     |                             |                  |                     |              |

**HIC**: \( n \) (%), median intensity score (0, 1 +, 2 +, 3 +)

**β-catenin (n)**

**DTF**: 15/15 (100), 2 + to 3 +

**STDC**: 0/10 (0)

**TGFβ (c)**

**DTF**: 15/15 (100), 2 + to 3 +

**STDC**: 8/10 (80), 2 + to 3 + 2/10 (20), 1 +

**CTGF (c)**

**DTF**: 10/15 (66.7), 2 + to 3 + 5/15 (33), 1 +

**STDC**: 4/10 (40), 2 + to 3 + 6/10 (60), 1 +
Table 5 (continued)

AD abdominal, AI apoptotic index, AR androgen receptor, BFT benign fibrous tumour, CDR chromosome density ratio, CI confidence interval, COX2 cyclooxygenase-2, CTGF connective tissue growth factor, DTF desmoid-type fibromatosis, E-AD extra-abdominal, EGFR epidermal growth factor receptor, EMMPRIN extracellular matrix metalloproteinase inducer, ERα oestrogen receptor-α, ERβ oestrogen receptor-β, FAP-alpha fibroblast activation protein-alpha, FT fibrous tissue, HER2 human epidermal growth factor receptor 2, HS hypertrophic scar, I-AD intra-abdominal, IHC immunohistochemistry, IRS immunoreactive score (staining intensity multiplied by percentage of positive tumour cells), LI labelling index (percent of positive immunostaining tumour cells), MCM5 minichromosome maintenance complex component 5, MMP matrix metalloproteinase, MT mutated, MVD microvessel density (mm²), n number of cases, NA not applicable, NS not specified, p Spearman’s correlation coefficient, PARP1 poly(ADP-ribose) polymerase 1, PCNA proliferating cell nuclear antigen, PDGFRα platelet-derived growth factor receptor-α, PDGFRβ platelet-derived growth factor receptor-β, PR-A progesterone receptor-A, PR-B progesterone receptor-B, r Pearson’s correlation coefficient, SD standard deviation, SOX11 SRY-box transcription factor 11, STDC scar tissue and normal dermal collagen, S45F serine to phenylalanine substitution in codon 45, S45P serine to proline substitution in codon 45, T41A threonine to alanine substitution in codon 41, T41I threonine to isoleucine substitution in codon 41, T42R threonine to arginine substitution in codon 42, TGFβ transforming growth factor-β, VEGF vascular endothelial growth factor, WISP1 Wnt inducible signalling pathway protein 1, WT wild-type, (c) cytoplasmic staining, (c + n) cytoplasmic and nuclear staining, (n) nuclear staining, (+) positive, (−) negative

† Indicates median age (years)
‡ Indicates median tumour size (cm).
1Fisher’s exact test
2Mann-Whitney U test
3Student’s t test
4χ² test
5Pearson’s correlation
6Spearman’s correlation
7Kruskal-Wallis test
8Dunn’s multiple comparison test

Significant p values indicated in bold
benign fibrous tumours (Fisher’s exact test, \( p > 0.05 \)) [50]. Two studies evaluated the expression of ADAM12 [49, 51]. ADAM12 expression was observed in 195 DTF cases, and its expression positively correlated with chromosome density (\( r = 0.30, p < 0.001 \)) [49, 51]. Misemer et al. also demonstrated a significant correlation between chromosome density and Wnt inducible signalling pathway protein 1 (WISP1) (\( r = 0.27, p < 0.001 \)) as well as fibroblast activation protein alpha (FAP-alpha) expression (\( r = 0.44, p < 0.001 \)) [51]. MMPs and related proteases were found to be

