Small molecules acting on RNA targets in cancer (SMART-C)

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Background: Targeting structured RNA with small molecules has emerged as a promising strategy to expand the repertoire of RNA-based therapeutics. Based on this rationale, we established SMART-C (Small Molecules Acting on RNA Targets in Cancer), a drug discovery program aimed at developing small-molecule modulators of cancer-relevant non-coding RNAs. Following target prioritization based on biological and translational criteria, miR-210 was selected as a priority target. miR210 is consistently overexpressed in multiple human cancers and is a major HIF-1α-regulated microRNA that contributes to a positive feedback loop sustaining HIF-1α-dependent signaling. Method: Starting from a previously reported small-molecule inhibitor of miR-210 with recognized limitations, analogues were designed and synthesized through structure–activity relationship studies. Biological characterization and assessment of drug-like properties guided compound selection. Pre-miR-210 binding, inhibition of Dicer-mediated processing and RNAover-DNA selectivity were investigated in vitro. Pharmacological activity was further characterized in human cancer cell models under different hypoxia-mimetic conditions, including genetic inhibition of the HIF-1α/miR-210 axis. Results: This approach identified miR-210 inhibitors with improved RNA-over-DNA selectivity and favorable drug-likeness. Selected compounds bound pre-miR-210 and inhibited its Dicer-mediated processing in vitro. In cancer cells, representative compounds dose-dependently inhibited HIF-1α-dependent transcriptional responses induced by different hypoxia mimetics. To assess the specificity of this pharmacological response, HIF-1α was genetically inhibited. Loss of HIF-1α-dependent signaling was accompanied by loss of compound activity, supporting pharmacological specificity. We then exploited HIF-1α inhibition to uncouple miR-210 maturation from HIF-1α-driven transcription. Under these conditions, compound treatment reduced mature miR-210 levels, supporting inhibition of miR-210 maturation in a cellular context. Conclusion: Overall, these findings identify selective miR-210 inhibitors as pharmacological tools to investigate miR-210 biology and as chemical tools for further drug discovery. Moreover, the miR-210 program provides a first proof-of-concept for the SMART-C approach, supporting its potential for the discovery and development of small molecules targeting cancerrelevant non-coding RNAs.