Chordoma of the Spine

A Comprehensive Review

Daniel M. Sciubba
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Editors

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Foreword

Everyone affected by chordoma is able to overcome the disease and maintain his or her quality of life: that's the vision of the Chordoma Foundation, and the future that this book seeks to help bring closer. Current population-wide statistics for patients with chordomas of the spine and sacrum suggest a wide gap between that future and the present. Hence, better treatments are urgently needed, particularly for patients with large or biologically aggressive tumors.

On the other hand, for many chordoma patients, an excellent outcome is already possible with state-of-the-art care. But, while achievable in principle, in practice, it is not simple, requiring sophisticated techniques and tight coordination among a well-informed, multi-disciplinary team of multiple surgical specialists, radiation oncologists, medical oncologists, and more.

Historically, knowledge about how to deliver such state-of-the-art care has not been widespread, resulting in inconsistent treatment, and, all too often, suboptimal outcomes for chordoma patients. This book is an important step towards broadening that knowledge, and, in turn, improving the care provided to chordoma patients. At the Chordoma Foundation, we see that, combined with better treatments for tumors that cannot be controlled with existing approaches and ample support for patients throughout their journey with the disease, as the keys to making chordoma a disease that can be lived with, if not cured. I am, therefore, delighted to see this book come to fruition and am confident that its impact will be felt, whether knowingly or not, by countless fellow patients.

Josh Sommer
Chordoma Foundation
Durham, NC, USA

Preface

Chordoma of the spinal column is an extremely rare clinical pathology, considered to be one of a handful of orphan disease that is amenable to surgical intervention. Given its rarity, the opportunity to acquire the experience necessary to treat chordomas safely is one that has been confined to only a few comprehensive cancer centers. However, improved awareness of the disease because of multi-institutional organizations such as *AOSpine* and patient advocacy groups such as the *Chordoma Foundation* have led to greater awareness of this clinical pathology. With this increased awareness has come a concordantly increased desire to discover the molecular underpinnings of chordoma and the optimal management paradigms for this disease.

In this text, we attempt to provide a comprehensive review of the epidemiology, pathogenesis, diagnosis, and management of chordomas of the mobile spine and sacrum. The book is divided into 4 parts comprising 16 chapters. The first part focuses on the pathophysiology and molecular drivers of chordoma. The second focuses on the epidemiology and clinical history, as well as the histological, oncologic, and radiographic work-up of chordoma. The third part focuses primarily on the technical aspects of surgery for chordoma. It is broken down by anatomic region, with the final two chapters focusing on the soft tissue and bony reconstruction following chordoma resection. The last part focuses on the exciting field of adjuvant therapies for chordoma. This includes both radiation therapies and novel chemotherapeutic options for recurrent, metastatic, and dedifferentiated chordoma.

Though we attempt to cover the gamut of chordoma treatment, we realize that ongoing advances in the science of chordoma will inevitably make this book obsolete. Nevertheless, we believe that in recruiting world experts from leading chordoma centers, including the Johns Hopkins Hospital, the Massachusetts General Hospital, the Mayo Clinic, Memorial Sloan Kettering, and others, we have been able to construct a central reference for spinal oncologists and general spine surgeons who may encounter chordoma patients in their practice. We greatly appreciate our colleagues who donated the time to make this book possible and to the patients whose experience with this rare disease have taught us along the way.

Baltimore, MD, USA — Daniel M. Sciubba
Boston, MA, USA — Joseph H. Schwab

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Heartfelt thanks to Karrie, Hayley, Camryn, and Duncan for all of their love; appreciation to Andy and Zach for their generosity and tireless grit in getting this book completed; admiration to Joe for his wisdom and friendship; and eternal gratitude to our patients who share their journeys and trust us with their lives.

Daniel M. Sciubba, MD

Thank you to Cristina, Peter, Annamaria, and Joe! As with all great efforts there are great teams. Caring for patients with chordomas requires a committed, capable team and I am lucky to be part of such a team at MGH. Thank you Zach and Andy, whose work sincerely made this book possible. Thank you Dan for your positive energy and keen insight.

