How chromosomes meet in the dark -- Switch that turns on X chromosome matchmaking

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A research group lead by scientists at the University of Warwick has discovered the trigger that pulls together X chromosomes in female cells at a crucial stage of embryo development. Their discovery could also provide new insights into how other similar chromosomes spontaneously recognize each other and are bound together at key parts of analogous cell processes. This is an important mechanism as the binding togetgher of too many of too few of a particular chromosome can cause a number of medical conditions such as Down's Syndrome or Turner's Syndrome.

In our cells most genes are expressed from both types of each chromosome linked gene, but the most notable exception to this rule are X-linked genes in female mammals. During embryo development, in a step necessary to survival, one of the X chromosomes is silenced in each female cell to ensure that the levels of X-derived products are equalized in XX females and XY males, via a process known as X-Chromosome Inactivation (XCI). Recent discoveries have revealed that for that stage in the process to happen the X chromosomes have to quickly pair off (or colocalize) in a way that allows each part of those pairs of X chromosomes to be very close together and be aligned in a particular way. Failure to achieve this close physical colocalization of the two X chromosomes will lead to XCI failure and cell death.

Chromosome colocalization events are common in cells. A prominent example being mesiosis: for sexual reproduction to succeed in producing viable cells all of the homologous chromosomes in the process have to, almost simultaneously, bind together in pairs.

Yet until now the mechanisms of chromosome self-recognition and colocalization remain deeply mysterious. Researchers have had no clear understanding of how the X chromosomes actually suddenly pair off so quickly and consistently allowing this to happen.

Dr Mario Nicodemi, from the Department of Physics at the University of Warwick and Dr Antonio Scialdone from the University of Naples have uncovered exactly how this process is switched on and published their findings in *PLOS* in a paper entitled Mechanics and Dynamics of X-Chromosome Pairing at X Inactivation.

University of Warwick physicist Dr Mario Nicodemi, has recently published research on just how one X chromosome is able to silence another as part of the XCI process. However for that stage in the process to happen the X chromosomes have to quickly pair off (colocalization) in a way that allows each part of those pairs of X chromosomes to be very close together and aligned in a particular way.

In this latest paper the Warwick and Naples researchers looked at a particular "DNA specific binding molecule" including a protein known as CTCF that seemed to play a role in pairing off of X chromosomes. In the past when other researchers had mutated CTCF, or deleted the sections of DNA that the CTCF bound to, they found that it disrupted the pairing up or colocalization of the X Chromosomes. Clearly then CTCF had a role to play in the process but it was not obvious how it did so with the precise timing and speed required.

Obviously sheer chance meant that CTCFs would randomly encounter and bind to an X chromosome. There was an even smaller probability then that such a pairing would then encounter another X chromosome and bind to it as well - the CTCF would effectively then force colocalization by this unlikely double chance encounter, forming a chemical bridge between the two chromosomes. However such a gradual

chance based occurrence did not fit with the speed and efficiency of how the actual process of colocalization of the X chromosomes really happened during XCI.

The Warwick lead research team created a model of the interaction between X chromosomes and CTCF proteins using polymer physics. They looked at models of chains of polymer beads that had almost the same number of chemical binding sites on their beads as the number of known CTCF binding sites in the key part of X chromosomes.

Their simulations using this system found that in that a key tipping point was reached if the amount of CTCF present in the system reached a critical threshold - a concentration of around 0.1 mg per millilitre or less. Below that point very little happened. Random bindings did occur but not often enough or quickly enough to build the sort of momentum necessary to produce the total and sudden of X Chromosomes colocalization required for successful X inactivation.

However once the threshold concentration is reached it produces a tipping point or thermodynamic switch. That particular concentration of CTCF was suddenly enough to ensure that the CTCF proteins could encounter and bind in quick succession to two X chromosomes forming a chemical bridge between them and almost instantly bringing about colocalization of the X chromosomes and making embryo development successful.

The researchers believe that this newly discovered "thermodynamic switch" not only explains how X chromosomes pair up during meiosis but also apply to a range of other cell processes that involve the recognition and pairing of DNA sequences including other homologous chromosomes. This is of particular importance, e.g., at meiosis, as the binding of togetgher of too many or too few of a particular chromosome can cause a number of medical conditions.

Source: University of Warwick