Decoding the gene- and genome-regulatory function of the non-coding RNA gene *CISTR-ACT*

Organisms regulate cell size and shape to function efficiently[1]. Although aberrant cell morphology and cytoskeletal organization have been associated with cancer, neurological disorders, and ageing[2,3], gene-regulatory mechanisms controlling cell size remain unknown. Using *in vitro* and *in vivo* perturbations, I reveal that the lncRNA *CISTR-ACT* (*CISTR*)[4,5] provides the genetic basis for cell size regulation across cell types and species. *CISTR* controls disease-related neuronal cell size, and is a causal gene for red blood cell size, which is indicative of various pathologies in routine blood counts. To disentangle the complexity of lncRNA functions, I dissected *CISTR-ACT*'s DNA- and RNA-encoded mechanisms. *CISTR* acts mostly *in trans* at the DNA and RNA levels to regulate cytoskeletal gene expression, ultimately affecting cell size. *CISTR*'s *trans*-regulation of cell morphogenesis genes is facilitated by its direct interaction with the transcription factor FOSL2 at the RNA level, and regulation of *FOSL2* gene expression at the DNA level. This study exemplifies how a functionally conserved lncRNA regulates cell size across species with multiple modes of action.

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