Kinase Activity in Recurring Primary Skull Base Chordomas and Chondrosarcomas: Identification of Novel Pathways of Oncogenesis and Potential Drug Targets

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■ BACKGROUND: **Chordomas and chondrosarcomas can occur in the skull base. Currently, 45% of chordomas and 56% of chondrosarcomas recur within 5 years of surgery. The role of adjuvant therapy is highly debated. No pharmacotherapies have been approved by the U.S. Food and Drug Administration for chordomas or chondrosarcomas. High propensity for recurrence and lack of definitive adjuvant therapy necessitate additional basic science research to identify molecular anomalies associated with recurrent disease.**

■ METHODS: **We pooled tumor lysates from patients based on clinical criteria into 4 groups: primary chordomas, primary chordomas that recurred, primary chondrosarcomas, and primary chondrosarcomas that recurred. We used a peptide labeling method, isobaric tags for relative and absolute quantitation, to uniquely identify each tumor group. Phosphorylated peptides were identified and quantified via mass spectroscopy to determine and predict active kinases.**

■ RESULTS: **Six groups of phosphorylated peptides were associated with primary tumors that later recurred. Specific kinases associated with primary chordomas that recurred were FES and FER. Specific kinases associated with primary chondrosarcomas that recurred were FES, FER, SRC family kinases, PKC, ROCK, and mitogen-activated protein kinase signaling (JNK, ERK1, p38).**

■ CONCLUSIONS: **These data provide clinicians with a means to screen skull base chordomas and chondrosarcomas to help identify tumors with a propensity to recur. Many of these kinases can be efficaciously inhibited by Food and Drug Administration–approved drugs that have not yet been used in clinical trials for treatment of skull base chordomas or chondrosarcomas. Validation of kinases identified in this study may advance treatment options for patients with these tumors.**

INTRODUCTION

Chordomas and chondrosarcomas are related neoplastic lesions that can occur in the skull base. The prognosis and clinical outcome for patients with these tumors is relatively poor. With surgery alone, the 5-year survival rate for chordomas of the skull base is 68%–83%[1-4] and for chondrosarcomas of the skull base is 74%.[5] The 5-year recurrence-free survival rates are 56% for chondrosarcomas[5] and approximately 45% for chordomas.[1,4] Surgery is currently the standard clinical treatment recommendation for both tumors and is the most significant predictor of improved patient outcome.[5-8]

Adjuvant therapy for these neoplasms is heavily debated in the literature.[6-11] Skull-based chordomas are considered to be resistant to radiotherapy, although high doses of radiotherapy may have some clinical efficacy.[8] The use of radiotherapy in chondrosarcomas of the skull base has a relatively greater degree of efficacy with 5-year survival rates >90% in some clinical series.[12] However, radiotherapy alone is not recommended for skull base chondrosarcomas because of poor survival compared with survival of patients who underwent surgery.[7,8,13] At the present time, no U.S. Food and Drug Administration (FDA)–approved drugs exist for the treatment of chordomas[7,8,10] or chondrosarcomas.[5-8]

The lack of evidence for appropriate clinical management of chordomas and chondrosarcomas of the skull base may stem from the low prevalence of these tumors in the general population.

Key words
- Chondrosarcoma
- Chordoma
- Kinase
- Proteome

Abbreviations and Acronyms
FDA: U.S. Food and Drug Administration
iTRAQ: Isobaric tags for relative and absolute quantitation
MS: Mass spectroscopy

