trithorax and the regulation of homeotic gene expression in Drosophila: a historical perspective

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ABSTRACT Animals homozygous for a spontaneously arising allele of the trithorax (trx) gene exhibit highly variegated homeotic transformations of their thoracic and abdominal segments. This paper retraces the sometimes tortuous history of the analysis of trx function, from the fortuitous recovery of the first trx allele, to the present understanding that trx encodes a highly conserved chromatin binding protein that is required to maintain the expression of the Antennapedia and Bithorax complex genes.

KEY WORDS: cell-heredity, trithorax, homeotic, Drosophila

Introduction

Exactly twenty years ago I had the good fortune to isolate a spontaneous allele of the Drosophila gene that I subsequently named trithorax (trx). This event not only provided me with the basis for my doctoral thesis but more significantly gave me an opportunity, early in my career, to meet and discuss my research with Antonio García-Bellido. Coincidentally, the experiment that led to the serendipitous recovery of trx – although unrelated to the analysis of the regulation of the Bithorax (BX-C) complex in which trx is implicated – had itself been inspired by García-Bellido’s seminal work on compartmentalization and selector genes (García-Bellido et al., 1973, 1976; García-Bellido 1975).

As a student of genetics I had received an all too brief exposure to the revolutionary new ideas that were emanating from the Universidad Autonoma in Madrid in the mid-1970s – but the brilliant exposition of the Compartment Hypothesis and the role of the Selector gene engrailed given one winter’s evening by Peter Lawrence (Lawrence and Morata, 1976) had been enough to convince me that the future of developmental biology lay in understanding the genetic basis of lineage restrictions. Armed with this conviction, I arrived in the laboratory of J.R.S. Whittle at the University of Sussex, England determined to identify other genes that, like engrailed, might be involved in regulating the development of specific compartments. My first strategy was to scour the Red Book (Lindsley and Grell, 1968) for mutants with phenotypes that could be construed as being compartment specific. Amongst the most promising candidates, the first two that I selected for study were shifted (shf) and elbow (el). The narrowing of the spacing between the LIII and LIV veins in shf wings suggested a possible effect on the growth or patterning of the anterior compartment, whilst the curvature and reduction of size of el mutant wings seemed to me to indicate a defect specific to the posterior compartment of the wing. With little other rationalization than this, I decided to investigate the effects of combining both mutations in the same animal. But what was to arise from the crosses performed to generate the double mutants was certainly nothing that I had anticipated. Amongst the F2 progeny of my shf and el flies were a number of animals with enlarged and misshapen halteres that, on closer inspection, clearly exhibited signs of being partially transformed to wing tissue (see Fig. 1). Satisfied that my experiment had worked, albeit with an unexpected outcome, I preserved these homoeotically transformed flies in 70% ethanol before showing them to my adviser! His reaction when he saw the pickled flies was predictable, since, unlike me, he immediately realized that this phenotype was almost certainly unrelated to either the el or shf mutations. Fortunately, the cultures were still producing a few pupae and from these I was able to obtain enough flies from which to attempt to recover what we now suspected to be a new spontaneously arising mutation.

A variegated homoeotic mutation

Much to our relief, the following generation yielded the same assortment of flies displaying variable homoeotic transformations of their halteres (see Fig. 1). I now attempted to establish a pure line of

Abbreviations used in this paper: BX-C, bithorax complex; ANT-C, Antennapedia complex; bx, bithorax; tx, trithorax; shf, shifted; el, elbow; iab, infra-abdominal; Antp, Antennapedia; Scr, Sex combs reduced; Pc, Polycomb; esc, extra sex combs; Dfd, Deformed; en, engrailed; Ubx, Ultrabithorax; pbx, postbithorax; bxd, bithoraxoid; TRE, trithorax response element; Mll, Mixed lineage leukaemia; bp, base pairs; KDa, kilo-Dalton; DNA, deoxyribonucleic acid.

