Molecular Dissection of Rhabdomyosarcoma Tumorigenesis

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Rhabdomyosarcoma is a tumor of skeletal muscle-type histogenesis and the most common pediatric soft tissue cancer. Rhabdomyosarcoma is often caused by one of two chromosomal translocations, t(1;32)(q35;q14) or t(2;13)(p36;q14), that are rhabdomyosarcoma - specific and diagnostic, and both drive equivalent PAX-FKHR fusion oncogenic transcription factors. Despite aggressive multimodal therapy, the 5-year survival rate of patients with advance-staged rhabdomyosarcoma remains less than 30% and has not improved in three decades. We intend to genetically characterize the molecular underpinnings of rhabdomyosarcoma to find new potential drug targets for treatment. Since PAX biology is structurally and functionally conserved (as is syncytial muscle development and structure), we have generated a new transgenic PAX-FKHR Drosophila model, which we have used to conduct a forward unbiased genetic screen to identify dominant modifiers of PAX-FKHR pathogenesis when expressed in growing muscle tissue. We also performed microarray analysis of fly PAX-FKHR tissue versus control tissue. We are now actively profiling genetic loci of interest for phenotypes in mammalian murine C2C12 myoblasts. After testing a subset of candidate genes identified in the screen, we have found that the genes identified as genetic modifiers of PAX-FKHR pathogenicity in the fly screen are indeed active in mammalian myoblast biology and PAX-FKHR pathobiology. These genes include loci normally involved in myogenesis and genes not previously correlated with mammalian skeletal muscle development or PAX biology. Our results suggest that the PAX-FKHR Drosophila transgenic model and genetic screening are revealing previously unknown gene targets that will likely underlie rhabdomyosarcoma pathogenesis. The discovery of new genes seminal to rhabdomyosarcoma pathobiology will be a valuable tool in the conceptual design of new therapies to target rhabdomyosarcoma and thus improve treatment.

Rhabdomyosarcoma $x therapy
Oncogene Proteins, Fusion $x genetics
Myoblasts $x physiology