Joseph H. Schwab, MD, MS

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Abbreviations

ADC	Apparent diffusion coefficient
ALL	Anterior longitudinal ligament
ASA	Anterior spinal artery
ASIS	Anterior superior iliac spine
BMI	Body mass index
BNCT	Benign notochordal cell tumor
BSSMO	Bilateral-sagittal split mandibular osteotomy
C	Cervical
CBVA	Chin-brown vertical angle
CDK4/6	Cyclin-dependent kinases 4 and 6
CDKN2A	Cyclin-dependent kinase inhibitor 2A
CGE	Cobalt gray equivalent
CGH	Comparative genomic hybridization
CI	Confidence interval
CIRT	Carbon ion radiotherapy
CK	Cytokeratin
cm	Centimeter
CSC	Cancer stem cell
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTV	Clinical target volume
DFS	Disease-free survival
DNA	Deoxyribonucleic acid
DS	Double scatter
DSS	Disease-specific survival
EA	Enneking appropriate
EBR	En bloc resection
EGFR	Epidermal growth factor receptor
EI	Enneking inappropriate
EMA	Epithelial membrane antigen
EZH2	Enhancer of zeste 2
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization

FVFG	Free vascularized fibular graft
Fx	Fraction
GM	Gluteus maximus
GTV	Gross tumor volume
GVNR	Giant vertebral notochordal rest
Gy	Gray
GyRBE	Gray-equivalent relative biologic effectiveness
HADM	human acellular dermal matrix
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HR	Homologous recombination
hTERT	Human telomerase reverse transcriptase
ICA	Internal carotid artery
ICU	Intensive care unit
IGRT	Image-guided radiation therapy
IHC	Immunohistochemistry
IMRT	Intensity modulated radiation therapy
IOBL	Intraoperative blood loss
JAK	Janus kinase
KIT	Tyrosine-protein kinase KIT
LAG-3	Lymphocyte-activation gene 3
LC	Local control
LD	Latissimus dorsi
LECA	Lateral extracavitary approach
LMG	Labial-mandibular-glossotomy
LR	Local recurrence
LRFS	Local relapse-free survival
MAP	Mean arterial pressure
MGH	Massachusetts General Hospital
miRNA	microRNA
MRI	Magnetic resonance imaging
mRNA	messenger RNA
MSKCC	Memorial Sloan Kettering Cancer Center
mTOR	mammalian target of rapamycin
MUC1	Polymorphic epithelial mucin/Mucin 1
NCDB	National Cancer Database
NCI	National Cancer Institute
OC	Occipitocervical
OER	Oxygen enhancement ratio
ORR	Overall response rate
OS	Overall survival
P32	Phosphorus-32
PARP	Poly(ADP)-ribose polymerase
PBS	Pencil-beam scanning

PD1	Programmed cell death protein 1
PDGFB	Platelet-derived growth factor β
PDGFR	Platelet-derived growth factor receptor
PDGFRA	Platelet-derived growth factor receptor α
PDGFRB	Platelet-derived growth factor receptor β
PD-L1	Program cell death ligand 1
PFS	Progression free survival
PI3K	Phosphoinositide-3-kinase (PI3K)
PLL	Posterior longitudinal ligament
PR	Partial response
PRC2	Polycomb repressive complex 2
PSIS	Posterior superior iliac spine
PTEN	Phosphatase and tensin homolog deleted on chromosome 10
PTV	Planned tumor volume
Rb	Retinoblastoma
RBE	Relative biological effectiveness
RFS	Recurrence-free survival
RT	Radiation therapy
RTK(s)	Receptor tyrosine kinase(s)
S-100	Low molecular weight protein soluble in 100% ammonium sulfate at neutral pH
S2AI	S2-alar-iliac
SBRT	Stereotactic body radiation therapy
SD	Stable disease
SEER	Surveillance, epidemiology, and end results
SHH	Sonic hedgehog
SI	Sacroiliac
SMARCB1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1
SNP	Single nucleotide polymorphism
SRS	Stereotactic radiosurgery
STAT	Signal transducer activator of transcription
SVA	Sagittal vertical axis
SWI/SNF	Switch/sucrose non-fermentable
T	Thoracic
TBXT	T-box transcription factor T
TCR	T cell receptor
TCR	Transmandibular-circumglossal-retropharyngeal
TES	Total en bloc spondylectomy
TKI(s)	Tyrosine kinase inhibitor(s)
TMC	titanium mesh cage
US	United States
VBR	Vertebral body replacement
VEGFR	Vascular endothelial growth factor receptor

