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Review

Genetics of rare mesenchymal tumors: Implications for targeted treatment in DFSP, ASPS, CCS, GCTB and PEComa☆

Piotr Rutkowski[a,*], Joanna Przybył[b], Tomasz Świtaj[a]

[a] Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, 5 Roentgen Street, Warsaw, Poland
[b] Department of Molecular and Translational Biology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, 5 Roentgen Street, Warsaw, Poland

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ABSTRACT

Soft tissue and bone sarcomas comprise a heterogeneous group of mesenchymal tumors that include roughly 130 distinct diagnostic entities. Many of them are exceptionally rare, with only few cases diagnosed worldwide each year. Development of novel targeted treatment in this group of tumors is of special importance since many sarcoma subtypes are resistant to conventional chemotherapy and the effective therapeutic options are limited. In this review we aim to discuss the molecular implications for targeted therapy in selected rare soft tissue and bone sarcoma subtypes, including dermatofibrosarcoma protuberans (DFSP), alveolar soft part sarcoma (ASPS), clear cell sarcoma (CCS), giant cell tumor of bone (GCTB) and perivascular epithelioid cell neoplasms (PEComas).

This article is part of a Directed Issue entitled: Rare cancers.

Contents

Abbreviations: DFSP, dermatofibrosarcoma protuberans; ASPS, alveolar soft part sarcoma; CCS, clear cell sarcoma; GCTB, giant cell tumor of bone; PEComas, perivascular epithelioid cell neoplasm; PDGFRB, platelet-derived growth factor receptor, beta; MET, met proto-oncogene; MITF, microphthalmia-associated transcription factor; mTOR, mechanistic target of rapamycin; RANKL, receptor activator of NF-kappa-B ligand; PR, partial response; SD, stable disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to progression; TSC, tuberous sclerosis complex; SAGE, subependymal giant cell astrocytomas; AML, angiomyolipoma; LAM, lymphangioleiomyomatosis; CCST, clear cell "sugar" tumor of the lung.

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* Corresponding author at: Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, 5 Roentgen Street, 02-781 Warsaw, Poland. Tel.: +48 22 6439375; fax: +48 22 6439791.
E-mail address: rutkowskip@coi.waw.pl (P. Rutkowski).

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1. Introduction

Soft tissue and bone sarcomas comprise a heterogeneous group of malignant tumors of mesenchymal origin. Better understanding of molecular events underlying sarcoma tumorigenesis is important to improve diagnosis and to propose new therapeutic targets. Development of novel agents for targeted treatment is of special importance since many sarcoma subtypes are resistant to conventional chemotherapy and the effective therapeutic options are limited. However, the sarcoma research is circumscribed by their low incidence and scarcity of samples available for analysis. In this review we aim to discuss the molecular implications for targeted therapy in selected rare soft tissue and bone neoplasms subtypes, including dermatofibrosarcoma protuberans (DFSP), alveolar soft part sarcoma (ASPS), clear cell sarcoma (CCS), giant cell tumor of bone (GCTB) and perivascular epithelioid cell neoplasms (PEComas).

1.1. Genetics of soft tissue and bone sarcomas

Genetically, the majority of soft tissue and bone sarcomas can be classified into two groups. Approximately 2/3 of sarcoma subtypes have highly rearranged karyotypes, usually with very complex genomic aberrations, including non-balanced translocations, genomic deletions and amplifications, and changes in the number of chromosomes. The remaining 1/3 of sarcomas often carry tumor specific chromosomal translocations or oncogenic point mutations, with relatively few other genomic abnormalities (Coindre, 2006; Chibon et al., 2010). Fusion genes expressed in sarcomas usually encode aberrant chimeric transcription factors, however the *COL1A1-PDGFB* fusion gene, characteristic for DFSP encodes a chimeric protein exhibiting growth factor activity (Osuna and de Alava, 2009). Molecular studies show that fusion genes are crucial, initiating factors in tumorigenesis of many translocation-related sarcoma subtypes (Osuna and de Alava, 2009). Chromosomal translocations are usually subtype-specific, therefore their detection using reverse transcription polymerase chain reaction (RT-PCR) or fluorescence *in situ* hybrydization (FISH), significantly aids differential diagnosis of soft tissue and bone sarcomas. Advances in the understanding of molecular events underlying sarcoma pathogenesis may also contribute to the development of promising targeted therapies. Genomic and genetic abnormalities frequently observed in DFSP, ASPS, CCS, GCTB and PEComas are summarized in Table 1.

