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UNMASKING THE CELL OF ORIGIN OF EWING SARCOMA: A SEQUENTIAL TRANSFORMATION PROCESS THAT REQUIRES A PRIOR PRENATAL GENETIC ALTERATION AND AN EPIGENETIC POSTNATAL CONTEXT

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1. Project summary

The Ewing sarcoma family of tumors (ESFT), an exclusively human aggressive bone and soft tissue tumor, is the most common bone malignancy in Spain. ESFT peaks in the second decade of life and is predominantly seen in Caucasians, less in Hispanics and Asians, and rarely in blacks. This cancer most often initiates in the long bones and the pelvis, but it can occur in any bone. Less often, Ewing sarcoma originates in the soft tissues. Despite ESFT being so rare, treatment of ESFT improved in the 1980s-90s with reported durable remissions in 50–70% of non-metastatic patients. However, patients that present with metastatic disease have low survival rates and relapsed disease is almost always fatal. Patients with both localized and metastatic disease are treated with multimodal therapy consisting of surgery and/or radiation for local disease control and intensive chemotherapy. Patient age is an independent predictor of worst outcome with patients older than 18 years with metastasis or pelvic primary tumors remaining virtually incurable.

Pediatric cancers differ from adult tumors especially by their very low mutational rate, and their biology highly depending on the normal growth context. ESFT genomes are among the most simple reported to date and are uniquely characterized by a chromosomal rearrangement, creating fusion oncogenes (aberrant genes able to cause cancer). Although these unique oncogenes are required to generate a tumor, experimental introduction in cells is only tolerated in human stem cells and does not provide those cells with the ability to reproduce a tumor in the animal. These indicate that something else (epigenome) of the cell in which the oncogene is expressed is necessary for its transformation ability. The epigenome refers to all the chemical modifications of the DNA and DNA-packing proteins (histones) that are able to regulate gene expression without involving alterations in the DNA sequence; for instance, epigenetic gene regulation is the underlying mechanism of cell differentiation throughout embryogenesis. Unfortunately, the unknown ESFT cell-of-origin (and its epigenome) has hampered the identification of proper experimental in vivo models to study ESFT biology and vulnerabilities. Our preliminary results indicate that the oncogene is the only genetic event required for cell transformation when expressed in appropriate prenatal embryonic stem cells and stimulated in vivo with pubertal-like environmental conditions. We aim to characterize the ESFT cell of origin (1st hit) and to define the environmental cues (puberty) required to promote ESFT in vivo (2nd hit)

by using appropriately modified human embryonic stem cells and in vivo experimental mouse models.

2. Results

The study was successfully accomplished and revealed that, indeed, embryonic human stem cells are able to tolerate the oncogene and differentiate into the three embryonic germ cell layers. We describe moderate alterations of the cell architecture of those mesenchymal stem cells harboring the oncogene. Surprisingly, these cells do not become immortal. Furthermore, when these cells harboring the oncogene are injected into immunosuppressed animals it is really hard to generate tumors. Incidence is very low and timings very prolonged. Some factors that increase the capacity of these cells to generate tumors in vivo include the degree of immunosuppression of the animal lines, and the sex of the animal, males being more prone to develop tumors than females. More recent experiments show that increasing the levels of oncogene expression by re-infection of cells harboring the oncogene raises the ability to generate tumors in the animals significantly faster and at higher incidence (40%).

3. Relevance

The model we have developed will allow the study of any translocation derived tumor. As with the Ewing sarcoma model, we have already introduced other oncogenic translocations (CIC-DUX, EWS-ERG.) from sarcoma, leukemia or central nervous system tumors.

Our results confirm in sarcomas the double hit model developed initially in leukemia by Mel Greaves and colleagues whereby the first hit (genetic) occurs during fetal development and the post-natal growth context is what finally determines tumor development. With this knowledge we can now start preventive strategies for these rare cancers similar to what is being developed for leukemia.

4. Scientific bibliography

Manuscript in preparation.