

Molecular Pathogenesis and Histological Variability of Dermatofibrosarcoma Protuberans

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Abstract. Dermatofibrosarcoma protuberans (DFSP) is a kind of infrequent tumor of the soft tissues distinguished by its gradual proliferation and a preference for regional reoccurrence, despite its limited capacity for metastasis. At the molecular level, a significant majority of DFSP cases manifest the t (17;22) (q22; q13) chromosomal translocation, resulting in the fusion of the collagen type I alpha chain (COL1A1) gene and platelet-derived growth factor B chain (PDGFB) gene. This fusion results in PDGFB overexpression, consequently activating the PDGF Receptor-beta (PDGFR-β). The activated PDGFR-β serves as a central nexus for numerous intracellular signaling pathways, initiating cascades including Phosphatidylinositol 3-kinase (PI3K)/Akt, Mitogen-Activated Protein Kinase (MAPK)/extracellular signal-regulated kinase (ERK), and STATs pathways. These cascades collectively enhance DFSP cell growth, proliferation, and invasiveness. Histologically, DFSP tumors are predominantly fibroblastic and display distinct immune cell infiltration patterns in their microenvironment. Elevated expression of CD4+ naïve cells, CD4+ Th2 cells, CD8+ central memory T cells, B cells, and macrophages is evident, while levels of CD4+ central memory T cells and eosinophils are diminished. Immunohistochemical analyses further highlight that most DFSP cells exhibit positive cytoplasmic CD34 expression, whereas factor XIIIa and α-smooth muscle actin are notably absent. Clinically, DFSP presents in diverse subtypes, each characterized by its unique histological profile. Prominent subtypes encompass classic DFSP, fibrosarcomatous DFSP (FS-DFSP), pigmented DFSP, giant cell fibroblastoma, myxoid DFSP, atrophic DFSP, and the granular cell variant. This review aspires to deliver an exhaustive insight into DFSP, accentuating its molecular underpinnings and clinical presentation, with the ultimate goal of advancing our understanding and management of this distinct dermatological entity.

Keywords: DFSP; t (17; 22) (q22; q13) translocation; PDGFR-β; Subtypes.

1. Introduction

Dermatofibrosarcoma Protuberans (DFSP) is one of infrequent tumors of soft tissues, with approximately 1% proportion among all soft-tissue sarcomas. However, DFSP holds the distinction of being the prevailing sarcoma affecting the integumentary system. As the depth of understanding of DFSP has grown in recent decades, its characteristic t (17; 22) (q22; q13) chromosome translocation has been implicated as the molecular mechanism underpinning the pathogenesis of this tumor, with the fusion of the collagen type I alpha chain (COL1A1) gene and the platelet-derived growth factor B chain (PDGFB) gene triggering a series of signaling pathways that drive tumor growth [1]. From a clinical standpoint, it is typically observed that DFSP commonly manifests as a firm nodular lesion without any noticeable symptoms. Additionally, it is often reported by patients that this lesion gradually increases in size in several months or even years, highlighting the relatively inactive nature of the initial phases of DFSP. Cases of DFSP have been documented in a wide range of age groups, but predominantly affect adults in their twenties to fifties. One of the clinical hallmarks of DFSP is the tenacious tendency to recur after surgery, which is attributed to its clinically extensive spread and tentacle-like projections extending into the surrounding tissues. Although the clinical presentation of DFSP may appear simple in the early stages, the propensity for local invasion of the tumor, combined with the multiple histologic subtypes and the unique clinical and histopathologic features of each, make clinical vigilance essential.

2. Molecular Pathogenesis of DFSP

2.1. Chromosomal Translocation of COL1A1 and PDGFB

The primary characteristic of DFSP is the presence of a distinct t(17;22)(q22;q13) chromosomal translocation. This translocation occurs on chromosome 17, which encodes COL1A1, and chromosome 22, which encodes PDGFB [2]. COL1A1 is used to express the instructions to produce the components of type I collagen, the most abundant collagen in the body and the main component of the extracellular matrix. PDGFB is critical in encoding the B-chain subunit of platelet-derived growth factor (PDGF-B protein), which serves as a mitogen for mesenchymal stromal cells and is essential for generating new blood vessels (also called angiogenesis). Additionally, PDGFB is intricately involved in initiating vital signaling pathways that regulate cell growth, differentiation, and migration.

