Physiological Significance of Signal Pathway in Uterine Sarcomagenesis

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Soft tissue sarcomas are neoplastic malignancies that typically arise in tissues of mesenchymal origin. The identification of novel molecular mechanisms leading to mesenchymal cell transformation and the establishment of new clinical therapies and diagnostic method has been hampered by several critical factors. First, this type of malignant tumor is rarely observed in the clinic with fewer than 15,000 newly cases diagnosed each year in the United States. Another complicating factor is that soft tissue sarcomas are extremely heterogeneous as they arise in a multitude of tissues from many different cell lineages. Clinical trials have shown no definite survival benefit for adjuvant radiotherapy or chemotherapy and have been hampered by the rarity and heterogeneity of soft tissue sarcoma types. In order to glean insight into the pathobiology of soft tissue sarcoma, scientists are now using murine models whose genomes have been specifically tailored to carry gene deletions, gene amplifications, and somatic mutations commonly observed in human soft tissue sarcomas. The use of these model organisms has been successful in increasing our knowledge and understanding of how alterations in relevant oncogenic, tumor suppressive, and signaling pathways directly impact sarcomagenesis. It is the goal of many in the pathobiological community that the using these murine models will serve as powerful in vivo tools to further our understanding of sarcomagenesis and potentially identify targeted molecules for new biomarkers and therapeutic strategies.

Benign mesenchymal tumors, uterine leiomyomas are the most common pelvic tumor in women, found in approximately 80% of all women, with an estimated lifetime risk of 70% in white women and 80% percent in black women. Soft tissue sarcomas are a rare malignant tumour with less than 15,000 new cases diagnosed each year in the United States. Uterine leiomyosarcoma (Ut-LMS) is rare, and account for approximately 2-6% of all malignant uterine tumors. The histopathologic classification of these malignant neoplasms is based on the differentiation and/or growth pattern of the neoplastic cells and their presumed cell of origin. Though soft tissue sarcomas are highly debilitating malignancies as they are often associated with significant morbidity and mortality. Ut-LMS are biologically very heterogeneous as evidenced by the fact that these tumors arise from a plethora of different tissues and cell types. They are classically defined by their tissue of origin and are additionally stratified by their histopathology or patient's age at diagnosis [1]. While these classifications have proven useful, modern pathobiological and clinical techniques have the ability to further stratify sarcomas based on their genetic profiles [2]. Cytogenetic and karyotype analyses revealed two divergent genetic profiles in soft tissue sarcomas. The first and most simple genetic profile is the observation of translocation events in soft tissue sarcomas with an otherwise normal diploid karyotype. On the other hand, most soft tissue sarcomas display a more complex genetic phenotype, suggesting genomic instability plays an important role in many soft tissue sarcomas. Understanding the biological characters of sarcoma including Ut-LMS may lead to identification of new diagnostic candidates or therapeutic targets against human uterine sarcoma.

The proteasomal degradation is essential for many cellular processes, including the cell cycle, the regulation of gene expression and immunological functions [3-5]. Stimulation with interferon (IFN)- β induces the expression of large numbers of responsive genes, subunits of proteasome β -ring, i.e., low-molecular mass polypeptide (LMP)2/ β 1i, LMP7/ β 5i, and LMP10/multicatalytic endopeptidase complex-like (MECL)-1/ β 2i [6,7]. A molecular approach to studying the correlation of IFN- β with tumor cell growth has drawn attention. Homozygous mice deficient in Lmp2/ β 1i show tissue- and substrate-dependent abnormalities in the physiological functions of the immune proteasome [7]. Ut-LMS reportedly occurred in female LMP2/ β 1i- deficient mice at age 6 months or older, and the incidence at 14 months of age is about 40% [8]. Histopathological examinations of LMP2/ β 1i-lacking uterine mesenchymal tumors revealed characteristic abnormalities of Ut-LMS [8]. In recent reports, the experiments with human clinical materials and mouse uterine tissues revealed a defective expression of LMP2/ β 1i in human Ut-LMS that was traced to the IFN- β pathway and the specific effect of somatic mutations of JAK-1 molecule on the transcriptional activation of LMP2/ β 1i gene [9,10]. Furthermore, molecular analysis of human Ut-LMS cell lines and murine uterine mesenchymal tumors clarified the physiological significance of LMP2/ β 1i in malignant myometrium transformation, thus implicating LMP2/ β 1i as an anti-tumorigenic candidate in human myometrium [9-11].

