MicroRNA-138 Selectively Inhibits DNA Repair Pathway and May Improve Cancer Therapy

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MicroRNAs (miRs) are small non-protein encoding RNAs that post-transcriptionally regulate gene expression by inducing mRNA degradation or translational repression of their targets. The role of miRs in regulating cellular processes such as DNA replication and repair is a subject of intense investigation, particularly as aberrant miR expression has been associated with cancer. As part of a cell-based approach to identify miRs that modulate the DNA repair response, postdoctoral fellow Dr. Yemin Wang and colleagues in the Human Biology Division screened 810 human miR mimics for candidates that altered the accumulation of phosphorylated histone H2AX (γH2AX) in response to ionizing radiation (IR), as γH2AX recruits signaling and repair proteins to sites of DNA damage. They identified two such miRs, miR-138 and miR-542-3p, and discovered that the more potent miR-138 directly targets H2AX mRNA, thereby reducing both H2AX mRNA and H2AX and γH2AX protein expression levels. MiR-138 is highly conserved, highly expressed in brain tissues and originates from 2 genomic precursors (miR-138-1 and miR-138-2), both of which were shown to reduce H2AX expression. Indeed, when Wang *et al.* examined normal brain tissue, 10 glioma cell lines and 26 glioblastoma tissue samples, they observed a tendency of inverse correlations between miR-138 and H2AX expression.

Based on previous findings that H2AX-deficient cells are sensitive to IR and exhibit DNA double-strand break repair defects, the authors investigated whether miR-138 sensitized cells to IR and chemotherapy agents, as both radiotherapy and chemotherapy rely on the induction of DNA damage. They found that overexpression of miR-138 sensitized cells to DNA damaging chemotherapy agents and IR, resulting in a significantly higher number of chromosome breaks and mild defect in homologous recombination repair compared to control cells. Wang *et al.* showed that sensitization was not due to general cellular toxicity, but that miR-138 overexpression did appear to slow down cell growth without significantly affecting cell-cycle distribution. Perhaps it should come as no surprise then, that miR-138 allelic loss and downregulation has also been frequently associated with cancer (e.g., nasopharyngeal cancer, anaplastic thyroid carcinoma, metastatic head and neck squamous cell carcinoma, hepatocellular carcinoma). Therefore, Wang *et al.* propose miR-138 as a

novel cancer therapeutic and have presented a powerful approach to identify other miR-based therapies.

Wang Y, Huang JW, Li M, Cavenee WK, Mitchell PS, Zhou X, Tewari M, Furnari FB, Taniguchi T. 2011. MicroRNA-138 modulates DNA damage response by repressing histone H2AX expression. *Molecular Cancer Research* 9:1100-11.