In response to stress, p53 mediates transient cell-cycle arrest or terminal fates, such as apoptosis or senescence, and its activity is regulated at multiple levels to control downstream signaling. Purvis and colleagues describe an additional mode of p53 regulation via alterations in its protein dynamics. Different types of radiation damage are known to affect the frequency and amplitude of p53 protein level fluctuations and can induce either pulsed or sustained p53 pathway activation. The authors tested whether perturbing these dynamics using the p53 inhibitor Nutlin-3 altered the downstream cellular response to γ-irradiation, which normally induces repeated p53 pulses and leads to cell-cycle arrest. Using a mathematical model, the authors identified the optimal concentration and timing of Nutlin-3 treatment necessary to achieve a constant level of p53 signaling. In contrast with pulsed p53 signaling, which activated genes involved in cell-cycle arrest, DNA repair, and p53 regulation, sustained p53 signaling induced by sequential Nutlin-3 treatments led to continuous upregulation of these genes as well as an increase in the expression of a subset of apoptosis and senescence marker genes. In addition, sustained p53 levels resulted in increased β-galactosidase positivity and a reduction in cell division in response to γ-irradiation, indicative of senescence. These results suggest that sustained p53 levels accelerate commitment to senescence following this type of DNA damage and that protein dynamics contribute to the modulation of p53 signaling specificity. Although additional work is needed to investigate the interplay between these dynamics and posttranslational p53 modifications, targeted manipulation of p53 protein dynamics may represent a novel therapeutic strategy to induce apoptosis or senescence in cancer cells.


A subset of KRAS-wild-type metastatic colorectal cancers initially respond to cetuximab and panitumumab, monoclonal antibodies that block the epidermal growth factor receptor (EGFR), but ultimately develops resistance within 5 to 6 months. Misale and colleagues continuously treated KRAS, BRAF, and PIK3CA-wild-type colorectal cancer cell lines with cetuximab and observed that cells that developed resistance had selectively acquired amplifications or activating mutations of KRAS that were sufficient to induce cetuximab resistance in vitro. Deep sequencing of tumor biopsies from patients with colorectal cancer that had developed cetuximab or panitumumab resistance revealed the emergence of KRAS mutations in 7 of 11 tumors, whereas tumors that had not been treated with anti-EGFR antibodies did not develop KRAS mutations. Additionally, analysis of KRAS allelic frequency in plasma samples from patients treated with cetuximab showed that KRAS mutations in circulating tumor DNA could be identified as early as 10 months before disease progression was confirmed by radiologic assessment. Diaz and colleagues also noted the development of KRAS mutations in the serially acquired serum samples of 9 of 24 patients receiving panitumumab prior to or concurrently with radiographic progression. Mathematical models based on the circulating tumor DNA data indicated that tumor cells harboring KRAS mutations were present in a subclonal population prior to panitumumab treatment and would become observable in circulating DNA an average of 22 weeks after initiation of treatment, suggesting that the time to disease recurrence is the time it takes preexisting KRAS-mutant subclones to repopulate the tumor. Collectively, these findings establish that noninvasive detection of KRAS mutations in the serum may be an early indicator of acquired resistance to anti-EGFR antibody therapy and suggest that combined treatment with inhibitors targeting downstream KRAS effectors such as MEK may be able to reverse or delay cetuximab or panitumumab resistance.