1.2. Epidemiology of rare soft tissue and bone sarcomas

Sarcomas represent approximately 1% of all malignancies diagnosed in adults. Current World Health Organization (WHO) classification distinguishes approximately 130 histological subtypes of soft tissue and bone tumors (Fletcher et al., 2013), and many of these subtypes are diagnosed at rate lower than 1 case per million population per year, which poses a diagnostic and therapeutic challenge. Cancer registries often jointly classify the exceptionally rare sarcoma subtypes as “other sarcomas” or “rare variants” which causes a void in data describing the incidence and survival of sarcoma patients. Epidemiological data are also affected by the discrepancies in pathological reporting and coding of particular rare sarcoma subtypes (*e.g.* DFSP was not considered as sarcoma in selected epidemiological studies, but as a skin neoplasm) (Wibmer et al., 2010). These inconsistencies raise a concern that the uncommon sarcoma subtypes may be under-reported. Available epidemiological data regarding sarcoma subtypes described in this review are presented in Table 2.

2. Dermatofibrosarcoma protuberans

DFSP is a rare locally aggressive sarcoma of cutaneous origin, with low metastatic potential. Disease related deaths are very infrequent, unless the tumor undergoes fibrosarcomatous transformation, that is associated with worse prognosis (Sandberg and Bridge, 2003). DFSP is characterized by either reciprocal chromosomal translocation t(17;22)(q11;q13.1) or a supernumerary ring chromosome derived from t(17;22) which results in formation of *COL1A1-PDGFB* fusion gene in the vast majority of cases (Sandberg and Bridge, 2003). COL1A1-PDGFB chimeric protein is processed into functional platelet-derived growth factor beta (PDGFB) ligand that causes PDGFRB signaling activation *via* autocrine stimulation loop in tumor cells (Simon et al., 2001).

Advances in the understanding of molecular events underlying DFSP tumorigenesis made receptor tyrosine kinase PDGFRB the essential therapeutic target in this neoplasm (McArthur, 2004). Imatinib mesylate, a tyrosine kinase inhibitor acting selectively against KIT receptor tyrosine kinase, PDGFRA/B (platelet-derived growth factor receptors alpha/beta), ABL (c-abl oncogene 1, non-receptor tyrosine kinase), ARG (Abl-related gene (Arg) nonreceptor tyrosine kinase) and CSF1R (colony stimulating factor 1), was the first agent tested for systemic therapy of DFSP. The initial *in vitro* and *in vivo* studies demonstrated significant DFSP cell growth inhibition after exposure to imatinib (Greco et al., 2001; Sjöblom et al., 2001). Subsequently, its efficacy was evaluated in small series of patients with metastatic and locally advanced DFSP (Maki et al., 2002; Rubin et al., 2002; Pedeutour et al., 2003; Ruka et al., 2003; Labropoulos et al., 2005; Mizutani et al., 2004). In 2006, imatinib has been approved in the dose of 800 mg daily for therapy of unresectable, recurrent and/or metastatic DFSP.

The potential of imatinib in DFSP was further explored in three phase II clinical trials (Table 3). The first, Imatinib Target Exploration Consortium Study B2225, showed 100% response rate (50% of complete responses) in locally advanced cases, and one partial response lasting 7 months in metastatic setting (McArthur et al., 2005; Heinrich et al., 2008). Combined analysis of two clinical studies (European Organization for Research and Treatment of Cancer trial no. 62027 and the Southwest Oncology Group trial no. S0345) comprising 24 patients with advanced (inoperable and/or metastatic) DFSP demonstrated clinical benefit rate above 70% and median time to progression of 1.7 years (Rutkowski et al., 2010). The largest single center study enrolled 15 patients treated in routine clinical practice, and it confirmed the dramatic activity of imatinib in advanced DFSP, with clinical benefit rate of 80% (Rutkowski et al., 2011). The reported data indicate that toxicity of imatinib therapy in DFSP is minimal with the most common side effects including dyspepsia, nausea, vomiting and myelosupression (Rutkowski et al., 2010, 2011; Llombart et al., 2013). Moreover, it has been shown that DFSP with fibrosarcomatous transformation (DFSP-FS) is also sensitive to imatinib, although the responses seem to last shorter (Stacchiotti et al., 2011a). DFSP-FS tumors lacking t(17;22) do not respond to imatinib (McArthur et al., 2005).

Detection of oncogenic *COL1A1-PDGFB* fusion is obligatory to confirm diagnosis of DFSP in every case prior to the start of imatinib therapy, using RT-PCR or FISH (Patel et al., 2008; Kerob et al., 2008; Llombart et al., 2013). Several issues remain to be addressed, regarding the action mechanism of imatinib and possible resistance to this treatment in DFSP. It was assumed that imatinib inhibits phosphorylation of constitutively activated PDGFRB. Nevertheless, efficacy of imatinib is striking also in tumors expressing relatively low amounts of activated PDGFB receptor. Apparently, inhibition of even low-level receptor tyrosine kinase may be clinically beneficial if tumor cells rely predominantly on that signaling mechanism.

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