The Xist lncRNA exploits three-dimensional genome architecture to spread across the X chromosome.

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Public Summary:
Large noncoding RNAs (lncRNAs) are increasingly appreciated to play important roles in the cell. A number of lncRNAs act to target chromatin regulatory complexes to their sites of action. Here we found that the mouse Xist lncRNA, which initiates X-chromosome inactivation, spreads from its site of transcription to distant sites on the X chromosome purely through their close three-dimensional proximity to the Xist gene. upon distal spread, Xist initially localizes to the periphery of active genes on the X chromosome but gradually spread across them using its A-repeat domain, until the Xist RNA bound broadly across the inactive X chromosome in differentiated female cells. Our work reveals an important mechanism that explains how Xist RNA initiates X chromosome inactivation.

Scientific Abstract:
Many large noncoding RNAs (lncRNAs) regulate chromatin, but the mechanisms by which they localize to genomic targets remain unexplored. We investigated the localization mechanisms of the Xist lncRNA during X-chromosome inactivation (XCI), a paradigm of lncRNA-mediated chromatin regulation. During the maintenance of XCI, Xist binds broadly across the X chromosome. During initiation of XCI, Xist initially transfers to distal regions across the X chromosome that are not defined by specific sequences. Instead, Xist identifies these regions by exploiting the three-dimensional conformation of the X chromosome. Xist requires its silencing domain to spread across actively transcribed regions and thereby access the entire chromosome. These findings suggest a model in which Xist coats the X chromosome by searching in three dimensions, modifying chromosome structure, and spreading to newly accessible locations.