2.2. Fusion Gene

After chromosome displacement, COL1A1 and PDGFB fuse. This process initiates with a chromosome break between chromosome 17 and chromosome 22. After the break, the distal end of chromosome 17 joins the distal end of chromosome 22, and in most DFSPs this fusion site is located between COL1A1 and PDGFB. The breakpoint of PDGFB is usually located in intron 1, whereas the location of the breakpoint of COL1A1 ranges from exon 6 to exon 49 with a high degree of variability [2]. The PDGFB fragment will be regulated by the COL1A1 fragment after gene fusion, and the COL1A1 is actively transcribed in DFSP cells, which in turn induces the fusion gene's dysregulated over-expression of the PDGFB fragment and production of excess PDGF-B protein. DFSP cells under conditions of PDGF-B overproduction generate an autocrine stimulatory loop, i.e., the cells produce a factor that is used as a self-receptor, which in the case of DFSP is the mitogen PDGF-B. Essentially, DFSP cells will be able to self-supply on growth-stimulating signals to promote their own growth and proliferation.

2.3. Activation of PDGF Receptor (PDGFR)

2.3.1. PDGF-B overexpression and PDGFR Activation

Increased levels of PDGF-B lead to activation of PDGF receptors, particularly activation of PDGF receptor-beta (PDGFR- β). PDGFR- β serves as the principal receptor for PDGF-B. The overproduction of PDGF-B by DFSP cells results in its binding with PDGFR- β present on the surface of both DFSP cells and neighboring cells within the tumor microenvironment (TME), this binding event induces the dimerization of the receptor and subsequently initiates its activation. This dimerization then stimulates the inherent kinase activity of PDGFR- β , resulting in the phosphorylation of the receptor and amplifying its activity.

2.3.2. Intracellular Signaling Pathways

Activation of PDGFR- β triggers a series of signaling cascades, and its phosphorylation creates docking sites for downstream signaling molecules. That is, upon activation, PDGFR- β becomes a hub for various intracellular signaling pathways. Activation of these downstream pathways, including phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT), mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) and janus kinase (sJAK)/signal transducers and activators of transcription (STATs), promotes DFSP cell proliferation, cell motility and morphology changes, angiogenesis, and inhibits apoptosis [3].

2.3.3. PI3K/ Akt pathway

The activation of PI3K is facilitated through its interaction with phosphorylated tyrosine residues located on PDGFR- β . The activation of PI3K triggers the enzymatic reaction that catalyzes the transformation of phosphatidylinositol 4, 5-bisphosphate (PIP2) into phosphatidylinositol 3,4,5-trisphosphate (PIP3) specifically at the cellular membrane. PIP3 binds to AKT as well as

phosphatidylinositol-dependent kinase-1 (PDK1) (an upstream activator of AKT) on the plasma membrane partially activating AKT, which is then activated in the complete form in a secondary activation via a downstream signaling pathway.

Upon complete activation, AKT undergoes intracellular translocation, engaging in interactions with diverse substrates, thereby facilitating their phosphorylation. The AKT protein kinase have a crucial function in the regulation of numerous substrates and cellular processes. In the context of DFSP cells, the activation of AKT typically facilitates cell survival, growth, proliferation, and metabolism. The AKT pathway contributes an essential part in promoting cell survival by exerting inhibitory effects on those pro-apoptotic molecules. The BCL2 associated agonist of cell death (BAD) is a protein that promotes apoptosis. When phosphorylated by AKT, BAD becomes inactivated and separates from the Bcl-2/Bcl-xL complex. Previous study shows that BAD-mediated apoptosis is higher in normal tissue samples than in cancer cell samples [4]. It can be inferred that the inactivation of the BAD inhibits apoptosis in DFSP cells via the PI3K/Akt pathway activation.

Furthermore, AKT boosts the growth as well as the proliferation of DFSP cells by enhancing cell cycle progression via regulating cell cycle proteins D1, p27, and p21, and activating mTOR complex 1 (mTORC1) to promote protein synthesis and growth.

