CDKs in Sarcoma

Subjects: Pathology

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Sarcomas represent one of the most challenging tumor types to treat due to their diverse nature and our incomplete understanding of their underlying biology. Recent work suggests cyclin-dependent kinase (CDK) pathway activation is a powerful driver of sarcomagenesis. CDK proteins participate in numerous cellular processes required for normal cell function, but their dysregulation is a hallmark of many pathologies including cancer. The contributions and significance of aberrant CDK activity to sarcoma development, however, is only partly understood. Here, we describe what is known about CDK-related alterations in the most common subtypes of sarcoma and highlight areas that warrant further investigation. As disruptions in CDK pathways appear in most, if not all, subtypes of sarcoma, we discuss the history and value of pharmacologically targeting CDKs to combat these tumors. The goals of this review are to (1) assess the prevalence and importance of CDK pathway alterations in sarcomas, (2) highlight the gap in knowledge for certain CDKs in these tumors, and (3) provide insight into studies focused on CDK inhibition for sarcoma treatment. Overall, growing evidence demonstrates a crucial role for activated CDKs in sarcoma development and as important targets for sarcoma therapy.

cyclin-dependent kinase | sarcoma | cell cycle | therapeutics | retinoblastoma | CDK inhibitors

1. Introduction

Sarcomas are rare, highly diverse malignancies. They account for just 1% of all adult human cancers, although their frequency is significantly greater (roughly 20%) among pediatric tumors. These lesions arise from mesenchymal tissue, where approximately 80% occur in soft tissue and 20% in bone [1]. Currently, there are over 70 subtypes that classify lesions based on tissue resemblance and molecular characteristics [2]. Two broad groups of sarcomas exist—those with simple karyotypes, often characterized by a specific, disease-driving alterations and those with complex karyotypes, where there are multiple genomic losses, gains, and amplifications [1]. Standard treatment for localized disease remains surgical resection with adjuvant radiation and/or chemotherapy used in certain types of sarcoma. Regrettably, many patients experience recurrence and metastasis, requiring systemic therapies that are unfortunately not very effective. Additionally, since these lesions are heterogeneous, responses to generalized treatments are variable and typically do not translate between different subtypes [3]. To combat sarcomas more effectively, the key pathways promoting their development and progression

need to be elucidated. Recent advances suggest that activating alterations in cyclin-dependent kinase (CDK) pathways are major drivers of sarcomagenesis.

CDKs are serine/threonine kinases involved in key cellular processes, primarily cell cycle progression and transcription. As monomeric proteins, CDKs lack enzymatic activity due to a structural conformation that buries the catalytic and substrate binding domains [4]. To become active, CDKs require association with a regulatory subunit known as a cyclin, hence their designation as cyclin-dependent kinases. Humans have 20 CDKs that are classically divided into two main groups — cell cycle (CDKs 1, 2, 3, 4, 6, and 7) and transcriptional (tCDKs 7, 8, 9, 12, 13, and 19), with CDK7 contributing to both processes. Many CDKs that control cell cycle progression can bind multiple cyclins, allowing for dynamic regulation throughout the cell cycle as well as increased substrate possibilities. CDKs associated with transcription bind a single, specific cyclin, whose expression is not regulated in a cell cycle-dependent manner [5]. “Other” CDKs (5, 10, 11, 14–18, and 20) do not fit into the two canonical roles and, instead, exhibit diverse functions that are often tissue specific. For example, CDK11 variants have multiple functions in mediating transcription, mitosis, hormone receptor signaling, autophagy, and apoptosis [5][6]. Likewise, in the nervous system CDK5 promotes neurite outgrowth and synaptogenesis while in pancreatic β cells it reduces insulin secretion [7][8][9]. As CDKs control crucial processes required for cell survival and propagation, their hyperactivation (typically through mutation, gene amplification, or altered expression of their regulators) is commonly observed in cancer.

