11-4-2019

Homolog Pairing at the Push of a Button

Jack R. Bateman
Bowdoin College

Judith A. Kassis
National Institute of Child Health and Human Development (NICHD)

CellPress

Homolog Pairing at the Push of a Button

Jack R. Bateman[1,*] and Judith A. Kassis[2,*]
[1]Biology Department, Bowdoin College, Brunswick, ME 04011, USA
[2]*Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892, USA
*Correspondence: jbateman@bowdoin.edu (J.R.B.), jkassis@mail.nih.gov (J.A.K.)
https://doi.org/10.1016/j.devcel.2019.10.014

Homologous chromosomes pair in somatic cells in *Drosophila*, but how this occurs is poorly understood. In this issue of *Developmental Cell*, Viets et al. (2019) show that proteins and chromatin structure mediate pairing and argue against a DNA sequence-based mechanism.

Eukaryotic genomes are highly organized within the interphase nucleus, with chromosomes occupying distinct territories and folding into predictable domains along their lengths (Szabo et al., 2019). In *Drosophila* and other dipterans, an additional layer of organization exists wherein homologous chromosomes are intimately paired from end to end in most somatic cells, a property called somatic homolog pairing (Joyce et al., 2016). While several past studies have examined and characterized somatic homolog pairing, the molecular mechanisms that allow homologous chromosomes to identify one another and physically pair remain poorly understood. Viets et al. (2019) shed light on this question by identifying and characterizing "buttons" as discrete chromosomal segments that have a high capacity for homolog pairing.

Two general models can be used to frame the problem of how homologous chromosomes identify one another. In the first, the DNA sequence itself could be read by an unknown mechanism—in this case, pairing activity would be continuous and additive, predicting that any long stretch of DNA homology would pair more easily than a shorter region of homology. In an alternative model, pairing could be mediated by distinct features of chromatin structure, such as patterns of local DNA conformation and/or bound proteins. In this discontinuous model, certain genomic regions may have a higher capacity to pair than others and could therefore serve as molecular buttons to bring two chromosomes together. Early studies on somatic pairing in *Drosophila* embryos showed that some regions of the genome pair earlier than others, supporting a discontinuous model (Fung et al., 1998).

To explore the mechanisms driving pairing in *Drosophila*, Viets et al. (2019) designed an ectopic pairing strategy that employed large transgenes encoding duplicate genomic segments inserted at an ectopic genomic location. If the genomic segment carried by a transgene has the capacity to mediate somatic homolog pairing, it may pair with the endogenous locus that shares homology with that transgene, which can be detected via DNA-fluorescence *in situ* hybridization (DNA-FISH) and three-dimensional imaging. Alternatively, transgenes that are not able to mediate pairing would not pair with their endogenous counterparts. The authors tested dozens of different transgenes in this assay and found that some transgenes have the capacity to pair with their endogenous counterparts, whereas other transgenes do not. Notably, all of the transgenes were of similar size, with no significant difference in transgene length between those that paired with their endogenous location and those that did not. Thus, the data support that the capacity to pair in this assay is confined to discrete genomic segments, consistent with a button model for somatic homolog pairing.

What, then, differentiates transgenes that drive pairing from those that do so poorly or not at all? Viets et al. compared genomic features of transgenes from these two categories and found significant differences in binding of specific insulator proteins and their associated co-factors (Matzat and Lei, 2014). Moreover, they also found that the two categories of transgene differ significantly in their total clusters of unique insulator binding sites, with pairing transgenes having more clusters, leading the authors to propose a potential "insulator code" that could be a component of a unique address for each homologous button. Perhaps just as interesting is the list of genomic features that did not differ significantly between pairing and non-pairing transgenes, including transcriptional activity, Polycomb group binding sites, and patterns of histone modifications.

In addition to assessing bound proteins, Viets et al. analyzed DNA topology in their pairing and non-pairing transgenic sequences. Surprisingly, they found that pairing transgenes were more likely to encompass regions of chromatin folding commonly referred to as topologically associated domains (TADs), a major component of three-dimensional genome architecture (Szabo et al., 2019). The authors further explored a potential role for TAD structure by comparing the pairing capacity of several transgenes derived from overlapping genomic segments and found that only the transgene with a complete TAD could drive ectopic pairing. However, not all transgenes that paired encompassed an entire TAD, and some transgenes with complete TADs did not promote ectopic pairing, suggesting that TAD structures could facilitate pairing but may not be entirely instructive.

Finally, the authors assessed a role for pairing in influencing gene expression. Classical studies have established that when chromosomes are paired, regulatory DNA present on one chromosome can act in *trans* on the homologous chromosome, a phenomenon known as transvection (Lewis, 1954). Viets et al. employed their ectopic pairing assay in a classic necessary/sufficient analysis of the *spineless* gene and showed that, while pairing was essential for transvection to occur, not all pairing transgenes supported transvection, demonstrating that close proximity is not sufficient for regulatory regions to act in *trans*. Interestingly, the presence of a single insulator site could confer the ability to support transvection to a paired transgene, further implicating insulators as important regulators of *trans*-interactions,

in agreement with other recent reports (Lim et al., 2018; Piwko et al., 2019).

