Yun Ji et al., Madridge J Cancer Stud Res. 2017
http://dx.doi.org/10.18689/2640-5180.a2.004

Enhancing the efficacy of T cell-based immunotherapies using miR-155 engineered tumor-specific CD8$^+$ T cells

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Lymphodepleting regimens are employed prior to adoptive immunotherapy to augment the antitumor efficacy of transferred T cells by removing endogenous homeostatic 'cytokine sinks'. These conditioning modalities, however, are often associated with severe toxicities. We found that miR-155 enabled B16 melanoma-specific CD8$^+$ T cells to mediate profound antitumor responses in lymphoreplete hosts that were not potentiated by immune-ablation. miR-155 enhanced T cell responsiveness to limited amounts of homeostatic γc cytokines by restraining the expression of the Akt inhibitor Ship1 and multiple negative regulators of Stat5, such as Socs1 and Ptpn2, resulting in delayed cellular contraction and sustained cytokine production. To translate these findings into new clinical trials, we tested whether the overexpression of miR-155 in human T cells would enhance the antitumor efficacy of CD19-specific chimeric antigen receptor (CD19-CAR) cells against systemic acute lymphoblastic leukemia xenografts. As a safety measure, the suicide gene, inducible caspase 9, was included in the miR-155 construct. We found that miR-155 also augmented the antitumor efficacy of T cells in this xenograft tumor model. Recapitulating our findings in mouse cells, human T lymphocytes overexpressing miR-155 showed increased Stat5 signaling and enhanced survival. Our results indicate that overexpression of miR-155 in tumor-specific T cells can be employed to increase the effectiveness of adoptive immunotherapies in a cell intrinsic manner without the need of life-threatening, lymphodepleting maneuvers.

Biography:

Dr. Yun Ji obtained her Ph.D. from Iowa State University in 2004. Following a postdoctoral fellowship at Georgetown University she joined the National Cancer Institute in 2007. In 2016 Dr. Ji was appointed as a Staff Scientist at the Experimental Transplantation and Immunology Branch in the National Cancer Institute.Dr. Ji is interested in the mechanism of CD8$^+$ T cell development and differentiation. Her research focuses on the identification and characterization of key transcription factors, miRNAs, and epigenetic modulators essential for CD8$^+$ T cell activation, differentiation, and function, with a goal of improving T cell-based immunotherapy against cancer.