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Genomic Analysis of Sarcomagenesis

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Abstract

Sarcomas are neoplastic malignancies that typically arise in mesenchymal tissues. Like most genetic diseases, this type of cancer is rarely observed in less than 15,000 new cases per year in the United States. The identification of molecular mechanisms generating sarcomas and developing a new tests and therapies are complicated by very heterogeneous Sarcomas arising in many tissue lineages. Thus analyzing a substantial frequency of specific clinical samples requires analysis of extensive total patient populations. Mouse models genomes have been tailored with gene deletions, amplifications, and point mutations reported in human sarcomas to minimize the number of human patients required. Given that ~80% of mouse mutations result in similar sarcomagenesis and suppressive therapies, confirmation in humans is required. Thus mouse models serve as powerful *in vivomodels* to establish new biomarkers and develop therapies.

Keywords: Leiomyosarcoma; LMP2; Tumor protein 53 (TP53); Retinoblastoma (Rb).

Introduction

Malignant sarcoma tumors are highly debilitating and significantly associated with morbidity and mortality. Defined sarcomas arise from a plethora of tissues that are additionally stratified by their histopathology or patient's age at diagnosis [1]. Modern rapid genomewide, pathobiological and clinical analysis further define and stratify sarcomas [2]. Cytogenetic analyses have revealed two divergent genetic profiles. The first karyotypic profile includes about a dozen specific translocations that initiate a specific cancer of all categories. In comparison, most sarcomas display a more complex genotype consistent with more complex phenotypes and rapidly advancing oncogenic tissues.

IFN- γ -inducible factor LMP2/b1i related to uterine mesenchymal transformation

Proteasomal degradation is essential for multiple cellular categories including the modulation of cell cycle, gene expression, and immunological function [3,4,5]. Interferon (IFN)- γ induces the expression of large numbers of responsive genes including subunits of the proteasome *b-ring*, i.e., low-molecular mass polypeptide (LMP)2/b1i, LMP7/b5i, and LMP10/multicatalytic endopeptidase complex-like (MECL)-1/b2i [7]. A molecular approach to investigating the relationship between IFN- γ and tumor cell growth has been enhanced by genomewide sequencing. Homozygous mice deficient in *lmp2/b1i* show tissue- and substrate-dependent abnormalities in proteasome functions [7]. Uterine leiomyosarcoma (Ut-LMS) reportedly occurred in female *Lmp2/b1i*-deficient mice beginning at 6 months of age, to an incidence of 37% at 12 months of age [8]. Histological studies on *lmp2/b1i*-without uterine tumors have characteristic Ut-LMS abnormalities [8]. Recent study, experiments with mouse and human uterine tissues revealed a defective human LMP2/b1i expression in Ut-LMS in the IFN- γ pathway along with specific effect of JANUS KINASE 1 (JAK1) somatic mutations on the LMP2/b1i transcriptional activation [9]. Furthermore, analysis of a human Ut-LMS cell line clarified the biological significance of LMP2/b1i in malignant myometrium transformation, implicating LMP2/b1i as an anti-tumorigenic candidate [9,10].

Tumor suppressors and oncogenic pathways involved in sarcomagenesis

The tumor protein 53 (TP53) tumor suppressor pathway is a well characterized signal cascade in tumorigenesis [11]. *TP53* is a transcription regulator gene that activates numerous DNA

damage-dependent checkpoint responses plus apoptotic genes that ablate many malignant tumors. In addition to *TP53* loss of function via inherited mutations, the *TP53* pathway is commonly disrupted during sporadic sarcomagenesis [12,13]. However, a substantial proportion of sarcomas retain wild-type *TP53* but phenotypically display a loss of *TP53* function. These research findings suggest that changes in other components of the *TP53* signal cascade; such as amplification of MDM2, a negative regulator of *TP53* pathway, may result in *TP53* inactivation [14,15]. Furthermore, mice and humans with elevated levels of MDM2 due to a common single nucleotide polymorphism in the *MDM2* promoter (*MDM2*SNP309) are both more susceptible to sarcoma formation [16]. Additionally, deletion or silencing of *p19^{Arf}*, an inhibitor of the MDM2-*TP53* axis, often results in development of sarcomas. Together, these findings indicate that while inactivation of the *TP53* pathway is observed in the vast majority of human sarcomas, the mechanisms that disrupt of the pathway vary greatly.

The Retinoblastoma (*Rb*) [17] pathway is a second major tumor suppressor pathway that is deregulated in many sarcomas. Individuals inheriting a germline *RB1* gene mutation typically develop retinal cancer early in life. In addition these children have a significantly higher propensity to develop sarcomas than the general population [18]. While the inheritance of germline *RB1* alterations increases the risk of sarcoma, there are also numerous examples of sporadic sarcomas harboring spontaneous mutations and deletions in *RB*, particularly osteosarcomas and rhabdomyosarcomas [19]. Furthermore, *P16^{INK4A}*, a negative regulator of the CDK-CYCLIN complexes that phosphorylate and activate *RB1*, is often deleted in sarcomas [20]. Together, these findings illustrate the importance of *Rb* pathways in sarcomagenesis.

Conclusion

The substantial differences in the cellular origins of sarcomas, the lack of availability of tumor specimens in small medical practices, and the heterogeneity within individual tumors has impeded the thorough understanding of sarcoma biology. The availability of numerous genetic knock-outs, knock-ins, and conditional alleles coupled with tissue-specific Cre-recombinase expressing mouse lines, enables determining the impact of individual genes and mutations in mouse sarcomagenesis. Going forward, tumor analysis from multiple murine-derived tumor types can be readily compared and contrasted to identify critical changes in specific sarcomas. Molecular approaches have clearly demonstrated that while there are driver mutations including translocations, sarcomagenesis is a multi-hit disease. These mechanisms in animals can then be tested in the minimal number of human subjects to determine whether the same principles apply. The use of these mouse models mimicking the human disease condition will enhance defining critical therapeutic approaches that impact treating these debilitating diseases.

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