VMAT	Volumetric arc therapy
VP-16	Etoposide
VRAM	Vertical rectus abdominis muscle
WBB	Weinstein-Boriani-Biagini
XRT	X-ray therapy
YAP	Yes-associated protein

Part I

Pathophysiology and Molecular Mechanisms of Chordoma

Notochordal Morphogenesis and the Origin of Chordoma

1

Matthew L. Goodwin and David C. Clever

Abbreviations

BNCT	Benign notochordal tumor
GVNR	Giant vertebral notochordal rest
SEER	Surveillance, epidemiology, and end results (program)
SHH	Sonic hedgehog

Introduction and Epidemiology

Chordomas are slow-growing, locally aggressive tumors thought to be derived from remnants of the notochord [1]. Based upon this, much of the knowledge regarding the clinical behavior of chordoma, in terms of lesion localization and tumorigenesis, is informed by animal studies of notochordal development. Here, we review the basic science of notochordal morphogenesis, which will serve as a basis for understanding chordoma, its potential origins, and clinical behavior.

Notochordogenesis

In vertebrate embryos, the notochord is an evolutionarily preserved midline structure that is thought to play a critical role in left-right development as well as regulation of local tissue development during embryogenesis [2, 3]. The embryonic notochord is a rod-shaped structure that lies just ventral to the neural tube. Abnormal

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development of the notochord structure may lead to malformation of the neural tube, spine, and gut [4, 5].

Descriptions of the process of notochord formation vary slightly from reference to reference, undoubtedly due to the variety of experimental models used to study notochord development. In an effort to consolidate varying views on the notochordal process as it pertains to humans, de Bakker et al. employed a 3D reconstruction of multiple histological sections from 2 to 6 weeks in human embryos [6, 7]. The resultant description of human notochord formation is one of the more comprehensive descriptions of notochordal development (Fig. 1.1).

Beginning at days 17–19, what is described as the "notochordal process" begins. The notochordal process initially is characterized by an accumulation of cells on the ventral surface of the endoderm in an epithelial pattern. Just cranial, these same cells form a broader and thicker network deemed the prechordal plate [8]. Except for at its most caudal end, these midline cells gradually become the notochordal