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Fig. 1. (a) Wild type haltere (H) and examples of variably transformed halteres in trx\textsuperscript{1} homozygotes (b and c). Note the transformation of both anterior (*) and posterior (arrow) structures.

the putative new mutation by selecting phenotypically mutant animals and inter crossing them. The results were again surprising: in the first place, not all of the progeny exhibited the homolectic phenotype; but amongst those that did, the transformations were frequently much more severe than had been observed in the previous generation. In extreme cases almost the entire haltere was replaced by a near complete wing composed of both anterior and posterior compartment structures, a phenotype reminiscent of that of flies homozygous for both the bithorax; postbithorax (bx;pbx) homolectic mutations (Lewis, 1963,1964). Moreover, it was clear that the homoecosis was not restricted to the haltere: large apical bristles, characteristic of the distal tibia of the mesothoracic leg were present on the metathoracic leg. This finding was not unprecedented, since E.B. Lewis had already shown that bx and pbx mutations transform the metathoracic legs as well as the halteres towards a mesothoracic character (Lewis, 1963,1964). What was without precedent, however, was the finding that the same large apical bristles were also present on the prothoracic legs of the affected flies—and in line with this representing a transformation of the prothorax towards mesothorax, the sex comb of the prothoracic leg in males was found to be either reduced in size or completely replaced by thin bristles typical of the mesothoracic basitarsus.

While the effects on the metathorax were consistent with the new mutation being a hypomorphic BX-C mutation—the bx\textsuperscript{1} allele for instance exhibits a similarly variable phenotype though its effects are restricted to the anterior compartment of the metathorax—the effects of the new mutation on prothoracic development suggested otherwise. Although Ubx function would subsequently be shown to be required in the posterior prothorax (Morata and Kerridge, 1981), at this time no involvement of the BX-C in prothoracic development was recognized. In any case, the effects of this new mutation were largely restricted to the anterior compartment of the prothoracic leg, a compartment for which no selector gene function had yet been identified. Moreover, a minority of affected individuals also showed signs of a transformation of the dorsal prothorax to mesothorax; in the most extreme cases, this resulted in the development of flies with six wings (see Fig. 2), a phenotype from which the mutation derived its name \textit{trithorax (trx)}. The phenotype of the trx\textsuperscript{1} mutation—as we now designated it (Ingham and Whittle, 1980)—was thus intriguing for several reasons: not only did it imply the existence of a gene distinct from the BX-C that controls metathoracic development; it also provided support for the notion advanced by García-Bellido (García-Bellido, 1975), amongst others, that each body segment is a derivative of a ground state of differentiation represented by the mesothorax.

While complementation analysis with various BX-C mutations supported the view that trx\textsuperscript{1} is not a BX-C allele, the definitive proof came from recombination analysis. Meiotic mapping placed trx proximal to the BX-C at 54.3 on the right arm of chromosome 3, a position confirmed by its inclusion in various deficiencies of the cytogenetic region 88B that include the red locus (which itself maps to 54) (Ingham and Whittle, 1980). Interestingly, this map position corresponds closely to that determined for the mutation \textit{tetraperta}, whose phenotype, as described by Astauroff (Astauroff, 1930), bears a remarkable resemblance to that of trx. Unfortunately, this mutation had long since been lost so allelism could not be established, but it seems more than likely that \textit{tetraperta}, discovered nearly half a century earlier, was in fact the original trx allele.

\textit{trithorax} is a maternal effect homolectic mutation

The localization of trx to 88B was highly significant since García-Bellido (García-Bellido, 1977) had previously reported that individuals heterolectic for certain deficiencies of this region exhibit, at low penetrance, weak bithorax-like transformations of the haltere. Moreover, such transformations were apparently only observed when the \textit{Df(3)red} chromosome was introduced from the maternal parent, leading to the suggestion that the deficiency uncovers a maternally expressed gene required for the correct activation of BX-C genes. This proposal fitted well with the characteristics of the trx mutation described above; in particular, it suggested that the observed increase in phenotypic strength of the progeny of their relatively weakly transformed parents reflected the fact that the latter were most likely derived from mothers which were heterolectic for the mutant trx allele and therefore carried one wild type copy of the gene. To confirm this interpretation, reciprocal crosses were performed between females and males known to be either heterolectic or homolectic for the trx allele; as expected, trx homolectic females derived from homolectic fathers showed a much higher penetrance and expressivity of the phenotype than those derived from heterolectic mothers (Ingham and Whittle, 1980). These experiments thus clearly established that expression of trx is required both during oogenesis and embryogenesis for the normal development of the adult segments.

To investigate at what stage of embryonic development trx activity is required we took advantage of the fact that the trx\textsuperscript{1} allele is temperature sensitive. Thus when homolectic flies are reared at 18°C the penetrance and expressivity of the phenotype was much reduced compared to siblings raised at 25°C. By manipulating the culture temperature at different times during embryogenesis it was found that there is a critical requirement for the gene during the first four hours of embryogenesis (Ingham and Whittle, 1980). Not only was this timing consistent with the maternal effect of the mutation; more significantly, it coincided with the developmental stage at
Fig. 2. A six winged fly! Each of the three thoracic segments (T1-3) bears a wing in some shape or form - those in the prothoracic (T1) segment have not everted properly and remain partly surrounded by peripodial membrane, hence their rather ugly appearance.

which cells are known to become committed to a single segment, as deduced by cell lineage analysis. Taken together, these characteristics suggested that trx might itself be somehow involved in the initiation of segmental fates.

