A NOVEL EXON SPECIFIC ISOFORM EXPRESSION REPORTER SYSTEM (EXSISERS) APPLICABLE TO REAL-TIME, LIVE-CELL, AND HIGH-THROUGHPUT QUANTIFICATION OF P53 PROTEIN ISOFORMS

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A novel intein-luciferase reporter system (EXSISERS) enables real-time quantification of p53 isoforms and identified drug candidates that selectively kill colorectal cancer cells by upregulating pro-apoptotic p53 isoforms.

KEY POINTS

- EXSISERS was integrated into TP53 coding exons 2, 4, and 7 of HCT116 cells using CRISPR/Cas9 to non-invasively distinguish FLp53, Δ40p53, Δ133p53, and Δ160p53 in real-time, overcoming limitations of immunoblot, immunoprecipitation, and mass spectrometry methods.
- Screening 4,863 anti-cancer compounds identified drug candidates that upregulate pro-apoptotic p53 isoform members and induce 60-90% cell death in colon cancer cell lines at nanomolar concentrations.
- Drug treatment of primary colonic organoids predominantly induced cell death in malignant cells but not in healthy colonic organoids.
- Higher Δ40p53:FLp53 ratios are linked to increased apoptotic and decreased tumor recurrence rates, while Δ133p53 and Δ160p53 are negative regulators with tumor-progressive abilities.
- This work provides a universally applicable method to expand colorectal cancer treatment options by targeting p53 isoforms, which have been considered undruggable.

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