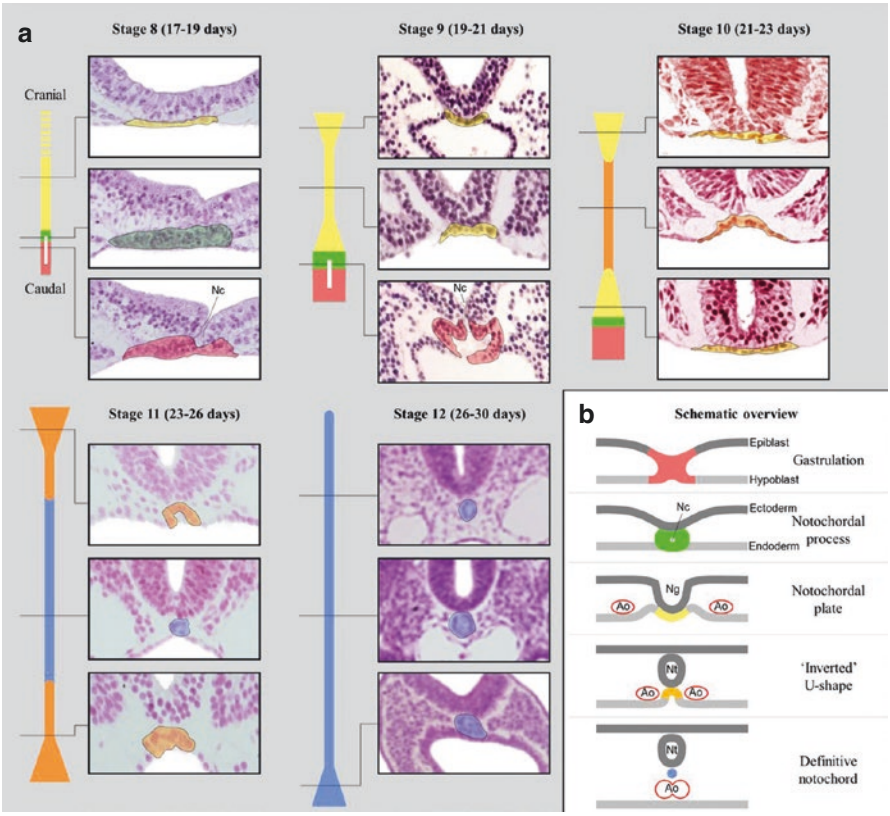

Fig. 1.1 Development of the notochord. (**a**) Taken from numerous human tissue samples, this cartoon and corresponding histology displays perhaps the most accurate and complete view of notochordal development, from days 17 to 30. (**b**) The five stages of notochord development. (Used with permission from de Bakker et al. [7])

plate during days 19–23. By definition, the early notochord is a one-cell thick layer structure along the neural tube that is intercalated with the roof of the developing gut. During days 23–26, a notochordal plate is present along the entirety of the cranial-caudal axis, and notochordal ridges begin the formation of what will be the definitive notochord, completed in days 26–30. This definitive notochord becomes incorporated into the mesoderm, migrating away from the gut and maintaining its neural tube association. The mature notochord is then thought of as a factory of signaling molecules and chemical moieties that play a multitude of essential roles in directing further embryonic development and tissue maturation and differentiation.

Among several important functions, the mature notochord plays an important role in directing vertebral column formation and segmentation. The bony elements of the spinal column are derived from the sclerotome components of each segmental somite [9]. Each sclerotome migrates to surround the notochord. An intimate relationship largely driven by *Homeobox (Hox)* and *Sonic Hedgehog (SHH)* signaling pathways exists between the embryonic notochord and each sclerotome to maintain appropriate vertebral column development and segmentation along the cranial-caudal axis from skull base to sacrum [10]. In this process, segments of the notochord become embedded within the developing vertebral column, specifically in the regions that ultimately become the intervertebral disk [11].

Fate of Notochord Cells

The intervertebral disk (Fig. 1.2) consists of a nucleus pulposus, or the softer inner part, and the annulus fibrosus, or the tougher outer layer. Utilizing methods that "fate map" cells, the nucleus pulposus appears likely to develop from the embryonic notochord [12, 13]. How these cells transition from notochord to nucleus pulposus has not been fully determined, although some combination of physical restraints from the developing vertebrae and attractive/repulsive signaling has been proposed [14]. While the distinct molecular and environmental cues are likely multifaceted and incompletely elucidated, recent gene expression studies have implicated the sonic hedgehog and transforming growth factor-beta pathways as important regulators in notochordal maturation into the mature nucleus pulposus [15].

While all cellular components of the nucleus pulposus cells appear to be of notochordal origin, not all notochordal cells end up transitioning to nucleus pulposus cells. In fact, some notochordal cells can be found within the bony aspects of adult vertebrae [14]. In a study of human cadavers, nearly all adult vertebrae were found to contain evidence of remnant notochordal cells [16, 17]. The vast majority of these notochordal remnant cells remain dormant. Yet it is these "notochordal islands" within the axial skeleton that are thought to be the cells of origin for both benign notochordal cell tumors and malignant chordoma tumors [18]. Given the ubiquitous nature of notochordal remnants within the axial skeleton, it is unclear why the vast minority progress to form both benign and malignant lesions. In the next section, we will explore the various tumor types thought to be derived from notochordal remnants as well as the proposed molecular mechanisms driving their development.

