Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

CD24 induces expression of Oncomir miR-21 via Src, and CD24 and Src are both post-transcriptionally downregulated by the tumor suppressor miR-34a

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Cancer is a complex disease that occurs as a consequence of multiple malfunctions in the key regulatory molecular networks. Understanding these networks is essential to combat cancer. In this study, we established novel network of cental players which cause cancer. In a series of colon and breast cancer cell lines, we found that CD24 activates Src, and induces the activation of c-Jun and expression of c-Jun and c-Fos. Thereby, CD24 increases the promoter activity and expression of miR-21, which in turn suppresses expression of Pdcd4 and PTEN (miR-21 targets). Co-transfection of a CD24 expression construct and an siRNA that silences Src showed that CD24-dependent upregulation of miR-21 is mediated by Src. Furthermore, CD24 induced invasion, migration and colony formation is mediated by Src. These data clearly show the importance of Src in the regulation of miR-21 by CD24.

With a bioinformatical approach, we found that CD24 and Src are predicted targets of miR-34a. Consequently, we found that miR-34a post-transcriptionally downregulates CD24 and Src expression, leading to the deactivation of c-Jun, reduced expression of c-Jun and c-Fos, inhibition of miR-21, and upregulation of Pdcd4 and PTEN. Furthermore, miR-34a-mediated inhibition of Src expression reduced colony formation, migration and invasion of colorectal cancer cells. The highlight of this study is that the tumor suppressor microRNA miR-34a inhibits the expression of an important tumor progression microRNA miR-21 by inhibiting CD24 and Src.

Additionally, to show *in vivo* relavance of the novel defined pathway we have screened resected tumor tissues from 26 colorectal patients, which showed significant lower expression of Pdcd4 and miR-34a, and higher expression of CD24, Src and miR-21 compared to the corresponding normal tissues. Moreover, CD24 positively correlated with the amount of Src protein in tumor tissues, and a trend towards an inverse correlation between miR-34a and Src protein levels was also observed. Our results reveal essential players in a complex network that regulates the progression of solid tumors, especially colorectal cancer. These findings therefore suggest to prioritize therapeutic approaches targeted at these molecules for to combat colorectal cancer.