In addition, AKT supports the energetic demands of DFSP cells' rapid growth and proliferation by enhancing the glucose transport proteins to translocate to cell plasma membrane and amplifying glycolytic activity. AKT augments the motility of these cells, contributing to the invasive and metastatic potential of DFSP. AKT is significant in the hypoxia-inducible factor 1- α (HIF-1 α) activation. According to the results of a previous study conducted on mouse endothelial cells, it was observed that the absence of HIF-1 α in these cells brought in approximately 50% decrease during the process of angiogenesis within the murine Matrigel model [5]. Angiogenesis is an important process for tumor maintenance and growth, and activation of HIF-1 α promotes angiogenesis in DFSP.

2.3.4. MAPK/ ERK pathway

The phosphorylated tyrosines on PDGFR- β serve as critical signaling protein pair nodes that are able to bind to the Grb2-SOS complex. This binding event facilitates the conversion of Ras-GDP from its inactive form to an active form Ras-GTP. The Ras-GTP acts as the initiator for the cascade activation of the MAPK/ERK pathway, leading to the recruitment and activity of the kinase Raf at the plasma membrane [6]. Once Raf is activated, it phosphorylates and activates MEK downstream of the cascade, which in turn phosphorylates and active ERK. Based on the research on DFSP cells, it has been observed that DFSP cells exhibit an enormous spike in mitotic activity, specifically when compared to normal fibroblasts, a 200% to 300% rise in DNA synthesis was observed. This increased mitotic activity appears to be directly associated with the activation of ERK signaling pathway [7]. In addition to this ERK targeting molecules including Elk-1, c-Fos and c-Myc have shown potential promotion of cell proliferation and mitosis [7].

2.3.5. JAK/ STATs pathway

The activation of PDGFR- β triggers the recruitment and activation of JAK, which is phosphorylated at different sites depending on the specific STAT subtypes, leading to dimerization and subsequent activation of the STATs. STAT3 plays a crucial role of angiogenesis in DFSP TME. STAT3 and HIF- α co-regulate vascular endothelial growth factor (VEGF); activated STAT3 and up-regulated HIF- α in the hypoxic environment of tumor growth up-regulate VEGF levels. Previous studies on human microvascular dermal endothelial cells (HMVEC) demonstrated that cell proliferation of HMVEC under high levels of VEGF was up to 60% higher than untreated HMVEC [8]. Increased HMVEC proliferation enhances DFSP angiogenesis and tumor metastasis.

3. DFSP Tumor Microenvironment

3.1. Fibroblasts

One of the features that distinguishes DFSP from other skin tumors is that it consists of elongated spindle-shaped fibroblasts arranged in a cartwheel pattern. These fibroblasts that make up the tumor are thought to originate from the dermis and are essentially produced as components of the extracellular matrix that provides support structures for the skin. The fibroblasts in DFSP have a high capacity for infiltrative growth, which makes excision a challenging procedure because these cells send out tentacle-like projections that extend into the subcutaneous fat, muscle layers, and surrounding skin [9]. The inability to effectively remove these cells through standard wide local excision surgery may account for the elevated incidence of local recurrence in cases of dermatofibrosarcoma protuberans DFSP.

3.2. Immune Cells

According to the comparison between DFSP samples and normal tissue of carcinoma sides, the expression of immune cells in DFSP TME compared to normal tissue consists of a significant difference. The analysis of immune cell abundance revealed an apparent rise in the expression of CD4+ naïve cells, CD4+ Th2 cells, CD8+ central memory T cells, B cells, and macrophages within the samples of DFSP [10]. Conversely, the expression of CD4+ central memory T cells and eosinophils was significantly decreased in DFSP samples [10]. The immune microenvironment of DFSP shares many features with other immune-cold tumors, but due to its unique genetic alteration (COL1A1-PDGFB fusion) and predominantly fibroblastic composition, which may lead to unique immune interactions, the understanding of the immune microenvironment of DFSP is incomplete at present and requires further exploration.

Based on the immunohistochemical analysis, it was observed that DFSP cells exhibited robust cytoplasmic expression of CD34, while displaying absence of expression for other immunohistochemical markers (e.g. factor XIIIa and alpha-smooth muscle actin). However, CD34 does not directly serve as a unique immunological marker for DFSP, as other immunological markers such as fibromas or Kaposi sarcomas also show positive CD34 expression [3].

