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Abstract	:	**Purpose:** Controlling small interfering RNA (siRNA) activity by external stimuli is useful to exert a selective therapeutic effect at the target site. This study aims to develop a technology to control siRNA activity in a thermo-responsive manner, which can be utilized even at temperatures close to body temperature. **Methods:** siRNA was conjugated with a thermo-responsive copolymer that was synthesized by copolymerization of N-isopropylacrylamide (NIPAAm) and hydrophilic N,N-dimethylacrylamide (DMAA) to permit thermally controlled interaction between siRNA and an intracellular gene silencing-related protein by utilizing the coil-to-globule phase transition of the copolymer. The composition of the copolymer was fine-tuned to obtain lower critical solution temperature (LCST) around body temperature, and the phase transition behavior was evaluated. The cellular uptake and gene silencing efficiency of the copolymer-siRNA conjugates were then investigated in cultured cells. **Results:** The siRNA conjugated with the copolymer with LCST of 38.0°C exhibited ~ 11.5 nm of the hydrodynamic diameter at 37°C and ~ 9.8 nm of the diameter at 41°C, indicating the coil-globule transition above the LCST. In line with this LCST behavior, its cellular uptake and gene silencing efficiency were enhanced when the temperature was increased from 37°C to 41°C.