Tumor protein 53 (TP53)-mediated tumor suppressor pathway is one of the most well characterized pathways in senescence/transform cells [12]. TP53 gene encodes a transcription factor required for the activation of numerous DNA damage-dependent checkpoint response and apoptotic genes, and thus its activities are often ablated in many senescence/transform cells. In addition to loss of physiological functions of TP53 via inherited germline mutations, TP53-mediated pathway is commonly disrupted by somatic mutations in TP53 gene during sporadic sarcomagenesis [13,14]. However, even though TP53 gene alterations are widely regarded as having a significant impact on sarcomagenesis, many soft tissue sarcomas retain wild type TP53, yet phenotypically display a loss of physiological function of TP53. These pathobiological findings suggest that changes in other components of TP53-mediated pathway; such as amplification of murine double minute 2 (MDM2), a negative regulator of TP53-mediated pathway, may result in TP53 inactivation [15,16]. Furthermore, both mice and humans with elevated expressions of MDM2 due to a high frequency single nucleotide polymorphism in the MDM2 promoter (Human Genome Mdm2SNP309 polymorphisms) are more susceptible to mesenchymal transformation [17]. Additionally, deletion or silencing of Cyclin-dependent kinase inhibitor 2A(CDKn2a)/p19 Alternative reading frame(p19Arf)(P14ARF in human molecule), an inhibitor of the MDM2-TP53 axis, often results in development of osteosarcomas [18]. However experiments with clinical materials unclearly show that initiation of human Ut-LMS is correlated with loss in physiological functions of TP53 [19,20]. Together, these data indicate that while inactivation of the TP53-mediated pathway is not clearly observed in the vast majority of human sarcomas, the mechanisms leading to disruption of the TP53-mediated pathway may vary greatly [19,20].

Retinoblastoma (RB)-mediated pathway represents a second major tumor suppressor pathway, which may be deregulated in many sarcomas. Individuals inheriting a germline RB somatic mutation typically develop malignant tumors of the eye early in life. However, in addition to retinal malignant tumors, these children have a significantly higher propensity to develop sarcomas than the general population [21]. While inheritance of a germline RB alterations increases sarcoma risk, there are also numerous examples of sporadic sarcomas harbouring spontaneous mutations and deletions of RB, particularly osteosarcomas and rhabdomyosarcomas [22]. Furthermore, p16 inhibits CDK4 (P16/INK4a), a negative regulator of the cyclin-depend kinase (CDK)-CYCLIN complexes that phosphorylate and activate RB, is often deleted in soft tissue sarcomas [23]. Together, these findings illustrate the importance of RB-mediated pathway in sarcomagenesis.

The vast differences in the cellular origins of soft tissue sarcomas, the lack of availability of tumour specimens, and the heterogeneity inherent within individual tumors has impeded our ability to fully understand the pathobiology of soft tissue sarcomas. However, given the availability of numerous genetic knock-outs, knock-ins, and conditional alleles coupled with the bevy of tissue-specific Cre-recombinase expressing mouse lines, we have the ability to systematically and prospectively interrogate how individual genes and somatic mutations impact sarcomagenesis. Going forward, tumor analysis from multiple murine derived tumor types can be compared and contrasted in order to identify critical changes in specific soft tissue sarcomas. The molecular approaches clearly demonstrate that while there are driver mutations/translocations, the sarcomagenesis is, in fact, a multi-hit disease. The use of these genetically modified murine models mimicking the human disease condition leads to identify diagnostic methods and/or critical therapeutic approaches, which can be taken to lessen the impact of these debilitating diseases.

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