Researchers are inventing and honing the technologies to provide increasingly clear pictures of the organization of the nucleus. One driving issue is the role of chromosome arrangement in gene expression. The intractable nature of this question lies in the fact that it is not yet possible to extract a “chromosome arrangement” and assay it for function. Instead, it must be observed in situ and correlated with patterns of gene expression. Today, as exemplified by Hiraoka et al. (1993) in this issue of the Journal of Cell Biology, as well as by others (for example, Selig et al., 1992; reviewed by Manuelidis, 1990; Trask, 1991; Jackson, 1991), we are equipped with a level of resolution that allows the positioning of each gene on a temporal and spatial map of the nucleus.

Hiraoka et al. (1993) focus on that magical moment in Drosophila development when the syncytial blastoderm undergoes cellularization and the embryo launches itself full force into zygotic gene expression. By following the two histone loci situated on their homologous chromosomes, the authors demonstrate two striking changes in chromosome arrangement: (a) the loci pair, implying the onset of pairing for all homologous chromosomes, and (b) the loci move from the center of the nucleus toward the apically positioned centromeres, apparently due to the condensation of heterochromatin flanking the centromere. These observations beckon us to that phenomenon called transvection and the possibility that chromosome structure can drive developmental decisions.

**Transvection**

For nearly 50 years after homologous chromosomes were found to be paired in the somatic cells of Dipteran insects such as Drosophila, researchers mused over the possibility that pairing influences gene expression. In 1954, Lewis crystallized a large body of work into the term “transvection,” implying that yes, gene expression can be altered depending upon whether or not genes are paired with their homologue. He illustrated transvection by showing how complementation is negated if the two alleles are not allowed to pair. They propose that transcription factors that have been attracted to the y<sup>106</sup> enhancers act upon the y<sup>2</sup> promoter by tracking or DNA looping. Similar models evoking looping and/or the intermolecular action of bound or free regulatory factors have been raised to explain transvection at other loci (see reviews).

Transvection is also involved in the interaction of the zeste<sup>1</sup> (z<sup>1</sup>)<sup>1</sup> mutation and the white gene (reviewed by Wu and Goldberg, 1989; Pirotta, 1991; also Chen et al., 1992; Laney and Biggin, 1992). The white gene is important for the red pigmentation of the eyes of the fly. When a white gene is paired with another white gene, it can be repressed in a mutant z<sup>1</sup> background such that the eyes become yellow. An unpaired white gene escapes repression. The zeste protein can bind DNA, alter transcription, as well as self-aggregate. This has led to the suggestion that the mutant z<sup>1</sup> protein represses by binding white and then aggregating to an excessive degree, perhaps doing so more efficiently when white genes are paired.

Mutations of zeste affect three other loci that exhibit transvection effects, although these loci differ in their responses to the different kinds of zeste mutations (reviewed by Tartof and Henikoff, 1991). Zeste protein has therefore been proposed to act generally, holding DNA segments together either intramolecularly during looping or intermolecularly during transvection. These ideas are being tested (reviewed by Pirotta, 1991; also Qian et al., 1992).

Is it possible that the paired state of genes plays a dynamic role in regulation? For example, a gene might be regulated by being switched between two states (Fig. 2): (a) the linearly locked state where the accessibility of DNA to

---

1. Abbreviations used in this paper: Psc, Posterior sex comb; z<sup>1</sup>, zeste<sup>1</sup>.
regulatory factors is reduced and enhancers are locked away from the promoter, and (b) the looped state where intramolecular looping can stimulate expression. In this view, mutant z' protein represses paired white genes by restraining them in the linearly locked state, while an unpaired white gene escapes repression because it cannot be linearly locked. The different responses of loci to the various types of zeste gene escapes repression because it cannot be linearly locked.

**Does Transvection Occur Outside Drosophila?**

The larger phenomenon that transvection represents, communication among alleles within a single organism, has evolved mechanisms to prevent rampant communication between paired homologues. This view is consistent with the benign effects of rearrangements and predicts that transvection will not be apparent unless the blockade is removed by, for example, specific kinds of mutations. Transvection at yellow is consistent with this proposal. Geyer et al. (1990) found that alleles with a dysfunctional promoter are able to complement y² while those that disrupt yellow posttranscriptionally fail. Apparently, cis activity of yellow enhancers precludes their action in trans.

This train of thought leads us to ask why transvection exists at all. The trivial response is that we are mistaken and have failed to find the circumstances under which it is required. Alternatively, transvection may exist because it confers advantages by, for example, permitting complementation that is otherwise not possible (also Zachar et al., 1985; Monk, 1990). Finally, transvection may exist because it uses factors that participate in a mechanism that is essential and also involves gene pairing. In fact, all genes of all organisms experience pairing at least once per cell cycle. This occurs when they pass through the replication fork and are not only near their replicated sister but are exchanging information with it. Such proximity has also been proposed to mediate replication control (Roberts and Weintraub, 1986; Abeles and Austin, 1991; Kittell and Helinski, 1991). Is it possible that some molecules of the replication machinery moonlight as modulators of transvection outside the confines of the replication fork?

Gene pairing also occurs in Drosophila tissues that harbor polytene chromosomes or undergo gene amplification. As proposed by Ashburner (1977), transvection could be the reenactment between homologues of the essential process that assures the uniform activation of genes within a single polytenized chromosome.

