miR-17 ~ 92 activates the canonical NF-κB signaling by targeting TNFAIP3, CYLD and Rnf11 in ABC-DLBCL lymphoma

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Aim/Background: ABC-DLBCL is an aggressive lymphoma characterized by constitutive NF-κB activation, but whether miRNAs dysfunction contributes to this event remains unclear. The purpose of this study is to reveal the correlations between miR-17 ~ 92 and NF-κB signaling in ABC-DLBCL.

Methods: MiRNA array platform was used for informatics and statistical interrelations. Potential miR-17 ~ 92 targets were identified and validated using computational prediction and reporter gene assays. The activity of NF-κB signaling was determined by reporter assays. The expression and regulation of miR-17 ~ 92 were studied using real-time quantitative PCR and Western blotting. Cell proliferation, cycle and apoptosis were detected by MTS and flow cytometry. Ubiquitination was studied by co-immunoprecipitation.

Results: The interactions between NF-κB signaling and miR-17 ~ 92 existed in ABC-DLBCL patients. Several important NF-κB negative regulators including TNFAIP3, CYLD and Rnf11 were predicted and validated to be targets of miR-17 ~ 92. Knock-down of miR-17 ~ 92 could suppress NF-κB activity and elevate targets protein expression in 293T cells. Furthermore, overexpression of miR-17 ~ 92 could also decrease targets protein level in ABC-DLBCL cells. Conditional overexpression of miR-17 ~ 92 could promote cells growth, accelerate G1/G0 phase to S phase transition, and suppress NF-κB inhibitor-induced apoptosis. Conversely, knock-down of miR-17 ~ 92 could inhibit cells growth and sensitize cells to NF-κB inhibitor-induced apoptosis. MiR-17 ~ 92 could induce IκB-α and NF-κB p65 phosphorylation and aberrant expression of NF-κB transcriptional target genes. However, miR-17 ~ 92 did not regulate NF-κB p52/p100 phosphorylation. Overexpression of miR-17 ~ 92 enhanced K63-linked ubiquitination and reduced K48-linked ubiquitination of RIP1. High expression level of miR-17 ~ 92 was associated with poorer survival in ABC-DLBCL patients.

Conclusions: Our results uncovered a novel mechanism for canonical but not non-canonical NF-κB pathway by modulation of miR-17 ~ 92 in ABC-DLBCL, and suggested that targeting miR-17 ~ 92 might be novel bio-therapeutic strategies for ABC-DLBCL patients.

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