4. Histological Variability of DFSP

4.1. Classic DFSP

The most prevalent subtype of DFSP is the classic form, which exhibits a wide distribution throughout the body. However, it is frequently observed on the trunk and proximal extremities, while it is less frequently observed on the head and neck region. The early appearance of DFSP is a small, firm and asymptomatic plaque or nodule on the skin, as the DFSP cells proliferate, the tumor increases in size and protrudes from the skin, and its color varies individually, ranging from pink to brown.

The cellular composition of classical DFSP is distinguished by the heightened proliferation of spindle-shaped cells, which exhibit potential to infiltrate the dermis and subcutaneous fat layer. Spindle-shaped cells typically exhibit a disposition in either a matted pattern or a cartwheel pattern, with individual neoplastic cells characterized by elongated nuclei and scant cytoplasm. The occurrence of mitosis is infrequent.

4.2. Fibrosarcomatous DFSP (FS-DFSP)

Fibrosarcomatous DFSP (FS-DFSP) is clinically similar to classic DFSP but usually has a faster growth and metastasis rate. The nuclei of FS-DFSP cells exhibit a heightened elongation, while the cellular composition within the tumor manifests in the "herringbone" pattern. FS-DFSP has a higher mitotic rate than classic DFSP and is more infiltrative, with tumor cells extending into subcutaneous tissue and muscle. In comparison to classic DFSP, FS-DFSP exhibits a heightened propensity for

local recurrence, often attributed to suboptimal resection of tumor margins during surgical intervention. Additionally, FS-DFSP demonstrates an increased likelihood of metastasis, frequently involving the lungs and lymph nodes. Mohs micrographic surgery has been widely recognized as a highly effective surgical technique for achieving complete resection of fibrosarcoma-derived dermatofibrosarcoma protuberans (FS-DFSP) and certain other subtypes.

4.3. Pigmented DFSP (Bednar Tumor)

Pigmented DFSP (PDFSP or Bednar Tumor) subtype is relatively rarely seen, and the most important histologic feature that distinguishes it from classical DFSP is a population of dendritic cells containing melanin. The clinical manifestation of PDFSP typically involves the development of a gradually progressing elevated cutaneous lesion. The pigmentation of the lesion varies from brown to black, influenced by the melanin content within the lesion. These melanin-containing dendrites are scattered in spindle-shaped cells similar to those of classical DFSP and are arranged in an overall cartwheel pattern. PDFSP has a lower growth and metastasis rate similar to classic DFSP, but PDFSP is more infiltrative reaching subcutaneous tissue.

4.4. Giant Cell Fibroblastoma

Giant cell fibroblastoma (GCF) is thought to be another subtype that appears primarily in children and adolescents. It manifests clinically as a gradual-expanding nodule or plaque. Histologically, the GCF exhibits a myxoid stromal composition characterized by collagen fibers. The tumor is primarily comprised of spindle-shaped fibroblasts, which are distributed in a distinctive cartwheel pattern. Notably, the GCF exhibits large multinucleated giant cells that are dispersed throughout the tumor. Although there is some controversies as to whether GCF is a subtype of DFSP, it is well established that GCF has the same t(17;22)(q22;q13) chromosome translocation found in DFSP [11].

In contrast to other subtypes of DFSP that have some metastasis, GCF hardly metastasizes, but GCF has been reported to transform into the more aggressive FS-DFSP in isolated cases.

4.5. Myxoid DFSP

Myxoid DFSP is a rarer subtype of DFSP that has a similar clinical presentation to classic DFSP, growing slowly as a cutaneous nodule or raised mass, but with a softer texture than classic DFSP due to the mucinous changes in the tumor. The most distinctive feature of this subtype is the myxoid stroma, the main component of these stroma is hyaluronic acid, so that myxoid DFSP will be observed with a more gelatinous appearance on the tissue features. Tumor cells of myxoid DFSP resembling the spindle cells observed in classic DFSP will be distributed within the myxoid stroma and display a distinctive cartwheel pattern [12]. However, while the cartwheel pattern is also observed in myxoid DFSP cells, the presence of extensive myxoid changes may obscure this characteristic structure. Myxoid DFSP also exhibits slow-growing, less metastatic, but locally infiltrative growth. The myxoid matrix's dispersing nature presents a challenge in achieving clear tumor margin resection during surgical procedures. It is due to the matrix's tendency to extensively penetrate into the surrounding tissues. The current understanding of myxoid transformation in DFSP remains insufficient, particularly regarding the intricate mechanism underlying the presence and accumulation of mucopolysaccharides.

