

## Immunological Research Progress of Dermatofibrosarcoma Protuberans

Zhong A and Chen J\*

Department of Burn and Plastic Surgery, West China Hospital, Sichuan University, China

### \*Corresponding author:

Junjie Chen,  
Department of Burn and Plastic Surgery, West  
China Hospital, Sichuan University, No. 37  
Guoxue Alley, Wuhou District, Chengdu City  
61000, Sichuan Province, China

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### 1. Abstract

Dermatofibrosarcoma protuberans is a rare, low-grade malignant soft tissue sarcoma. Although its overall incidence rate is low and its survival rate is high, the incidence of this disease has increased gradually in recent years. The high recurrence rate of this disease can be attributed to the limited understanding of its pathogenesis and the restricted treatment options available. In recent years, as research on cancer pathogenesis has become more extensive, there has been a growing emphasis on immune-related issues that are closely associated with the occurrence and progression of cancer. This article provides an overview of current research on the immune response to dermatofibrosarcoma protuberans, including studies on tumour-related antigen expression, antigen-presenting cell expression, immune cell infiltration, and radiotherapy. By summarizing and analyzing the research findings, we aim to provide a valuable reference for understanding the pathogenesis of this disease from an immunological perspective and proposing novel treatment strategies.

### 2. Introduction

Dermatofibrosarcoma Protuberans (DFSP) is a rare, low-grade malignant soft tissue sarcoma [1], with an average incidence of 0.8 to 4.1 cases per million people. However, in recent years, the disease's incidence has been increasing annually [2]. The prognosis is generally favorable, with a 5% metastasis rate [3] and a 10-year survival rate of 99.1% (95% CI: 97.6-99.7) [4]. However, the recurrence rate is as high as 30%-70% [5]. Current treatment options mainly include surgical resection, radiation therapy, and targeted therapy. However, they all face the challenge of high recurrence rates after treatment. Identifying factors that influence tumor re-

currence is an important approach to address this issue.

Over the past years, research on tumour pathogenesis has primarily focused on tumour cells. However, with the introduction of the "seed and soil" theory [6], there has been growing recognition of the crucial role that tumour microenvironment, such as immune-related factors, play in tumour occurrence and progression [7,8]. As a result, there has been a shift towards investigating the immune response to tumours in recent years.

Not only can the immune environment of normal tissues effectively inhibit tumour growth, serving as an important barrier for the body to defend against tumours, but also can tumour cells manipulate this environment to their advantage. By influencing and regulating the anti-tumour effect of immune cells, tumour cells can make the immune environment suitable for tumour growth. Consequently, normal differentiated cells in this environment can co-evolve with tumour cells and ultimately promote the formation and growth of tumours [9]. Thus, the question arises: is the occurrence and development of dermatofibrosarcoma protuberans also related to immunity? Particularly in cases of dermatofibrosarcoma protuberans with such a high recurrence rate, in what ways do immune changes impact its prognosis?

It has been found that the pathogenesis of DFSP is associated with immune deficiency in the body. Studies conducted by Huynh et al., Cohen et al., Hirano et al., and De Antoni et al. have revealed that dermatofibrosarcoma protuberans frequently develops at tattoo or vaccination sites. The possible mechanism for this phenomenon is that vaccination and tattoos hinder the local immune response of the body, leading to local immune disorder [10-13]. Kesserwan et al. conducted a study on 12 patients with adenosine deaminase-de-

found severe combined immunodeficiency (ADA-SCID), and discovered that 8 of them suffered from DFSP. ADA-SCID patients have severe immunodeficiency, affecting both humoral and cellular immunity. DNA repair defects may lead to t(17;22)(q22;q13) translocation, resulting in the overexpression of platelet-derived growth factor subunit B (PDGFB) in the skin, which is conducive to the occurrence and development of DFSP [14]. According to Jerry et al., chronic lymphocytic leukemia, small lymphocytic lymphoma, or non-Hodgkin's lymphoma with immune deficiency greatly increased the incidence of rare soft tissue sarcomas, such as DFSP. The study also suggested a correlation between immune deficiency and the incidence of DFSP [15]. We proceed from the following aspects to understanding the pathogenesis of DFSP from an immunological perspective

### 3. Tumor Immunogenicity

Tumors are often accompanied by the expression of mutant antigens, and it is believed that tumors with a high mutation burden exhibit strong immunogenicity. Such tumors can induce T cell recognition, stimulate T cell migration and aggregation, and initiate tumor-specific T cell immunity, enabling the immune system to play a surveillance role [16]. Melanoma, renal cell carcinoma, and hepatocellular carcinoma are known to possess strong immunogenicity, making them highly responsive to immunotherapy [17]. Tazzari et al. conducted a study on coding mutations in fibrosarcomatous carcinoma-fibrosarcoma (FS-DFSP) samples and found that the immunogenic mutation load in FS-DFSP was lower compared to highly mutated tumors like melanoma or lung cancer. In fact, the extent of mutation was more similar to colorectal and breast cancer [18]. M Meissner et al. reported a significant down-regulation of human HLA-I and HLA-II antigen expression in DFSP, with 80-88% of cases showing negative HLA-I expression in their study [19]. Defects in HLA expression may be associated with increased tumor aggressiveness, reduced T cell infiltration, and poor prognosis [20]. These studies suggest that the low immune response, resulting from the low immunogenic mutational burden and decreased HLA expression, may be associated with local tumor recurrence.

