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Time-course analysis of microRNA-induced mesenchymal-to-epithelial transition underscores the complexity of the underlying molecular processes

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ABSTRACT

Expression levels of the miR-200 family of miRNAs are significantly reduced during the epithelial-to-mesenchymal transition (EMT) and consequent metastasis of ovarian and other cancers. Consistently, ectopic over-expression of miR-200 family miRNAs in mesenchymal-like cells reverses the process by converting treated cells to an epithelial phenotype, thereby reducing invasiveness and increasing sensitivity to chemotherapeutic drugs. To better understand the dynamics and molecular processes underlying miRNA-induced mesenchymal-to mesenchymal transition (MET), a time-course study was conducted where miRNA-induced morphological and molecular changes associated with MET were monitored over a period of 144 hrs. Morphological transition from an elongated mesenchymal-like to a cuboidal epithelial-like phenotype is maximized at 48 hrs with cells returning to the elongated phenotype by 144 hrs. Changes in the expression of >3000 genes, including many previously associated with epithelial-to-mesenchymal transition (EMT), are most pronounced at 48 hrs, and approach starting levels of expression by 144 hrs. The majority of these genes are not direct targets of miR-429. Targeted (siRNA) inhibition of key miR-429 regulated genes previously implicated as drivers of EMT/MET, do not recapitulate miR-429 induced MET indicating that the underlying molecular processes are complex.