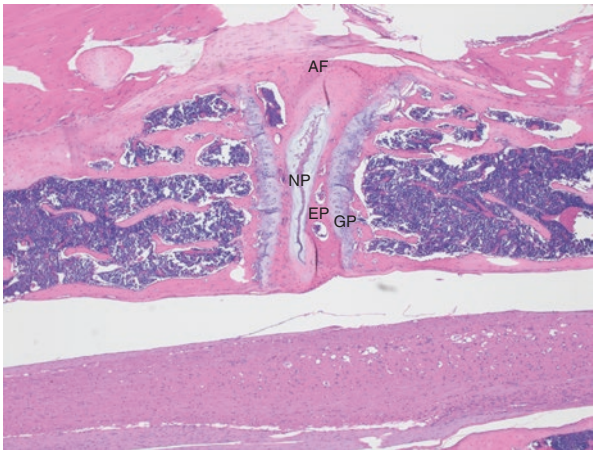

Fig. 1.2 Typical H&E stain of an endplate-disk-endplate. Note the nucleus pulposus (NP) at the center of the intervertebral disk. In this case, the tissue was taken from 7-month-old C57BL/6J mice. NP nucleus pulposus, EP endplate, AF annulus fibrosis, GP growth plate. (Image courtesy of Dr. Mieradili Mulati, Goodwin Lab (Washington University, St. Louis))

Benign Notochordal Tumors (BNCTs)

Benign notochordal tumors (BNCTs) are collections of unencapsulated sheets of vacuolated cells contained within axial bones (most commonly in vertebral bodies) that are thought to arise from notochordal remnants [19–21]. BNCTs have also been referred to as notochordal rests (and giant vertebral notochordal rests (GVNRs)), giant notochordal hamartomas, and benign notochordal cell lesions, giving credence to their presumed notochordal origin. These benign tumor-like lesions uniformly lack local bony destruction, soft tissue extension, or malignant/proliferative properties [1, 22]. While both chordoma and BNCTs are thought to arise from notochordal remnants, they have some important differences. Chordomas manifest as slow-growing yet destructive lesions that often grow beyond the bone, may be lytic in nature with variable enhancement on MRI, and often have an intrinsic capacity for extra-osseous metastasis. Like chordomas, BNCTs are found in the bones of the axial skeleton and skull base. Often incidentally noted on MRI, BNCTs are typically (but not always) small, well-demarcated, and lack soft tissue extension. On imaging, they may be sclerotic on CT and often lack significant post-contrast enhancement on MRI [23, 24].

One of the more controversial aspects of BNCTs is the hypothesis that they represent a precursor to chordoma development with biological potential for oncogenic transformation into malignant chordoma. As such, these lesions might represent an intermediate stage between a dormant notochordal remnant and a full blown malignant chordoma. This view stems from data showing that the anatomic distribution of BNCTs in the spine mirrors that of chordoma, and in excised sacral chordomas, 7.3% have nearby co-existent BNCTs [19, 25]. While attractive in principle given

their similarities in location, histologic appearance, and cellular origin, the pre-clinical and clinical data supporting BNCTs as a precursor to chordoma development are limited. There has been no documented BNCT-to-chordoma transition to date [20, 21]. Given this uncertainty and the rarity of BNCTs, they are currently treated in a variety of acceptable ways that range from serial imaging to complete *en bloc* excision [26]. In this setting, treatment choice is often driven by patient symptomatology.

The Ontogeny of Chordoma

While the presence of notochordal elements within the mature human axial skeleton seems to be a ubiquitous phenomenon, the transformation to malignant chordoma is an exceedingly rare process. Chordomas are rare tumors, accounting for 1.4% of all primary malignant bone tumors, and just 0.2% of spinal tumors, working out to <1 case/1,000,000 of the US population [27]. Data from the Surveillance, Epidemiology, and End Results program (SEER) database from 1973 to 2005 revealed that around 1/3 were found in the skull base, 1/3 in the spine, 1/3 in the sacrum, and the remaining ≈5% outside the neuroaxis [28, 29]. The average age of diagnosis is approximately 60 years, although cases of pediatric chordoma have been described and typically portend a very poor prognosis [30]. Moreover, chordomas of the skull base tend to present in younger patients relative to those tumors involving the sacrum or other areas of the axial skeleton [27]. Overall, survival in the SEER database at 5 years was 64% for all chordoma patients, with tumor size at diagnosis, the presence of distant metastases, local recurrence, and older age (excluding pediatric chordomas) all being poor prognostic factors [31]. Despite high rates of local recurrence, surgical resection is a mainstay of most chordoma treatment paradigms [32], as resection with appropriate margins typically leads to improved survival and decreased local recurrence [33].