The rarity and diversity of sarcomas has slowed efforts to identify key mutations driving these cancers. In addition, sarcomas are sometimes simplistically viewed as a single entity or described in broad, unspecified terms. As our knowledge of sarcoma biology has increased, there is a growing appreciation for CDK pathway dysregulation in promoting disease progression. This review discusses the current knowledge about CDK and CDK-related aberrations in the most common subtypes of sarcoma in both adult and pediatric patients. Additional consideration is given to CDK-targeted therapy in the pre-clinical setting as well as recent clinical trials.

Table 1 provides a consolidated listing of the genetic alterations in CDKs and CDK pathways within each human sarcoma, strongly predicting the hyperactivation of tumor promoting CDKs in these cancers. Notable overlap exists in the genetic alterations found within multiple sarcomas although there are unique genomic events that also distinguish each sarcoma type. A recent analysis of genomic profiles and clinical outcomes in two independent datasets of diverse soft tissue sarcomas identified the most frequently altered genes shared by most sarcomas, namely *TP53*, *CDKN2A*, *RB1*, *NF1,* and *ATRX* [10]. Strikingly, *CDKN2A* was the only gene whose inactivation was associated with worse overall survival across all types of localized soft tissue sarcomas. *CDKN2A* is a fascinating gene in cancer biology as it encodes not just one, but two powerful tumor suppressors [11][12]. Through shared DNA sequences that are translated in different reading frames, *CDKN2A* yields the $p16^{INK4a}$ inhibitor of CDK4 and CDK6 as well as the ‘Alternative Reading Frame’ protein, ARF [13]. While $p16^{INK4a}$ functions by activating the retinoblastoma (RB1) tumor suppressor, ARF inhibits cancer through multiple mechanisms including activation of

p53. Thus, the observation that *CDKN2A* loss correlates with worse patient survival across many sarcoma types suggests a central role for the $p16^{INK4a}$-CDK4/6-RB1 and/or ARF signaling pathways in sarcoma pathogenesis.

Table 1. Genetic alterations of CDK pathway genes in sarcoma

Gene	Protein	Alteration	Sarcoma Subtype
RB1	Retinoblastoma	Deletion, Mutation	UPS [10][14][15], MFS [10][16], PLPS [17][18], LMS [10][17][19], CS [20], OS [21][22], EwS [23], MPNST [24]
CDKN2A	$p16^{INK4a}$ and ARF	Deletion, Mutation	UPS [10][25], MFS [10][16], LMS [26], MPNST [10][27][28][29][30][24][31][32][33][34][35][36], CS [20], ARMS [37], OS [21][22], EwS [23]
CDKN2B	$p15^{INK4b}$	Deletion	MFS [10][16], MPNST [10][32][36]
CCND 1-3	Cyclin D1-3	Amplification	MFS [16], LMS [26], CS [20], OS [21][22]
CDK4	CDK4	Amplification	UPS [24], WD/DDLPS [10][18], SS [38], CS [20], ARMS [39][40], OS [21][22]
CDK6	CDK6	Amplification	MFS [13][41]
MDM2	Mdm2	Amplification	UPS [25], MFS [16], WD/DDLPS [13][17][18], CS [20], ARMS [37][40], OS [21][22]
TP53	p53	Deletion, Mutation	UPS [13][41], MFS [13][16], PLPS [18], CS [20], ARMS [37], OS [21][22], EwS [23], MPNST [13][24], LMS [13][17][42]
KRAS	Ras	Amplification	UPS [47], ARMS [40]

		Mutation	
NF1	Neurofibromin	Mutation	UPS [13], MFS [13][51], MPNST [13][27][28][29][30][24], ARMS [37][40]
ATRX	ATRX chromatin remodeler	Mutation	UPS [13], MFS [13], LPS [13]
TLS	Translocated in liposarcoma	translocation, (12;16)	M/RCLPS [18]
CHOP	C/EBP homologous protein		
MYC	Myc	Amplification	LMS [42], ARMS [39], OS [21][22], MPNST [32]
PTEN	Phosphatase and tensin homolog	Deletion	LMS [19], OS [21][22], MPNST [30][43]
SUZ12	Suppressor of zeste 12 protein homolog	Mutation	MPNST [28][29][30][24][31]
EED	Embryonic ectoderm development	Mutation	MPNST [28][29][30][24][31]
SSX	Synovial sarcoma, X	translocation, (X;18)	SS [44]
SS18	Synovial sarcoma translocation, chr18		