Fig. 5  Key molecular drivers associated with desmoid tumour pathophysiology. a \( \beta \)-Catenin primarily coordinates cell proliferation, differentiation and fate, with its deregulated signalling being intrinsically linked to the development of several human cancers, such as skin, colon and breast cancer [13, 14]. Cyclin D1 and c-Myc signalling is commonly deregulated in tumourigenesis due to their promotional effects on cell proliferation by enhancing the G1 to S-phase transition of the cell cycle [34, 35]. b Cyclooxygenase-2 (COX2) is an inducible member of the cyclooxygenase family involved in multiple physiological purposes. In colorectal cancer, COX2 has been extensively implicated in promoting angiogenesis, invasion and proliferation through the upregulation of growth factors such as platelet-derived growth factor [37, 38]. The multi-functional transforming growth factor-beta (TGF\( \beta \)) superfamily and related growth factors play complex and often opposing roles in cell proliferation, differentiation, regeneration and morphogenesis [41]. c Oestrogens are steroid hormones that promote growth, differentiation and reproduction throughout a range of human tissues. Their role in tumourigenesis has been extensively studied in breast cancer, where aberrant signalling drives proliferation, invasion and metastasis [44]. d Matrix metalloproteinases (MMPs) and related proteases play a pivotal role in cancer pathogenesis through their modulation of extracellular matrix, angiogenesis, cell migration and growth [48]. Vascular endothelial growth factor (VEGF) is a prominent angiogenic mediator whose expression is commonly upregulated in cancer tissue by various onco-genes, growth factors and hypoxia to sustain growth and invasion [52]. e The tumour suppressor genes \( RB1 \), \( CDKN2A \) and \( TP53 \) inhibit cell proliferation by arresting cells in the G1 phase of the cell cycle, with the latter protein being upregulated in response to DNA damage [53, 55]. f In its cell membrane function, \( \beta \)-catenin complexes with other proteins, such as \( \alpha \)-catenin and N-cadherin, to mediate epithelial cell-cell adhesion and stability [57]. Created with BioRender.com. PDGFR platelet-derived growth factor receptor.
over-expressed in DTF samples, with their expression further enhanced by the presence of aberrant β-catenin signalling.

3.3.4.2 Angiogenesis Vascular endothelial growth factor (VEGF) is a prominent angiogenic mediator whose expression is commonly upregulated in cancer tissue by various oncogenes, growth factors and hypoxia to sustain growth and invasion [52]. Matono et al. demonstrated a significant correlation between β-catenin nuclear immunoreactivity and VEGF overexpression (Fisher’s exact test, \( p = 0.04 \)). Mean microvessel density was also significantly higher in recurrent (13.97 mm\(^2\)) compared with primary tumours (9.56 mm\(^2\), Fisher’s exact test, \( p = 0.02 \)). VEGF-positive samples showed a trend towards a higher microvessel density, but this did not reach statistical significance (VEGF-positive, 10.62 mm\(^2\); VEGF-negative, 9.55 mm\(^2\); Fisher’s exact test, \( p = 0.84 \)) [24]. Furthermore, Colombo et al. confirmed the overexpression of midkine seen on gene expression profiling with 46% of DTF samples illustrating immunoreactivity [49]. These results highlight VEGF as a key angiogenic mediator in DTF pathogenesis with its expression appearing to occur in a β-catenin-dependent manner.

3.3.5 Cell-Cycle Regulatory Proteins

The tumour suppressor genes RB1, CDKN2A and TP53 inhibit cell proliferation by arresting cells in the G1 phase of the cell cycle, with the latter protein being upregulated in response to DNA damage [53, 55]. Stalinska et al. showed normal pRb and p16 expression in 94.4% and 50% of E-AD cases, respectively. Heterogeneous or low expression of pRb and p16 was seen in 5.66% and 50% of E-AD cases, respectively [56]. Gebert et al. found p53 expression in 32% of cases, which significantly correlated with β-catenin expression (\( \chi^2 \) test, \( p < 0.05 \)) [30]. The normal expression profiles of both pRb and p16 suggest an intact G1 cell-cycle regulatory function, whilst the increased p53 expression suggests a degree of aberrant cell-cycle progression in the context of β-catenin expression.