The work by Viets et al. demonstrates a remarkable ability of large transgenes to find their homologous regions on different chromosomes, seemingly defying the chromosome territory structure of the nucleus as they do so. Prior analyses of chromosome territories have been largely confined to fixed cells, presenting a static picture of the general positions of entire chromosomes—the study by Viets et al. may indicate that territories are more fluid than they seem and that mixing between territories is not unusual. Analyses of chromosome positions in living cells may help to shed further light on the potential dynamic nature of interphase chromosome biology. Furthermore, Viets et al. demonstrate a cell-type specificity to their ectopic pairing assay, suggesting that pairing can be dramatically influenced by the protein components and/or cell-cycle state of a tissue. Exploration of button activity in varying cell types could help elucidate crucial differences between cells that support ectopic pairing versus those that do not, perhaps helping us to better understand why somatic homolog pairing is common in dipterans but rare in other species.

Somatic homolog pairing was first described over a century ago (Stevens, 1908), and yet this amazing puzzle still defiantly resists a precise molecular explanation. The work by Viets et al. (2019) strongly implicates features such as insulators and TADs as key components of a pairing mechanism, providing clues to aid in solving this long-standing question.

REFERENCES

Fung, J.C., Marshall, W.F., Dernburg, A., Agard, D.A., and Sedat, J.W. (1998). Homologous chromosome pairing in *Drosophila melanogaster* proceeds through multiple independent initiations. J. Cell Biol. *141*, 5–20.

Joyce, E.F., Erceg, J., and Wu, C.T. (2016). Pairing and anti-pairing: a balancing act in the diploid genome. Curr. Opin. Genet. Dev. *37*, 119–128.

Lewis, E.B. (1954). The theory and application of a new method of detecting chromosomal rearrangements in Drosophila melanogaster. Am. Nat. *88*, 225.

Lim, B., Heist, T., Levine, M., and Fukaya, T. (2018). Visualization of transvection in living Drosophila embryos. Mol. Cell *70*, 287–296.

Matzat, L.H., and Lei, E.P. (2014). Surviving an identity crisis: a revised view of chromatin insulators in the genomics era. Biochim. Biophys. Acta *1839*, 203–214.

Piwko, P., Vitsaki, I., Livadaras, I., and Delidakis, C. (2019). The role of insulators in transgene transvection in *Drosophila*. Genetics *212*, 489–508.

Stevens, N.M. (1908). A study of the germ cells of certain diptera, with reference to the heterochromosomes and the phenomena of synapsis. J. Exp. Zool. *5*, 359–374.

Szabo, Q., Bantignies, F., and Cavalli, G. (2019). Principles of genome folding into topologically associating domains. Sci. Adv. *5*, eaaw1668.

Viets, K., Sauria, M.E.G., Chernoff, C., Rodriguez Viales, R., Echterling, M., Anderson, C., Tran, S., Dove, A., Goyal, R., Voortman, L., et al. (2019). Characterization of button loci that promote homologous chromosome pairing and cell-type-specific interchromosomal gene regulation. Dev. Cell *51*, this issue, 341–356.

Lifting Each Other Up: Epidermal Stem Cells in Tissue Homeostasis

Valerie Horsley[1,*]
[1]Department of Molecular, Cellular, and Developmental Biology and Department of Dermatology, Yale University, 219 Prospect Street, New Haven, CT 06520, USA
*Correspondence: valerie.horsley@yale.edu
https://doi.org/10.1016/j.devcel.2019.10.013

Multiple stem cells maintain and repair tissues, yet how they communicate is not well understood. In this issue of *Developmental Cell*, Veniaminova et al. (2019) report that each sebaceous gland is maintained by local stem cells and that Notch signaling regulates multiple aspects of their function, revealing tissue homeostasis mechanisms.

Stem cells are essential for tissue homeostasis and repair after injury. The epidermis provides an excellent model to understand stem cell regulation since multiple independent stem cell populations have been identified and shown to maintain the interfollicular epidermis, the outermost layer of the skin, and epidermal appendages, such as the hair follicle and the sebaceous gland (SG), the oil producing gland of the skin (Goldstein and Horsley, 2012). While it is clear that distinct stem cell populations in the epidermis can communicate and supply cells to replenish each other in extreme crisis events like tissue injury (Levy et al., 2007), the mechanisms by which this occurs during tissue homeostasis and with age are not well understood.

In the past several years, several groups have identified stem cells that can support the SG, which reside within the gland (Feldman et al., 2019; Horsley et al., 2006), in the upper hair follicle region (Jensen et al., 2009), and in the bulge region of the hair follicle (Frances and Niemann, 2012), which has generated confusion in the field regarding the source of stem cells for the SG (Kretzschmar et al., 2014). Interestingly, many mutant mice that impact SG homeostasis (for example, see Karnik et al., 2009) also possess defects in the epidermis and hair follicles, suggesting that SG stem cells may support these other