Role of the WTX gene family in cancer and development

Wilms tumor, the most common pediatric kidney cancer, is a prime example of the connection between cancer and cell development because it arises from kidney-specific stem cells and is composed of several cell types that resemble the earliest stages of kidney development. We recently identified WTX, a new X-linked tumor suppressor gene which is inactivated in up to 30% of cases of Wilms tumor, by comparing the DNA of primary tumor samples with that of normal tissues using array comparative genomic hybridization (CGH). WTX is the founding member of a new protein family (FAM123) and is expressed in the stem cell compartment of the developing kidney as well as in a variety of other tissues during embryogenesis. In collaboration with the Haber and Bardeesy laboratories, we have demonstrated that inactivation of WTX in mice leads to severe alterations in the development of several organs that arise from mesenchymal precursors, including kidneys, bones and fat.

Epigenomic approaches to the identification of novel pathways in cancer

Genome-wide chromatin profiling, which combines chromatin immunoprecipitation and high-throughput sequencing, is a new technology that has been used to study the epigenetic code of embryonic stem cells. As opposed to expression arrays, chromatin profiling provides a unique view of cellular differentiation programs by allowing the identification of both active and repressed domains in the genome through the analysis of histone modifications. Prominent active marks tend to be associated with transcription factors that play key roles in a given lineage. A mixture of repressive and active signals is often indicative of genes that are poised for transcription but are not yet active due to an incomplete process of differentiation. We have applied this technology to Wilms tumor and have uncovered a new set of genes.
Immunofluorescence image of a developing mouse kidney. The transcription factor Pax2 (red) is present in the stem cells that can give rise to Wilms tumor (adjacent to the surface of the organ) and in precursors to collecting ducts.

with potentially critical functions in blocking differentiation programs in tumor cells. Given that the mechanisms that regulate this tumor and its precursor stem cell population are not well defined, epigenomic profiling provides a powerful tool for directly identifying new pathways of potential clinical importance. We are now testing the function of the genes identified in Wilms tumor as well as extending our epigenomic analysis to other tumor types where developmental pathways are expected to play a key role.

**Selected Publications:**


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