3.3.6 Cell–Cell Adhesion

In its cell membrane function, β-catenin complexes with other proteins, such as α-catenin and N-cadherin, to mediate epithelial cell–cell adhesion and stability [57]. Ferenc et al. reported a lack of α-catenin expression in 34% of their sporadic DTF cases. E-AD cases demonstrated a significantly higher mean cellular α-catenin immunoreactivity at 61.5% compared with 42.3% in AD cases (Student’s \( t \) test, \( p = 0.0165 \)). N-cadherin expression was positive in 23% of all DTF cases. Nuclear β-catenin expression did not significantly correlate with α-catenin or N-cadherin expression (Pearson’s correlation, \( p > 0.05 \)) [25]. This study indicates a possible progressive tumour phenotype characterised by the loss of cell-cell adhesion markers, although the findings did not reach statistical significance.

4 Discussion

This review critically examined the current literature regarding the molecular pathogenesis of sporadic DTF in human tumour samples and utilised its findings to explore current and emerging novel therapies. Twenty-two articles exploring the molecular pathogenesis were included. Within these, Wnt/β-catenin pathway aberrations were extensively studied. Oestrogen, growth factor regulatory signalling and tumourigenic microenvironment changes were also implicated.

The role of aberrant Wnt/β-catenin signalling in desmoid pathogenesis is well established [15–18]. Accordingly, this review found aberrant β-catenin expression in almost half of DTF cases within each study [24–33]. Mutated β-catenin also enhanced its pathologic role compared with its wild-type counterpart, producing greater overexpression of downstream target genes such as cyclin D1 [26, 27, 29, 31]. DTF commonly harbors CTNNB1 mutations in position T41 and S45, which enhance β-catenin’s stability by decreasing phosphorylation-guided degradation (Fig. 6) [15, 58]. Additionally, Crago et al.’s next-generation sequencing study suggests a more pervasive role for mutated β-catenin with Wnt/β-catenin-activating mutations found in 95% of samples compared with 86% with conventional Sanger sequencing (\( n = 117 \)) [15]. Although Wnt blockade presents a desirable therapeutic target, adverse effects on immune function and gastrointestinal homeostasis have precluded the development of prospective sporadic DTF trials [14, 59]. In solid tumours, however, the decoy Wnt ligand receptor ipafricept (OMP-54F28) was evaluated in a phase I clinical trial, with two patients with DTF experiencing stable disease beyond 6 months [60]. In light of the undesirable effects of Wnt blockade, perhaps targeting more distal branches of the pathway may be of greater utility. In colorectal cancer, the demonstration of Wnt/β-catenin signalling crosstalk with the Notch pathway has prompted the use of targeted therapies against this interaction [61–63]. Most notably, the γ-secretase inhibitor nirogacestat (PF-03084014), a small-molecule drug that prevents activation of the Notch intracellular domain, was evaluated in a phase II clinical trial comprising 17 patients with actively progressive DTF disease. Here, 29% experienced a partial response after a median of 32 cycles with a further 65% achieving stable disease [64]. Following its success, the phase III DeFi trial is currently in progress evaluating nirogacestat in a similar cohort of adult patients with DTF, with the primary completion date reached in December 2021 [65]. Additionally, as a cell-cycle promoter, cyclin D1

△ Adis
blockade may also negatively augment desmoid growth by inhibiting the G1 to S phase transition of the cell cycle [34]. Palbociclib, an inhibitor of the cyclin D1 activating protein Cdk4/6, demonstrates an overall survival benefit in a randomised trial involving patients with advanced breast cancer [66]. With cyclin D1 emerging as an overactive protein, its inhibition may present an attractive therapeutic target.

