miR-342-3p regulates MYC transcriptional activity via direct repression of E2F1 in human lung cancer

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Accumulating evidence indicates that altered miRNA expression is crucially involved in lung cancer development, though scant information is available regarding how MYC, an archetypical oncogene, is regulated by miRNAs, especially via a mechanism involving MYC cofactors. Although various oncogenes have thus far been identified to be altered in various types of lung cancer, MYC is among the most frequently amplified and overexpressed. The MYC gene encodes a transcription factor that regulates a wide variety of genes involved in control of cell growth, proliferation, and apoptotic cell death. The transcriptional activity of MYC is tightly controlled for proper transcriptional regulation through various mechanisms, which include MYC expression itself at both transcriptional and posttranscriptional levels, as well as its interaction with cofactors that functionally cooperate with MYC. Unfortunately, very little is known thus far about how MYC is regulated by miRNAs in lung cancer cells, especially via the latter mechanism involving MYC cofactors.

In this study, we attempted to identify miRNAs involved in regulation of MYC transcriptional activity in lung cancer. To this end, we utilized an integrative approach with combinatorial usage of miRNA and mRNA expression profile datasets of patient tumor tissues, as well as those of MYC-inducible cell lines in vitro. Our results allowed us to identify multiple miRNAs reported as either directly downstream or upstream of MYC, supporting the robustness of our strategy. The former examples included the miR-17-92 cluster, miR-22, miR-26a, miR-30a-3p, and miR-30e-3p, all of which were previously shown to be under MYC-mediated transcriptional regulation, while the latter instances were comprised of let-7, miR-34a and miR-24, which have been reported to directly repress MYC expression via binding to a target site at the 3'UTR of MYC. Intriguingly, our integrative approach also led us to identify miR-342-3p, which we found to be a miRNA indirectly regulating MYC activity via direct inhibition of E2F1, a MYC-cooperating transcription factor. Furthermore, miR-342-3p module activity, which we defined as a gene set reflecting the experimentally substantiated influence of miR-342-3p on mRNA expression, was found to be inversely correlated with MYC activity reflected by MYC module activity in 3 independent datasets of lung adenocarcinoma patients. Our present findings also clearly demonstrate that miR-342-3p plays important roles to inhibit cell cycle progression and proliferation in lung adenocarcinoma cell lines.

Taken together, our integrative approach appears to be useful to elucidate inter-regulatory relationships between miRNAs and protein coding genes of interest, even those present in patient tumor tissues, which remains a challenge to better understand the pathogenesis of this devastating disease.

Loss of immunoproteasomes driven by EMT is associated with immune evasion and poor prognosis in non-small cell lung cancer

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Immunoproteasomes are a specialized form of mult-subunit complexes called proteasomes that degrade intracellular proteins through the ubiquitin-proteasome pathway. It can generate peptides with high specificity for binding onto MHC class I molecules, hence a suitable candidate for CD8+ T cell mediated cytotoxic responses. The expression of the immunoproteasome and its impact on antigen presentation in tumors of epithelial origin is not well established. We have investigated the constitutive and induced expression patterns of immunoproteasome subunits in non-small cell lung cancer (NSCLC) and their consequence on antigen presentation. We also assessed the impact of immunoproteasome expression on survival in early stage NSCLC.