### 4. Antigen-Presenting Cell Expression

Dermal dendritic cells are involved in immune phagocytosis, particularly while XIIIa<sup>+</sup> dendritic cells play a role in antigen presentation. Pascale et al. reported that XIIIa<sup>+</sup> dendritic cells were significantly reduced or absent in DFSP, suggesting that the progression of DFSP might have been related to the decline of immune phagocytosis and antigen presentation function [21]. FS-DFSP specimens after imatinib treatment and observed changes in tumor-infiltrating lymphocytes, immunohistochemistry, and gene expression profile were investigated. Following imatinib treatment, it was found that there was a significant anti-tumor immune response, in which the antigen presentation pathway was significantly

up-regulated. For instance, there was observed a significant increase in the infiltration of tumor-associated macrophages as antigen-presenting cells after treatment, thus promoting active anti-tumor response. Not observed was this phenomenon in the specimens before treatment.

### 5. PD-L1

The combination of programmed cell death ligand 1 (PD-L1) and programmed cell death receptor 1 (PD-1) can transmit inhibitory signals and reduce the proliferation of CD8<sup>+</sup> T cells in lymph nodes, which is related to the inhibition of the immune system under pathological conditions. Park S. et al. detected PD-L1 expression through immunohistochemistry in 35 non-recurrent DFSP and 9 recurrent DFSP resected specimens and found that PD-L1 expression was low or absent in non-recurrent cases and high in recurrent or metastatic cases, suggesting that PD-L1 was related to the occurrence and progression of DFSP [22]. Similarly, Tsuchihashi et al. found that PD-L1 expression was related to the fibrosarcoma-like transformation of dermatofibrosarcoma protuberans. Their research also discovered that PD-L1 was expressed in DFSP metastatic tumors but not in non-recurrent cases. Suggested by their analysis was that a fibrosarcoma transforming component in metastatic tumors could induce PD-L1 expression and promote metastasis by escaping immune surveillance [23]. Tumor PD-L1 expression was found to be high after imatinib treatment in FS-DFSP. However, PD-L1 expression was not detected in the tumor before imatinib treatment. Nonetheless, PD-1 expression was found on the surface of activated CD8<sup>+</sup> T cells. Thus, the inability of imatinib to eradicate transferrable FS-DFSP may have been related to interference with the PD-1/PD-L1 T cell inhibition axis.

### 6. Immune Cell Infiltration

#### 6.1. T Cells

T cells underwent development in the thymus and could differentiate into mature CD4<sup>+</sup> T cells and CD8<sup>+</sup> T cells, which were then exported to peripheral lymphoid organs [24]. CD4<sup>+</sup> T cells, also referred to as inducible T cells or helper T cells, played a crucial role in regulating the immune response and were considered as important hub cells [25]. CD8<sup>+</sup> T cells, also known as cytotoxic T lymphocytes, could kill pathogen-infected cells and cancer cells. After activating and differentiating into effector CD8<sup>+</sup> T cells, they secreted perforin and granzyme to kill tumor target cells and secreted other cytokines such as IFN  $\gamma$ , TNF  $\alpha$ . They played an important role in anti-tumor immune function. Tazzari et al. observed that untreated FS-DFSP specimens lacked T cell expression, whereas FS-DFSP tumor specimens after imatinib treatment showed high T cell expression, mainly comprising CD4<sup>+</sup> and CD8<sup>+</sup> T cells [18]. Additionally, Dancsok et al. discovered that non-translocation-related sarcomas were more likely to exhibit T-cell immune infiltration compared to translocation-related sarcomas [27]. In the subtype analysis of tumor-infiltrating lympho-

cytes, a higher number of CD8+ T cells was observed. This suggests that the immune system was aware of the tumor and primed to activate anti-tumor immunity, but became inert due to one or more immune regulatory mechanisms.

## 6.2. B Cells

B cells regulated cytokine-mediated signal transduction processes, promoted the release of tumor-specific antibodies, and collaborated with CD8+ T cells in the anti-tumor response, thereby affecting antigen presentation [28-29]. Tumor-related B cells were predominantly present in the tertiary lymphoid structures and tumor microenvironment. T cells and B cells could cooperate, promote each other, clone and expand, and provide T cells with homologous tumor-derived antigens, thereby jointly promoting the immune response's progress [30-31]. Stacchiotti et al. reported a significant upregulation of the gene encoding immunoglobulin and the antigen processing and presentation pathway in metastatic FS-DFSP tumor samples after imatinib treatment. Immunohistochemical staining with CD20 antibody revealed an increased immune infiltration of B cells in the tumor microenvironment, which was not observed in tumor samples prior to treatment [32]. However, there are various B cell phenotypes, and the research on the role of B cells in tumor development and anti-tumor immune response is still in the preliminary stage. As research in this area continues to evolve, there is great potential for immunotherapy with B cells as the entry point.

