Editorial

Chordoma model

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Patients suffering from chordoma, a mesenchymal cancer thought to arise from the notochord, face limited treatment options.1,5 Although this bone tumor can on occasion metastasize to distant sites, a major clinical challenge is imposed by infiltration of the tumor cells into surrounding structures that can limit the extent of resection. Irradiation prolongs survival, but the relative radioresistance demands delivery of a high dose to sensitive regions. To date, there are no approved medical treatments for chordoma, and efforts to identify effective drugs face barriers. First, there are only few established chordoma cell lines. This limitation presents a challenge to broadening our understanding of signaling pathways that can be targeted, and to verifying the significance of chordoma genomic alterations. Second, consistently reproducible in vivo models are lacking. The list of promising agents obtained from high throughput in vitro screening methods can be strategically shortened prior to human trials by testing in animal models. Presence of such barriers restricts progress and contributes to the poor outcome of patients with recurrent disease.

In their article in the Journal of Neurosurgery, Siu and colleagues6 describe a primary human chordoma xenograft model. The authors report that 1 of the 2 chordoma tumors implanted into athymic nude mice produced a serially transplantable xenograft that retains high genomic fidelity to the parental tumor. Additional comparative characterization of the tumors provides compelling evidence for successful establishment of a primary chordoma xenograft in that physaliphorous morphology and brachyury expression are maintained. Although this report describes successful implantation and propagation of a single specimen, the achievement is nevertheless important. Rather than dissociating the chordoma tumor tissue into single cells, culturing with animal serum on a plastic dish, and transplanting it into an in vivo environment, the investigators developed a primary xenograft that can be serially passaged. A primary xenograft better mirrors the original tumor compared with xenograft established from in vitro expanded tumor cells, and likely explains the greater than 99.9% genomic concordance observed by the investigators. UCH-1, an established chordoma cell line, can be xenografted, but it appears to require a highly immunodeficient background lacking natural killer cell activity (NOD-SCID IL-2 Receptor Gamma Receptor Null).4 The tumor reported by Siu and colleagues was derived from a patient with a clival chordoma. Most chordoma research is performed with tissues and cells derived from sacral chordomas, presumably because of the availability of a greater quantity of material. However, balanced representation will be important, considering that the development of the notochord demonstrates distinct regional morphogenetic origins, suggesting a histogenic basis for intertumoral heterogeneity.7

Modeling human diseases in animals allows for greater appreciation for pathogenesis, in addition to proving a platform to test potential drugs. The study investigators report that brachyury expression was higher in the xenograft than the primary tumor. Determining the mechanism responsible for upregulation of this important transcription factor would be of interest, and to see if it may be associated with enhanced proliferative index. Also, subsets of chordomas demonstrate loss of critical tumor suppressors PTEN or CDKN2A, disruptions potentially capable of altering the tumorigenicity of the chordoma cells.2,3 Molecular profiling of the parental tumor and xenograft may be worthwhile. Lastly, although chordomas can grow in a subcutaneous environment by direct invasion or metastasis, they are primary bone neoplasms. Establishing an orthotopic model by tumor implantation into trabecular bone would represent further progress in understanding this challenging disease. (http://thejns.org/doi/abs/10.3171/2011.10.JNS111716)

Disclosure

The author reports no conflict of interest.

References

Response

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We thank Dr. Park for his thoughtful comments regarding our manuscript and appreciate his work in this field. As noted in Dr. Park’s editorial, there are no approved medical treatments for patients with chordoma. One contributing factor to this is the lack of accurate preclinical model systems. Our study focused on developing a preclinical chordoma model in mice that more closely reiterates patient tumor biology in the hopes that this might serve as a tool to better understand this disease and aid in the development and evaluation of new therapeutics.

Traditional approaches to studying human malignancies are based on establishing cell line cultures in the laboratory and cell line–based xenografts. In our report, we undertook an alternative approach by injecting tumors directly after resection into immunocompromised animals, circumventing any in vitro growth. The rationale behind this approach was based on several factors including the observations of cellular and genetic changes that occur with in vitro growth of chordoma and other cell lines, the difficulty in establishing chordoma xenografts, and increasing reports that primary tumor xenografts more closely resemble parental tumors, genotypically and phenotypically. A recent study evaluating numerous reported chordoma cell lines also suggested that several of these lines are not of chordoma origin, further highlighting the changes that can occur in vitro.

In our study we injected 2 tumors, both from patients with clival lesions, into animals and were able to establish a serially transplantable primary xenograft from one of these tumors. We characterized this xenograft line and found that the tumors maintained the physaliphorous morphology and expression of brachyury as in the parental tumor. Genomic analysis demonstrated that the patient’s tumor and xenografts were greater than 99.9% concordant by whole-genome single-nucleotide polymorphism (SNP) array analysis. At the time we submitted our manuscript, this analysis compared the original surgical specimen and the P1 and P2 generation of animals. We have further expanded this line and continued its characterization. Our xenograft line is now in passage 7 and has been grown in over 100 mice. In our original report, we utilized the Illumina Human600W Beadchip (approximately 660,000 markers per sample) to analyze copy number variances. We have since used the Illumina HumanOmni1-Quad SNP array (approximately 1.1 million markers per sample) and found that the greater than 99.9% concordance rate was maintained between the patient’s tumor specimen, the original founding xenograft, and passages 2, 3, and 4, the latest passage analyzed (data not shown). Additionally, the tumors maintain expression of brachyury by immunohistochemical analysis in P4 (data not shown). Taken together, these results further support that this xenograft is a robust animal model that reproduces the original patient’s tumor sample. We agree with Dr. Park’s comments that additional studies such as molecular profiling and developing an orthotopic model of our and other primary xenografts may lead to a better understanding of this disease.

In addition to the paucity of preclinical model systems, several other factors account for the lack of effective therapeutics including the rarity of this disease, which has an incidence of approximately 1 per 1 million, as well as the lack of awareness. This latter aspect has changed dramatically over the past several years, principally due to the Chordoma Foundation (www.chordomafoundation.com). This foundation is focused on increasing awareness of this disease, coordinating international efforts to better understand chordoma and develop/identify efficacious therapies, providing verified chordoma cell lines to the research community, and directly and indirectly increasing funding for researchers in this field.

References


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