Oculopharyngeal muscular dystrophy (OPMD) is caused by a small expansion of a short polyalanine (polyAla) tract in the poly(A)-binding protein nuclear 1 protein (PABPN1). Despite the monogenic nature of OPMD, no treatment is currently available. Here we report an RNA replacement strategy that has therapeutic potential in cell and C. elegans OPMD models. We develop selective microRNAs (MicroRNAs) against PABPN1, and we report that MicroRNAs and our previously developed hammerhead ribozymes (hhRzs) are capable of reducing the expression of both the mRNA and protein levels of PABPN1 by as much as 90%. Since OPMD derives from a very small expansion of GCG within the polyAla tract, our hhRz and MicroRNA molecules cannot distinguish between the wild-type and mutant mRNAs of PABPN1. Therefore, we designed an optimized-codon wild-type PABPN1 (opt-PABPN1) that is resistant to cleavage by hhRzs and MicroRNAs. Co-expression of opt-PABPN1 with either our hhRzs or MicroRNAs restored the level of PABPN1, concomitantly with a reduction in expanded PABPN1-associated cell death in a stable C2C12 OPMD model. Interestingly, knockdown of the PABPN1 by selective hhRzs in the C. elegans OPMD model significantly improved the motility of the PABPN1-13Ala worms. Taken together, RNA replacement therapy represents an exciting approach for OPMD treatment [1)].

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