4.6. Atrophic DFSP

Atrophic DFSP is a relatively uncommon subtype within the spectrum of DFSP. Unlike other DFSPs that appear clinically as raised lesions, Atrophic DFSP usually demonstrates slightly hyperpigmented, flat, depressed, or atrophic plaques, the features that has led to its misdiagnosis [13]. The spindle cells in Atrophic DFSP are similar to those of classical DFSP and are arranged in a cartwheel pattern [13]. The reason for the atrophic appearance of the tumor area has been considered to be the collagen surrounding the tumor cells.

4.7. Granular Cell Variant

The granular cell variant of DFSP is a histologic subtype that is considered rare in occurrence. The existing literature has only documented a limited number of cases pertaining to this variant. This variant shares the clinical presentation of DFSP, but has some hallmark differences in histology. The feature of granular cell variant is that the tumor cells exhibit abundance of eosinophilic, granular cytoplasm, the cytoplasmic appearance arises from the accumulation of secondary lysosomes [14]. These granular cells have small nuclei and are often pushed to the periphery by granules in the cytoplasm. The tumor exhibits spindle-shaped granular cells that are organized in cartwheel pattern, and the tumor cells display positive expression of the biomarker CD68, indicating lysosomal activity [14]. This characteristic distinguishes it from Classic DFSP and the majority of other subtypes.

4.8. Myoid DFSP

Myoid DFSP was first described in 1996. It differs physiologically from Classic DFSP in that myoid DFSP is associated with spindle-shaped myoid nodules caused by stromal intravascular myointimal hyperplasia and is more mitotically active. The immunohistochemical analysis of the myoid portion of the tumor reveals a presence of alpha-smooth muscle actin with positive, while exhibiting weak or negative expression of CD34, in contrast to Classic DFSP and other subtypes [15]. This situation would likely confuse the diagnosis of myoid DFSP, but the characteristic chromosomal translocations of DFSP would still be present. Lesions of myoid dermatofibrosarcoma protuberans (DFSP) manifest as elevated, solid plaques or nodules on the skin, resembling the presentation of classic DFSP. However, due to myoid differentiation, these lesions may display diverse morphological characteristics. Considering the infiltrative characteristics of the tumor, it is imperative to prioritize wide local excision as the primary approach for treatment. The utilization of Mohs Micrographic Surgery is advantageous in ensuring precise excision with adequate tumor margins while safeguarding the integrity of the surrounding healthy tissue. Furthermore, the presence of myoid differentiation in Myoid DFSP can complicate its diagnosis, as it shares similarities with other tumors exhibiting myofibroblast or smooth muscle characteristics. Therefore, it is crucial to research the diagnostic modalities in order to identify more distinct biomarkers for accurate identification.

5. Conclusion

Dermatofibrosarcoma protuberans (DFSP) is a unique type of soft tissue tumor with a prominent genetic abnormality known as the t (17; 22) (q22; q13) chromosomal translocation. DFSP Not only shows variety of different rare histological subtypes, but its growth and progression involve a variety of cellular signaling pathways, manifestations that underscore its diagnostic and therapeutic complexity. However, the current understanding of DFSP remains incomplete, with fewer clinical case reports (especially for rare subtypes such as Granular Cell Variant) leading to overlapping immunohistochemical markers and major gaps in the understanding of the tumor microenvironment for different histological subtypes, and the lack of clarity of these features confounds accurate diagnosis in the clinic, and thus confounds the best therapeutic choices. Therefore, it is a pressing need for a comprehensive investigation into the TME of DFSP, with particular emphasis on elucidating the interactions between fibroblasts and immune cells. In addition, the molecular significance of the unique t (17; 22) (q22; q13) chromosome translocation in DFSP deserves to be thoroughly investigated, and understanding this complex mechanism may lead to innovations for potential targeted therapies. Furthermore, expanding epidemiological and clinical studies are needed to be emphasized, and the different subtypes, geographic and racial distributions as well as incidence rates can provide deeper insights into the underlying environmental or genetic causes of DFSP tumors. These factors provide avenues for prevention strategies and potential biomarkers for recognizing differences between subtypes.

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