

## Distinct Classes of Chromatin Loops Revealed by Deletion of an RNA-Binding Region in CTCF.

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### Public Summary:

Mammalian genomes are folded into topologically associating domains (TADs), consisting of chromatin loops anchored by CTCF and cohesin. Some loops are cell-type specific. Here we asked whether CTCF loops are established by a universal or locus-specific mechanism. Investigating the molecular determinants of CTCF clustering, we found that CTCF self-association in vitro is RNase sensitive and that an internal RNA-binding region (RBRI) mediates CTCF clustering and RNA interaction in vivo. Strikingly, deleting the RBRI impairs about half of all chromatin loops in mESCs and causes deregulation of gene expression. Disrupted loop formation correlates with diminished clustering and chromatin binding of RBRI mutant CTCF, which in turn results in a failure to halt cohesin-mediated extrusion. Thus, CTCF loops fall into at least two classes: RBRI-independent and RBRI-dependent loops. We speculate that evidence for RBRI-dependent loops may provide a molecular mechanism for establishing cell-specific CTCF loops, potentially regulated by RNA(s) or other RBRI-interacting partners.

### Scientific Abstract:

Mammalian genomes are folded into topologically associating domains (TADs), consisting of chromatin loops anchored by CTCF and cohesin. Some loops are cell-type specific. Here we asked whether CTCF loops are established by a universal or locus-specific mechanism. Investigating the molecular determinants of CTCF clustering, we found that CTCF self-association in vitro is RNase sensitive and that an internal RNA-binding region (RBRI) mediates CTCF clustering and RNA interaction in vivo. Strikingly, deleting the RBRI impairs about half of all chromatin loops in mESCs and causes deregulation of gene expression. Disrupted loop formation correlates with diminished clustering and chromatin binding of RBRI mutant CTCF, which in turn results in a failure to halt cohesin-mediated extrusion. Thus, CTCF loops fall into at least two classes: RBRI-independent and RBRI-dependent loops. We speculate that evidence for RBRI-dependent loops may provide a molecular mechanism for establishing cell-specific CTCF loops, potentially regulated by RNA(s) or other RBRI-interacting partners.

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