DYNAMICS OF THE P53 SIGNALING PATHWAY

Our lab is interested in understanding how the dynamic behavior of biological signals is controlled and how these dynamics affect cellular responses. We focus on the signaling pathway of the tumor suppressor protein p53, which is the protein most frequently inactivated in human cancer. Our single cell studies showed that DNA damage initiates a series of p53 pulses. To identify the origin of these pulses we used a combination of computational and experimental approaches and asked which of p53's regulators and feedbacks are required for triggering this dynamical behavior. The simplest explanation is that these pulses are oscillations intrinsic to the p53/Mdm2 negative feedback loop. We present evidence that this simple mechanism is insufficient to explain p53 pulses; we show that p53 pulses are externally driven by pulses in the upstream signaling kinases, ATM and Chk2, and that the negative feedback between p53 and ATM, via Wip1, is essential for maintaining the uniform shape of p53 pulses. The picture emerging from our work is that the p53 pulses arise from periodic examinations of the damaged DNA by ATM to determine whether the damage has been repaired; if not, additional pulses of both ATM-P and p53 are triggered. Our data open several new avenues of investigation to mathematically understand the origin of p53 pulses, and ways to manipulate p53 pulses to ask questions about their function in response to DNA damage.