Cancer Biology

Unique Animal Models & Rare Tumors

The Lee Lab: Modeling Rare Sarcomas & Stem Cells

The rare Ewing Sarcoma (ES) and Desmoplastic Small Round Cell Tumor (DSRCT) are noteworthy due to their poor prognosis and survival rates (<15% at 5 years at best), typical population (adolescents), and relatively distinct genetic features. These cancers most commonly arise from chromosomal translocations involving the EWS gene. The EWS gene's normal function is currently poorly understood, but it has a strong transactivation domain. The fusion partners involved are usually transcription factors that contribute a DNA binding domain, distinct to these and a few other rare cancer types. The lab of **Sean Lee** employs a variety of techniques to study both the tumorigenic mechanisms of fusion proteins and the normal physiological function of the EWS gene.

Modeling Rare Tumors in Mice

While several tissue culture cell lines are derived from these rare tumors, creating a viable mouse model for both ES and DSRCT has proven difficult. The Lee Lab engineered a mouse model with a conditional EWS and WT1 gene (one of the common transcription factors found fused to EWS in patients) fusion protein. In this model, control of the induction of the fusion protein in both a temporal and tissue-specific manner is possible. Gene expression analyses of patient samples, cell lines, and the mouse model have led to the identification of unusual sets of enriched genes, and kinases were chosen for follow-up specifically due to their "druggable" nature. Of 17 targetable kinases identified, one showed promise in reducing growth of an aggressive phenotype of a DSRCT cell line – proving a general validity of this analysis pipeline for identifying potential treatment targets.

The lab has also pursued a screening model with a commercially available kinase inhibitor library, and identified a small number of promising candidates. However, there is no current model of *de novo* tumorigenesis of these cancers in mice, as 1) global expression of the fusion gene products is highly toxic to both embryos and adult mice and 2) the cell of origin is unknown, precluding tissue-specific fusion protein expression modeling. That being said, the lab is aggressively pursuing the identification of the cell-of-origin of these cancers, and is well positioned to utilize their animal model to exploit this.

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Identification of Cancer Stem Cells

Cancer stem cells are the root cause of cancer mortality, responsible for cancer metastasis and refractory recurrence. The specific cancer stem cells in ES and DSRCT are not known. However, cancer stem cells are generally identifiable by 1) specific cell-surface markers 2) treatment with specific cell dyes that are readily ejected by cancer stem cells, or 3) the distinct "sphere-forming" characteristic of these cells in culture. The DSRCT cell culture line readily forms spheres of cells, which display an elevated expression of known stem cell markers, in addition to displaying an increased resistance to chemotherapeutics. Also observed is a markedly elevated ability to form tumors in mice when compared to the non-sphere-forming parental cell line – all hallmarks of cancer stem cells with direct clinical relevance.

By analyzing RNAseq data from these cells, the lab plans to identify potentially targetable proteins and pathways. These cells also potentially represent an in cellulo system for evaluating the potential of drugs specifically designed to target cancer stem cells. As a proof-of-concept, differentially expressed kinases have already been analyzed and the BCell-typical kinase BLK has been identified as being differentially expressed and important in DSCRT biology.

Basic Biology of EWS

The lab also studies the function of the normal EWS gene, whose true function is understudied and poorly understood. The mouse models design makes it possible to easily generate mice that are functionally null for this gene. The mice have a high infant mortality (>90% not surviving 24 hrs) and survivors remain small, have BCell defects, meiosis defects, and problems handling DNA damage. This is due to a defect in the development of brown fat, an essential tissue in the regulation of heat that relies heavily on well-functioning mitochondria. Mitochondrial dysfunction has recently been recognized as important in cancers, and is indirectly tied to the well-known Warburg effect in solid tumors. These discoveries about the basic biology of the EWS gene directly relate to the more cancer- and disease-focused expertise of this lab, and showcase the holistic and comprehensive approach that they take to the study of these rare cancer types.

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