The molecular processes involved in promoting chordoma ontogeny, proliferation, and biologic activity are heterogeneous. However, recurrent aberrations in a few conserved molecular pathways have been identified in familial and sporadic chordoma. The overall somatic mutational frequency in chordomas is modest. The pattern of somatic mutations observed in chordomas is common across several cancer histologies and shows age-associated accumulation, suggesting that these mutations are likely passenger phenomena as opposed to the driving mechanism in chordoma development [34].

Recently, the expression of the transcription factor brachyury has been established as a distinguishing feature of chordoma [35]. Brachyury is a transcription factor member of the T-box family. It is involved in coordinating a multitude of cellular processes, including cell migration and motility and preventing cellular senescence. Uniformly expressed in the developing notochord, pathologic analysis of brachyury has demonstrated its expression in nearly all chordoma samples, and its absence in other musculoskeletal tumor types [36]. This observation further establishes the link between the developing notochord and chordoma. It should be

noted that BNCTs also appear to express brachyury, although the pattern seems to be more focally positive areas surrounded by less positive areas, as compared to the diffuse positive brachyury staining seen in chordomas [1, 20, 37]. While one of the early reports of "notochordal rests" reports them as being brachyury negative [38], several studies that followed demonstrated that BNCTs do indeed express brachyury, albeit in what appears to be a slightly different histological pattern, as noted previously (focal vs diffuse) [1, 20, 37, 38].

The molecular mechanism supporting brachyury expression in chordoma is duplication of the chromosomal region containing the brachyury gene, rather than a de novo mutation within the brachyury gene coding region [34, 35]. This brachyury gene duplication phenomenon is present in many cases of both familial and sporadic chordomas. Brachyury is predominantly expressed in malignant tissues and not in mature normal tissues, making it an ideal target for anti-neoplastic therapies. While there has not been a drug developed to specifically target brachyury, recent clinical trials utilizing a vaccine targeted against brachyury have deemed this strategy safe, and in several cases, potentially effective [39]. Further investigation of therapies targeting brachyury, pharmacologically, and/or immunologically remain an active and interesting area of ongoing research.

Histologically, chordomas have a classic and consistent histomorphological appearance (Fig. 1.3), with "physaliphorous" cells throughout (from the Greek for physalis (bubble) and phorous (bearing)) [26]. These unique cells have abundant eosinophilic cytoplasm and intracytoplasmic vacuoles [40], possibly related to dysfunctional lysosomes [34, 41, 42]. While lysosomes are important in notochordal development [43], it is unclear if the vacuolar cytoplasmic appearance of malignant chordoma cells is a passive remnant of their notochordal origin or an important component of their transformation, proliferation, and survival. Interestingly, recent

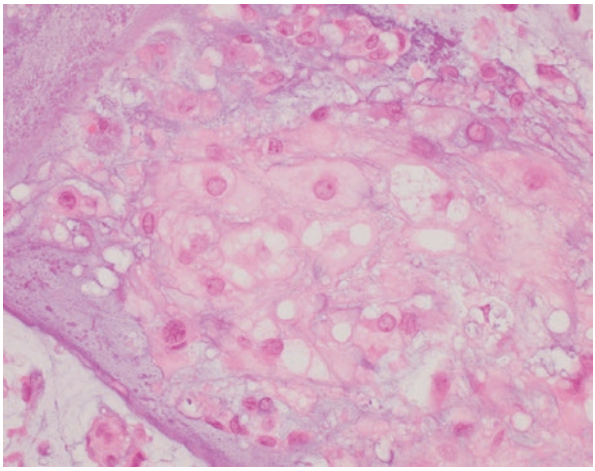

Fig. 1.3 Typical appearance of H&E stain of chordoma, featuring the classic physaliphorous cells. (Image courtesy of Dr. John Chrisinger (Washington University, St. Louis))

studies have identified recurrent inactivating mutations in the *Lyst* gene, which encodes the lysosomal trafficking regulator protein [34]. Whether targeting the lysosomal machinery represents a novel therapeutic strategy for the pharmacologic treatment of chordoma remains to be determined, but represents a promising area of future investigation.