IDH	Isocitrate dehydrogenase	Mutation	CS [45]
CDKN1C	$p57^{KIP2}$	Deletion	ERMS [46]
PAX1	Paired box 1	translocation, (2;13)	ARMS [40]
FOXO1	Forkhead box O1		
BRAF	B-Raf	Mutation	ARMS [40]
PIK3CA	p110a	Mutation	ARMS [40]
TWIST1	Twist family bHLH transcription factor 1	Amplification	OS [21][22]
CCNE1	Cyclin E1	Amplification	OS [21][22], MPNST [47]
EWSR1	Ewing sarcoma breakpoint region 1	translocation, (11;22)	EwS [48]
FLI1	Friend leukemia integration 1		

Abbreviations: UPS, undifferentiated pleiomorphic sarcoma; MFS, myxofibrosarcoma; WD/DDLPS, well- and de-differentiated liposarcoma; M/RCLPS, myxoid/round cell liposarcoma; LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumor; SS, synovial sarcoma; CS, chondrosarcoma; ERMS, embryonal rhabdomyosarcoma; ARMS, alveolar rhabdomyosarcoma; OS, osteosarcoma; EwS, Ewing sarcoma

2. Summary

Despite the diverse nature of sarcomas, activation of CDK pathways is a common alteration contributing to their development and progression. One of the more frequent changes is inactivation of the *CDKN2A* locus, resulting in loss of ARF-p53 and $p16^{INK4a}$-RB1 tumor suppressive signaling and consequent hyperactivation of cell cycle

CDKs. Loss of other CDK inhibitors, such as p27, and upregulation of cyclin partners, such as cyclins D and E, are also predominant events leading to aberrant CDK activation in sarcomas. While more remains to be learned about the roles and significance of CDKs in the many different types of sarcomas, especially for CDKs with transcriptional or other activities besides cell cycle regulation, it is clear these kinases are key players in sarcoma biology. Continued studies of CDK dysfunction in sarcomagenesis are expected to solidify their importance in this disease and further justify CDK-based therapies for patients. Currently, there is high enthusiasm in the clinic for newer generation CDK inhibitors that target CDK4 and CDK6, such as palbociclib, as these drugs are more specific and less toxic than earlier, more broadly acting compounds.

Based on impressive anti-tumor activities in pre-clinical studies, CDK4/6 inhibitors have become a central component of current phase 1 and 2 clinical trials for various types of sarcoma. These drugs offer promising treatment options for sarcoma patients who are in dire need of effective therapies to treat their cancers. Most of the ongoing clinical trials for sarcoma have just started accruing patients and many involve combination therapy to prevent acquired resistance to CDK-targeted monotherapy. Early phase studies in select soft tissue sarcoma subtypes are showing promising results, particularly for liposarcoma where there is frequent *CDK4* amplification. In a phase 2 study of patients with advanced or metastatic well-differentiated / dedifferentiated liposarcoma (NCT01209598), palbociclib therapy resulted in occasional tumor response along with a favorable progression-free survival rate of 57% at 12 weeks [42]. Currently, there is a multi-center phase 2 trial of palbociclib monotherapy in Spain for patients who have advanced sarcomas with elevated expression of CDK4 (NCT03242382). Moreover, CDK4/6 inhibitors are recognized as high priority agents by the Children's Oncology Group for testing in metastatic, relapsed Ewing sarcoma [43]. As our understanding of the CDKs expands and we learn more about their individual roles in sarcoma pathogenesis, it is fair to say these kinases represent increasingly valuable targets in the treatment of sarcomas.

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