**When and Where Does the Critical Pairing Event Occur?**

While many models propose the crucial pairing event to occur at transcription, other possibilities should be kept in mind when new cases of transvection are being considered. For instance, the evidence for nuclear compartmentalization (for example, see Carter et al., 1991; Leonhardt et al., 1992 and references within; reviewed by Manuelidis, 1990; Jackson, 1991) and the restriction of transcripts to nuclear "tracks" (Xing and Lawrence, 1991) lend plausibility to a proposal that transvection can occur posttranscriptionally by trans-splicing (Judd, 1979). If transcripts are clustered in the nucleus, they will enter the cytoplasm as a cluster, and subsequent translation may then result in a local high concentration of product in the cytoplasm, or in the nucleus if the proteins are shuttled back. If the activity of the products is concentration dependent, the consequence of homologue pairing may be realized only posttranslationally.

The critical pairing event may also occur before transcription if the paired, or unpaired, state can be imprinted such that when genes express themselves later, they do so with the memory of having been paired or not. For example, transvection may occur at the time of replication. If pairing of homologous genes results in paired replication forks, then the side by side arrangement of two replication machineries may
permit the cross-feeding of information from one replication fork to another in a way that allows factors, base modifications, or chromatin structure to be transferred from one replicating gene to its homologue, or to be coordinately determined by them. Because imprinting, however accomplished, could endure cycles of replication, the consequences of transvection might persist long after the critical pairing event, as has been proposed by Sabi and Laird (1992).

Zachar et al. (1983) also focus on events before transcription and propose that pairing functions to colocalize genes to the proper nuclear compartment. If diploidy or multigene families impose constraints on compartmentalization, somatic pairing certainly would be an elegant solution. With the technologies pioneered by Hiraoka et al. (1993) and others, it should now be possible to determine whether, in the absence of somatic pairing, homologous genes are drawn to the same compartment by other means and are therefore effectively paired, or whether compartments are duplicated. Alternatively, genes may be imprinted by passage through a compartment so that there is no need for homologues to reside simultaneously in one.

Chromatin Proteins

Because transvection causes genes to be modulated by the proximity of their homologues, it can be used to identify loci in Drosophila that establish chromatin structure. Thus far, two genes that can be mutated to become modifiers of z′ eye color have been found to encode chromatin proteins. These are Posterior sex combs (Psc) and Suppressor 2 of zeste [Su(z)2]. The two genes share a region of homology which is also conserved in mammals, highlighting the implication of these studies for a general understanding of chromatin (reviewed by Pignotta, 1991; van Lohuizen et al., 1991; Brunk et al., 1991; Martin and Adler, 1993).

Psc also belongs to a class of homeotic genes called the Polycomb group, which regulates two gene complexes, bithorax and Antennapedia. Both these complexes are graced with transvection (Lewis, 1954; Pattatucci and Kaufman, 1991). Two Polycomb group genes in addition to Psc encode proteins that act at the level of chromatin. These are Polycomb (Pc) and polyhomeotic (ph). It now appears that the products of Psc, Su(z)2, Pc, and ph work in concert to establish chromatin structure (Franke et al., 1992 and references within; Martin and Adler, 1993).

Enhancer of zeste [E(z)] also falls in the overlap of the modifiers of z′ eye color and the Polycomb group (Jones and Gelbart, 1990; Phillips and Shearn, 1990). E(z) mutant tissues that should be undergoing cell proliferation show few and abnormal mitotic figures, underlining the possibility that proteins mediating transvection may participate in other whole chromosome processes at the level of chromatin. These processes might include chromosome condensation, segregation, replication, recombination, stability, amplification, and dosage compensation.

The Heterochromatin Connection

When euchromatic genes are rearranged to be near heterochromatin, they frequently show variegated expression. The opposite is also true. Heterochromatic genes can varigate when rearranged to lie near euchromatin (reviewed by Spradling and Karpen, 1990; Reuter and Spierer, 1992). Explanations for this position-effect variegation have invoked the spreading of chromatin or other structures in cis across the heterochromatin/euchromatin boundary. Reminiscent of transvection, spreading in trans between paired homologues (reviewed by Tartof and Henikoff, 1991), or even between nonhomologous chromosome segments (Wakimoto and Hearn, 1990) has also been invoked.

Numerous enhancers and suppressors of position-effect variegation exist, and several identify members of the Polycomb group or another class of homeotic genes called the trithorax group (reviewed by Paro, 1990; Reuter and Spierer, 1992). Once again, Psc falls into the overlap (D. A. Sinclair, N. J. Clegg, T. A. Grigliatti, and H. W. Brock, manuscript submitted for publication). The similarities between the modifiers of position-effect variegation and the Polycomb group genes are further emphasized by a region of homology that is shared between the products of Pc and Su(var)205, a modifier encoding the heterochromatin-associated protein HP1. This homology is conserved in plants and mammals as well (Franke et al., 1992 and references within).

The biology of transvection, chromatin, and position-effect variegation are drawing together. In this light, it is exciting that Hiraoka et al. (1993) find homologous chromosomes initiating pairing at the same time that heterochromatin becomes condensed. The appearance of heterochromatin at the syncytial/cellular blastoderm transition has prompted researchers to ask whether such a structural change may play a role in gene regulation (Pimpinelli et al., 1985). Now researchers can further muse over the potential implications of the coincidence of two major changes in chromosome structure at this critical time in development.

The author thanks her generous colleagues, in particular George Church and Vince Pignotta, for years of inspirational conversations on transvection. In the interest of brevity, many primary articles were not cited, and apologies are extended to the authors.

Received for publication 6 November 1992 and in revised form 24 November 1992.

References


