**ABSTRACT**

MicroRNAs expressed in adipocytes are involved in transcriptional regulation of target mRNAs in obesity, but miRNAs critically involved in this process is not well characterized. Here, we identified upregulation of miR-221-3p and miR-222-3p in the white adipose tissues in C57BL/6 mice fed with high fat-high sucrose (HFHS) chow by RNA sequencing. *Mir221* and *Mir222* are paralogous genes and share the common seed sequence and *Mir221/222AdipoKO* mice fed with HFHS chow demonstrated resistance to the development of obesity compared with *Mir221/222*$^{flox/y}$. *Ddit4* is a direct target of *Mir221* and *Mir222*, and the upregulation of *Ddit4* in *Mir221/222AdipoKO* was associated with the suppression of TSC2 (tuberous sclerosis complex 2)/mammalian target of rapamycin complex 1 (mTORC1)/S6K (ribosomal protein S6 kinase) pathway. The inhibition of miR-221-3p and miR-222-3p linked to reduced adipogenesis, and it may be a potential candidate for miRNA-based therapy.