In response to various mechanical and environmental stresses, cellular components of the nucleus pulposus are driven toward biologic senescence. Activation of cellular senescence programs within cells of the nucleus pulposus has been implicated in the molecular pathogenesis of degenerative disk disease [44]. Given the common notochordal origin between the nucleus pulposus and notochordal remnant chordoma precursor cells, it is suspected that chordoma precursor cells possess appropriate machinery for cellular senescence to take place. One might propose, then, that the pathogenesis of chordoma development depends on the subversion of programmed cellular senescence. The *CDKN2a* gene has also been demonstrated to be recurrently mutated at a significantly high frequency in human chordomas [34, 45]. *CDKN2a* is a well-known tumor suppressor gene that encodes two proteins through alternative splicing: $p16^{INK4a}$ and $p14^{ARF}$. Interestingly, p16 is absent in >50% of chordomas [46]. The loss of a potent mediator of cellular senescence at such a high frequency in human chordomas further supports the notion that the core pathogenesis of chordoma development is the failure of cellular senescence. Whether activation of cellular senescence pathways provides a future therapeutic strategy for chordoma treatment remains to be shown, but should be an active area of future research.

Finally, it should be noted that extra-axial soft tissue chordomas, although rare, do exist, and have led to questions on the origin of chordoma [47]. These very rare tumors are histologically indistinguishable from axial chordomas, and express brachyury much like their more common axial counterparts [47]. However, unlike axial chordomas, there are no BNCTs found in extra-axial locations, suggesting the BNCT-to-chordoma pathway may be sufficient but not necessary for chordoma genesis [47]. On the other hand, expression of brachyury mRNA has been previously found outside of the axial skeleton in noncancerous adult tissues (in the absence of the protein) [48, 49]. Thus, it is possible that nonaxial cells may develop a mutation that leads to aberrant expression of the brachyury gene, and eventual chordoma formation.

Summary

Chordomas, locally aggressive slow-growing tumors, are thought to typically be derived from notochord remnants. The notochord, a critical midline structure featured prominently in the early weeks of embryogenesis, plays a critical role in left-right development as well as regulation of local structural development. In adult humans, the nucleus pulposus in the intervertebral disk appears to derive from this notochord, although remnant notochordal cells are found throughout adult vertebrae as well. The development of chordomas likely arises from these remnants, although

many of the underlying mechanisms remain elusive. Among factors involved in this transition to a chordoma, expression of the brachyury gene appears central, as non-chordoma tumors and normal adult tissues lack the significant overexpression of this gene characteristic of chordoma. While wide resection remains the "gold standard" when possible (with or without radiation), advances in our understanding of chordoma and its origins are leading to more targeted, and potentially more efficacious, therapies.

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Molecular Morphogenesis and Genetic Mechanisms of Spinal Chordoma

2

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Abbreviations

CGH	comparative genomic hybridization
CSC	cancer stem cell
FISH	fluorescent in-situ hybridization
HR	homologous recombination
hTERT	human telomerase reverse transcriptase
miRNA	microRNA
mRNA	messenger RNA
OS	overall survival
PARP	poly(ADP)-ribose polymerase
PFS	progression-free survival
Rb	retinoblastoma
SNP	single nucleotide polymorphism
YAP	Yes-associated protein

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Introduction

Chordoma is a rare malignant primary tumor of the axial skeleton. Accounting for 1–4% of primary malignant bone tumors and the most common primary tumor of the spine [1, 2], chordomas most commonly arise in sacrococcygeal areas, skull base, and mobile spine [3, 4]. Unlike other malignant tumors, chordomas demonstrate a characteristic slow growth pattern with a propensity for local invasion of critical bony and neural structures [4]. Although unusual, metastases can occur years after initial diagnosis. Given the frequently large tumor burden at time of diagnosis and proximity of these tumors to vital structures, appropriate surgical excision represents a considerable challenge. Furthermore, these lesions are resistant to conventional chemotherapy and radiotherapy [5]. As a result of the challenges facing clinical chordoma management, local disease recurrence is common, ranging from 30% to 85%, with median 5- and 10-year survival rates at 67.6% and 39.9%, respectively [4].

