In essence, cancer is a disease caused by inappropriate cell proliferation. We investigate the mechanisms that limit cell division in normal cells and the ways that these controls are eroded in cancer cells. Our research focuses on the E2F transcription factor and the retinoblastoma tumor suppressor (RB). E2F controls the expression of a large number of target genes that are needed for cell proliferation. This transcriptional program is activated when normal cells are instructed to divide, but it is deregulated in tumor cells, providing a cellular environment that is permissive for uncontrolled proliferation. pRB has multiple functions, but one of its most important roles is to limit the activity of E2F; as a result, most tumor cells select for changes that remove this control.

The original discovery of the RB1 gene was made possible by the fact that its mutation is a causal and rate-limiting event in the development of retinoblastoma. In recently published studies, we have examined both the causes and consequences of pRB inactivation. An exciting new development in this area of research is the discovery that the loss of pRB undermines genomic stability.

Careful analysis of pRB-deficient cells has revealed that pRB loss leads to centromere dysfunction, reduced cohesion, and chromosome instability (CIN). CIN is a common feature in tumor cells. High levels of CIN correlate with poor prognosis and promote tumor relapse after seemingly effective anticancer treatments. The finding that pRB loss causes CIN raises the possibility that the functional inactivation of pRB may be an underlying source of much of the aneuploidy seen in tumor cells. Understanding what causes these changes may have therapeutic implications, and a major goal of our current work is to find ways to suppress these defects. Such conditions may limit the ability of pRB-deficient tumor cells to evolve.

In a second line of experimentation, we sought to identify pathways that either enhance or suppress the ability of pRB to function. Although pRB is typically viewed as a target of cdk regulation, a screen of the kinome revealed that multiple kinases have a major impact on the capability of pRB to arrest the cell cycle and/or induce senescence. Interestingly, one such kinase was LATS2, a component of the HIPPO pathway. Subsequent experiments...
The depletion of pRB results in a high frequency of lagging chromosomes. pRB was selectively depleted from RPE1 cells, a non-transformed cell line, and the appearance of lagging chromosomes during anaphase was scored in cells stained to show the kinetochore (green), microtubules (red) or DNA (blue).

revealed that LATS2 is important for the activation of DREAM repressor complexes, and that the ability of pRB to trigger the formation of DREAM complexes was compromised when LATS2 levels were low. LATS2 is closely linked to the RB gene on human chromosome 13, and a large proportion of cancer cells show loss of heterozygosity for RB1 and LATS2, but apparently fail to mutate the remaining allele of RB1. We speculate that heterozygosity for LATS2 may reduce the need to mutate RB1. Potentially, increasing LATS2 activity in these cells may enhance the ability of pRB to block cell proliferation.

Selected Publications:


