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Cell division is one of the most basic processes of living organisms, yet the mechanisms regulating this complicated process remain unclear at many points. Understanding the regulators that are involved at different stages of the cell cycle is critical to determining how and why cells lose normal controls and checkpoints, resulting in transformation and oncogenesis. This understanding can lead the way toward identifying new drugs and drug targets, as well as developing novel therapies to fight cancer. The research in this laboratory is specifically focused on understanding the regulation of the onset of DNA replication or S phase in vertebrates. This point in the cell cycle is a major checkpoint of cell division where cells must correctly initiate the replication of the genome following mitosis while ensuring that replication occurs once and only once per cell cycle. Our studies utilize mammalian cells in culture and egg extracts from the frog, *Xenopus laevis*, to understand the molecular mechanisms regulating the proper initiation and completion of DNA replication.

One major project in the lab is focused on understanding how cyclin-dependent kinase (CDK) inhibitors, negative regulators of the cell cycle, determine the proper timing of DNA replication. Cancer cells typically express little or no CDK inhibitor proteins which has been correlated with genomic instability due to premature entry into S phase, but why CDK inhibitors are aberrantly regulated in cancer cells is unclear. Our studies have focused on how the ubiquitin-proteasome system (UPS) regulates CDK inhibitor protein levels during the cell cycle and during a cell cycle checkpoint response. We have identified a novel pathway of regulation for Cip-type CDK inhibitor proteins during the initiation of DNA replication and DNA repair. Other studies in the lab focus on understanding how the tumor suppressor proteins, Retinoblastoma (Rb) and BRCA1, influence the timing and fidelity of DNA replication. Past studies have demonstrated that Rb influences DNA replication by inhibiting the E2F-dependent transcription of genes required for S phase onset. Our recent studies suggest that Rb can also influence S phase onset by associating with components of the pre-replication complex and directly regulating the initiation of DNA replication independently of transcriptional events. Past studies have suggested that BRCA1 and its binding partner, BARD1, exhibit ubiquitin ligase activity that appears to be important for maintaining DNA repair and genomic stability. Our recent studies have identified the deubiquitinating enzyme, USP7, as a novel negative regulator of BRCA1-BARD1 ubiquitin ligase activity. Our studies indicate that elevated levels of USP7 inhibit the recruitment of BRCA1 to DNA repair foci following ionizing irradiation and suggest that USP7 activity is elevated in epithelial breast cancer cells.