Targeted growth factor inhibitory therapy is a promising treatment modality in DTF management. Historically, the benefits of TKIs on small DTF cohorts were rationalised by the potential expression of c-Kit and PDGFR [67]. Since then, the absence of c-Kit staining has negated this view [43, 68]. Accordingly, this review reported no c-Kit expression [30, 42, 43]. Consequently, the use of TKIs is now rationalised by the demonstration of PDGFR expression. In this review, only one study observed the expression and phosphorylation of PDGFRβ in a small DTF cohort with COX2 overexpression (n = 8 sporadic), with a larger cohort comprising 27 sporadic DTF samples demonstrating a significantly higher PDGFRβ expression compared with normal fibrous tissue [39, 40]. Evidently, because of the limited focus on human DTF samples, our findings offer an incomplete understanding on the role of growth factors in desmoid pathogenesis with a much greater appreciation...
coming from the expanding evaluation of TKI therapy. The first TKI trialled in DTF, imatinib, is a multi-targeted TKI that primarily inhibits c-Kit and PDGFRβ [69]. In a phase II trial comprising 40 patients with unresectable and progressive DTF, the primary endpoint of non-progressive disease at 3 months is 91%, with a 2-year progression-free survival rate of 55% [70]. In a similar DTF cohort, the phase III double-blind trial testing the multi-targeted TKI sorafenib produces a 2-year progression-free survival rate of 81% compared with 36% in the placebo group [71]. Furthermore, in the phase II DESMOPAZ trial, the antiangiogenic TKI pazopanib prevents disease progression over 6 months in 84% compared with 45% in patients receiving methotrexate-vinblastine combination chemotherapy [72]. In addition to the mechanism of imatinib, both sorafenib and pazopanib also inhibit VEGFR2/3 [69], suggesting the angiogenic component of DTF pathogenesis may prove a more attractive therapeutic target than PDGFR alone.

A growing body of retrospective evidence implicates oestrogen in desmoid pathogenesis. Clinically, DTF arises more commonly in female individuals of reproductive age, with accelerated tumour growth observed during pregnancy and with oral contraceptive use [5–9]. Supporting these observations at the molecular level, this review identified ERβ expression in all respective studies, albeit within a broad range of expression values and a low proportion of positively stained cells [36, 42, 43, 45–47]. Furthermore, a positive correlation was also demonstrated between ERβ expression, cyclin D1 and proliferation markers [36]. This finding further supports the emerging anabolic role of ERβ signalling that has previously been described in promoting the regeneration of injured skeletal muscle tissue [73, 74]. This, in conjunction with its opposing tumour-suppressor effects in breast cancer [75], suggests a tissue-specific proliferative role in mesenchymal tissues. Although these histological data provide a potential rationale for oestrogen blockade in DTF treatment, studies evaluating its effect have produced conflicting results. Supporting its use, a systematic review of anti-oestrogen therapy found tamoxifen to produce an overall response rate of 58% (n = 22/38) from a cohort comprising 47.7% sporadic DTF [76]. In the only prospective evaluation of anti-hormonal therapy, however, the combination of tamoxifen and sulindac in a phase II trial produces an overall response rate and 2-year progression-free survival rate of 8% and 36%, respectively, in a paediatric cohort of 59 patients with DTF [77]. In light of such results, the use of anti-hormonal therapy and non-steroidal anti-inflammatory drugs is not endorsed by The Desmoid Tumour Working Group’s latest consensus-based treatment guidelines [21].

4.1 Limitations

The inclusion of retrospective case series limited this review because of their high level of bias [22]. Eight studies also potentially utilised overlapping patient cohorts as suggested by shared authorship, inclusion periods and specimen archives [24, 25, 27, 29, 31, 32, 40, 56]. Furthermore, key clinical information such as age, sex, tumour size and sporadic status was omitted throughout included papers. Consequently, patients with FAP were inadvertently included in this review. Included studies also utilised varied cut-offs and staining patterns to define protein overexpression, leading to marked result heterogeneity. There were also a number
of limitations to this review’s methodology. Only articles written in the English language and published after 1999 were included. The elucidation of DTF pathogenesis was also restricted by a number of factors, such as the exclusion of animal and cell culture studies, patient follow-up and treatment effects on molecular markers.

5 Conclusions

The presence of aberrant Wnt/β-catenin signalling in sporadic DTF pathogenesis is well established and may be effectively targeted via downstream augmentation. This review also elucidated the tumour microenvironment’s emerging role in desmoid development with preliminary evidence favouring angiogenic antagonism. This study is the first of its type to systematically review the molecular pathogenesis of human sporadic DTF in the era of targeted therapies. Future work may wish to further evaluate the additional signalling pathways implicated in DTF pathogenesis and the mechanisms of its associated novel therapies.

Declarations

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