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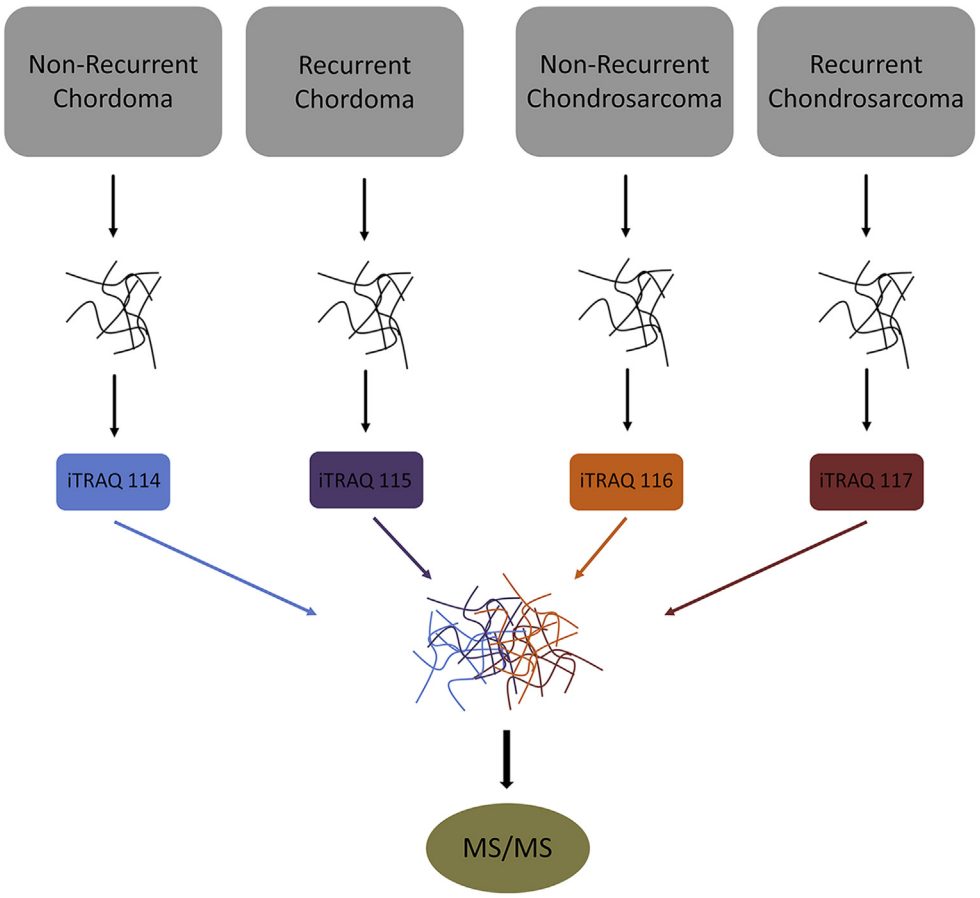

Figure 1. Schematic depicts the workflow used to complete iTRAQ experiment. Protein lysate is pooled into groups based on clinical criteria. The pooled lysates are labeled with a unique iTRAQ tag, and then all samples are pooled into a single group and analyzed in a single liquid chromatography tandem mass spectrometry (MS/MS) run to eliminate run-to-run variation associated with label-free techniques.

Epidemiologic studies have shown these tumors are relatively rare, with chondrosarcomas accounting for 6% of tumors in the skullbase[12] and chordomas accounting for 4% of tumors in the skull base.[7] In general, most clinicians can expect a degree of uncertainty when treating patients with chordomas.[7,8] Although patients with chondrosarcomas experience relatively greater benefit from adjuvant radiotherapy compared with patients with chordomas,[11] these tumors are often difficult to resect.[14] This further complicates the management of these neoplasms given the lack of concrete clinical recommendations for patients who do not qualify for radiotherapy or fail radiotherapy.[12,15]

Histopathologic examination of chordomas and chondrosarcomas is inadequate in predicting rapidly progressive tumors. To develop evidence-based recommendations for the management of these tumors, basic science research is needed to determine molecular markers, which identify aggressive phenotypes that require additional medical interventions, and to identify drug targets, which can be targeted through new pharmacotherapy or repurposing of existing pharmacotherapy. Several recent studies have attempted to address this need. In chordomas, studies have implicated transforming growth factor−β signaling, Akt signaling, mitogen-activated protein kinase signaling, and tyrosine kinase signaling as potential markers for aggression and thus potential targets for drugs.[16-20] However, clinical trials and case studies that have attempted to use a targeted molecular approach to therapy have not resulted in significant improvement over current clinical guidelines for chordomas.[10] In skull base chondrosarcomas, metalloproteinase activity, mitogen-activated protein kinase signaling, and Akt signaling have been implicated as markers for aggression and therapy,[21] although these targets have not resulted in clinically efficacious treatments.[5,12] Despite this deficit, these studies do share a common theme in that intracellular phosphorylation is implicated as the primary mechanism for disease progression in both chordomas and chondrosarcomas. The complexity of the human kinome may account for the lack of translation of basic science research into clinical management of these cancers[22-24]; thus, global analysis and higher resolution studies of the phosphorylated proteome (phosphoproteome) may provide the necessary data to translate these basic science studies into appropriate clinical therapy.