## 6.3. NK Cells

NK cells are innate cells that can directly kill tumors, particularly in the removal of metastatic and small tumors. Traditionally, CD56+CD3 lymphoid cells are widely defined as human NK cells. Stacchiotti et al. used a CD57-specific antibody to test for the expression of NK cell immune infiltration and found that NK-mediated cleavage component genes NKG7 and GZMB were present in metastatic FS-DFSP samples treated with imatinib [32]. The subset of CD56+CD3 cells (8.86%) in tumor-infiltrating lymphocyte (TIL) samples following imatinib treatment of FS-DFSP, was not present in untreated original samples. Similarly, Sayitoglu et al. analyzed the NK cell-activated receptors DNAM-1 and NKG2D and their respective ligands as potential therapeutic targets for various sarcoma subtypes. They found that genetically modified (GM) NK cells could enhance DNAM-1 and NKG2D's anti-sarcoma response, providing a new perspective for the development of effective sarcoma-specific immunotherapy [33]. It might be supposed that NK cell subpopulations with direct tumor-killing abilities were present in imatinib-treated DFSP tumor samples, and genetically modified NK cells could enhance anti-sarcoma responses, offering new therapeutic strategies for sarcoma immunotherapy.

## 6.4. Tumor Associated Macrophages

Tumor-associated macrophages (TAMs) are a crucial class of inflammatory and immune-regulating cells in tumor tissue. These

cells differentiated into different polarization types under the influence of tumor chemokines within the tumor microenvironment, with the two most classic types being the M1 macrophages involved in Th1 response and the M2 macrophages involved in the Th2 response through the classic activation and alternative activation pathways, respectively [34]. The phenotype and function of TAMs were similar to those of M2 macrophages, and they could promote tumor growth, invasion, and metastasis. TAMs secreted chemokines such as CCL5 and CCL20, which recruited naturally regulated T cells (nTreg) to promote the occurrence of a host immunosuppressive environment [35]. MMP1 promoted tumor invasion by degrading type I, type II, and type III collagen [36]. MMP12 was a protease secreted by macrophages, which could promote immune suppression and tumor progression [37]. These macrophages produced matrix metalloproteinases (MMPs), which played an essential role in tumorigenesis and angiogenesis. Taku et al. detected TAMs and MMPs in the DFSP tumor matrix and found that the increased expression of TAMs, MMP1, and MMP12 might have been one of the mechanisms leading to local invasion of DFSP [38].

## 7. Radiotherapy

For DFSP resistant to imatinib, Mervin et al. found that radiotherapy could achieve the unexpected effects of tumor regression [39]. Formenti et al. believed that the systemic anti-tumor effect induced by radiotherapy was mediated by the immune system [40]. Radiotherapy would spread epitopes; that is, the autoantigens released by tumor cells after damage could start tumor-specific T cells, thus leading to more autoantigens released and tumor-specific T cells starting up, leading to further damage to tumor cells [41]. Radiotherapy might have also helped to activate tumor-specific T cells, and radioimmunotherapy might have become an ideal treatment method for DFSP [42].

## 8. Summary

Through literature review, we find that the current research on dermatofibrosarcoma protuberans and immunity at home and abroad mainly included the following progress: DFSP samples had defective HLA expression, which was related to immune escape, which might have led to increased tumor invasion, poor prognosis, or local recurrence; XIIIa+dendritic cells were few in DFSP samples, which showed that antigen-presenting function was weakened and immune phagocytosis function was decreased; The change of tumor microenvironment of DFSP sample promoted local immunosuppressive microenvironment and invasion; It was also found that some patients could benefit from radiotherapy. The possible mechanism was that tumor cells release their antigens after damage and start tumor-specific T cells. Among all types, the worst prognosis of FS-DFSP might have been related to its higher PD-L1 expression, leading to escape from immune surveillance. Several articles reported the study on the treatment of DFSP with imatinib. It was

found that the antigen presentation function was up-regulated after treatment, thereby enhancing the active anti-tumor effect; High expression of T cells, thus improving tumor recognition ability; B cell immune infiltration increased, and immunoglobulin gene was significantly up-regulated, thus up-regulating antigen processing and presentation pathway; Suspiciously related NK cells were found, and their activated receptors and ligands could activate NK immunity if they were used as targets. However, after treatment with imatinib, it promoted the high expression of PD-L1 and the up-regulated expression of PD-1 in the sample, which was considered to be the possible reason why the treatment could not control the metastasis and recurrence of FS-DFSP. In conclusion, the occurrence, progression, and treatment efficacy of DFSP are all closely related to immunity. In the future, we can expect to conduct research on DFSP and explore treatment directions from an immunological perspective.

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