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How a tumor cell responds to the shutdown of one or several pro-oncogenic microRNAs

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The global pursuit of targeted oncotherapeutics has increasingly focused on modulating oncogenic microRNAs. Our contribution to this field is the development of a novel class of mesyl phosphoramidate oligonucleotides (μ-ASOs) targeting miR-21, miR-17, and miR-155. This work sought to unravel the fundamental cellular consequences of their application. We found that these compounds act as precise molecular keys, initiating a profound intracellular reprogramming. Their exceptional nuclease resistance and unique capacity to recruit RNase H facilitate efficient and sustained target silencing, reducing miRNA levels by 50–75%. This primary trigger sets off a cascade: the subsequent restoration of pivotal tumor suppressor proteins, such as PTEN and PDCD4, orchestrates a comprehensive anti-tumor response. This is functionally manifested as a 3 fold induction of apoptosis, a 7 fold suppression of cell migration, and up to an8 fold inhibition of tumor growth in vivo. The therapeutic narrative becomes even more compelling when these agents are used in combinatorial regimens which unlock potent synergy, driving the efficacy to new heights.

To deconstruct this reprogramming at a systems level, we conducted a deep proteomic analysis of Caco-2 cells 72 h post-transfection. Crucially, the mesyl modification itself showed no nonspecific off-target effects on the proteome. Instead, each μ-ASO elicited a distinct and specific molecular signature. Suppression of miR-17 predominantly altered the expression of proteins governing cell proliferation and the chaperone response. Inhibition of miR-155 modulated targets involved in apoptosis, immune response, and nucleocytoplasmic transport. The most pleiotropic impact was observed with the miR-21-directed μ-ASO, which significantly affected proteins regulating apoptosis, cell cycle, proliferation, adhesion, and DNA repair. The combination of μ-ASOs affected a similar broad spectrum of functions – proliferation, adhesion, and DNA replication/repair – yet achieved this through an entirely nonoverlapping set of molecular targets, suggesting a powerful and convergent phenotypic response.

Ultimately, our findings illustrate that μ-ASOs do not merely inhibit a single target; they rewire the oncogenic circuitry of the cell through a cascade of specific molecular events, offering a powerful, sophisticated, and well-tolerated strategy for cancer therapy.

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