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Systems-level analysis of the regulation and function of p53 dynamics in cancer.

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Living cells use complex signaling pathways to detect environmental stimuli and generate appropriate responses. As methods for quantifying intracellular signaling have improved, several signaling pathways have been found to transmit information using signals that pulse in time. The transcription factor p53 is a key tumor suppressor and stress-response regulator that exhibits pulsatile dynamics. In response to DNA double-strand breaks, the concentration of p53 in the cell nucleus increases in pulses with a fixed amplitude, duration, and period; the mean number of pulses increases with DNA damage. p53 regulates the expression of over 100 target genes involved in a range of cellular stress responses including apoptosis, cell cycle arrest, and changes in metabolism. p53 pulsing directly impacts p53 function: altering p53 dynamics by pharmacologically inhibiting p53 degradation changes patterns of target gene expression and cell fate. While p53 pulsing serves an important signaling function, it is less clear what it accomplishes mechanistically. Here we will describe our recent efforts to determine the impact of p53 pulsing on the dynamics and coordination of target gene expression.