Recently, scientific progress in understanding the genetic and molecular events underpinning chordoma tumorigenesis has provided insight into avenues for more effective targeted therapies. Indeed, the use of contemporary techniques such as comparative genomic hybridization (CGH), fluorescent in-situ hybridization (FISH), methylation assays, single nucleotide polymorphism (SNP) microarrays, and, more recently, whole-genome sequencing has advanced current understanding of the chordoma genomic and epigenetic landscape. Understanding these processes is important as they govern the biological behavior of the neoplasm and may harbor potential relevant targets for therapy. In this review, we highlight current concepts in the molecular morphogenesis and genetic landscape of spinal chordomas.

Genetic Hallmarks of Chordoma

Cytogenetics

Chordomas are cytogenetically heterogenous tumors that display complex karyotypes. While most chordomas display near diploid or moderately hypodiploid karyotypes, they feature complex genomic rearrangements including deletions and gains of chromosomal segments, gene copy number changes, and chromothripsis. Despite the diversity of chromosome abnormalities documented in the literature, molecular techniques such as G-banding, CGH, and FISH have been used to detect recurrent chromosomal aberrations including gains and losses at various regions throughout the genome (Table 2.1) [6]. Deletions affecting all chromosomes, except chromosome 5, have been identified in chordoma [7]. In 2011, Le and colleagues used genome-wide oligonucleotide microarrays to analyze copy number changes in 21 sporadic chordoma samples (2 clival, 7 spinal, 11 sacral) [6]. Consistent with previous results published by Hallor and colleagues (2 spinal, 24 sacral), they identified frequent losses in chromosomes 3, 4, 9p, 9q, 10, 13, 14, 18, and 22, and common gains in chromosomes 7 and 19 [6, 7].

Table 2.1 Common genomic alterations identified in chordoma

Locus	Genomic alteration	Associated genes	Gene functions	Clinical significance	References
1p36	Deletion	RUNX3	Tumor suppressor, chondrocyte maturation	1p36 LOH correlates with worse prognosis in skull base chordoma [8]. 1p36 loss associated with familial chordoma [9, 10].	[7, 11]
	Deletion	TNFRSF8, TNFRSF9, TNFRSF14	Apoptotic signaling		[8]
1q42.3	Truncating mutations	LYST	Lysosomal trafficking regulation		[33]
3p21	Deletion	PBRM1	Chromatin remodeling		[24, 33]
3p21	Deletion	SETD2			
3p21	Deletion	BAP1			
3q26	Deletion	PIK3CA	Tumor suppressor		
5p15	Promoter mutations	TERT	Telomerase activity	Promoter mutations associated with better survival [31].	[28, 31]
6q25	Deletion	ARID1B	Chromatin remodeling		[24]
6q27	Gain	Brachyury	Notochordal development	rs2305089 SNP associated with increased risk of chordoma development and improved survival [48, 53].	[33, 36, 39]
7q31	Gain	MET	Receptor tyrosine kinase		[81, 82]
9p21	Deletion/ LOH	CDKN2A	G1-S cell cycle checkpoint	9p LOH associated with shorter OS [80].	[33, 80, 83]
	Deletion	CDKN2B			
9p21	Deletion	MTAP	Purine salvage metabolism	MTAP deficient cells are sensitive to purine synthesis inhibitors [84].	[18]
10q23	Deletion	PTEN	Tumor suppressor	Lower PTEN expression correlates with shorter PFS and OS [20]. PTEN loss associated with degree of bone invasion [85].	[6, 15, 20]
11q22	Deletion	ATM	Cell cycle checkpoint kinase		[7]

(continued)