**trithorax and ether-induced bithorax phenocopies**

The temperature sensitive period of trx1 also suggested a link between the normal function of the gene and a curious phenomenon described many years earlier by (Gloor, 1947) and (Waddington, 1956) These authors had found that variable homoeotic transformations of the haltere to wing –so-called bithorax phenocopies– could be induced by exposure of embryos to ether vapor; and more recently, several authors had established the critical period for exposure to ether to be around the blastoderm stage, i.e., 3-3.5 h post-fertilization (Capdevila and García-Bellido, 1974; Bownes and Seiler, 1977). That this corresponds closely to the temperature sensitive period of trx1 was especially intriguing, since the transformations induced by ether treatment are virtually indistinguishable from those typical of trx1 homozygotes. So could ether be affecting a mechanism regulated by trx activity? Studies by Capdevila and García-Bellido (1978) had already demonstrated that heterozygosity for Df(3)red renders embryos more sensitive to ether treatment –so it was not surprising to find that ether induced transformations are also significantly increased in frequency in embryos heterozygous for trx1. Crucially, the transformations induced by ether treatment in these animals affect the prothoracic as well as the metathoracic segments (Ingham and Whittle 1980) –thus the effects of ether exposure should more properly be referred to as trithorax not bithorax phenocopies.

Consideration of the phenomenon of ether-induced homoeotic transformation had led Capdevila and García-Bellido to propose a model for the specification of segmental identity (Capdevila and García-Bellido, 1978), based on the notion of the differential activation of the BX-C developed by E.B. Lewis. Following his detailed genetic analysis of the complex, Lewis (1978) had postulated that the BX-C is comprised of a series of genes arranged in a proximal-distal order that reflects the spatial requirement for the function of each gene; thus, the bx and pbx genes, located at the centromere proximal end of the complex specify metathoracic character while distal to these, a series of infra-abdominal (iab) genes specify the development of successively more posterior abdominal segments. Increasing activation of the complex in a proximal to distal direction along the antero-posterior axis of the body would lead to successively more genes of the complex being expressed and hence to more posterior fates being specified. To explain how such differential activation of the BX-C along the antero-posterior body axis could be accomplished, Capdevila and García-Bellido (1978) invoked the existence of a maternally deposited inducer molecule, itself distributed in a concentration gradient along the antero-posterior axis of the egg. This inducer would act only transiently, initiating levels of BX-C expression that would be stably maintained throughout subsequent divisions by cell heredity. The effects of ether could thus be explained in terms of this model by postulating that ether somehow disrupts the activity or distribution of the inducer in the blastoderm embryo; according to this view, ether induced transformations should be clonally propagated –and evidence that this is the case came from cell lineage analysis of phenocopied animals (Capdevila and García-Bellido, 1974).

Because of the increased sensitivity of Df(3)red heterozygotes, the idea that this deletion might uncover the locus encoding the putative inducer seemed an attractive one. Moreover, Capdevila and García-Bellido (1978) had found that deficiency heterozygotes exhibit transformations of their abdominal as well as metathoracic segments; these posterior to anterior transformations were exactly of the type expected to result from reduced activity of the different infra-abdominal genes, again strengthening the idea that the Df(3R)red deletes a global inducer of the BX-C. While relatively weak and infrequent in Df(3)red heterozygotes, such abdominal transformations occur with high penetrance and expressivity in trx1 homozygotes (Ingham and Whittle, 1980; see Fig. 3). Thus trx1 showed all the characteristics expected of a point mutation in the putative inducer locus: it has a maternal effect, a temperature sensitive period around the blastoderm stage of embryogenesis and transforms both the metathoracic and the abdominal seg-

Fig. 3. Wild-type (a) and trx1 homozygote (b) male abdominal segments. Note the loss of dark pigmentation typical of the 5th abdominal segment (*) and the additional darkly pigmented tergite posterior to the sixth segment (arrow) in the mutant; both of these features are indicative of a transformation of the segments to more anterior identities.
ments to more anterior segmental fates. But how could the prothoracic transformations seen in \textit{trx}$^1$ homozygotes be reconciled with this model?

\textbf{\textit{trithorax} mimics mutations at the Antennapedia complex}

An answer to this question was soon to be provided by the discovery of the Antennapedia complex (ANT-C) by Thomas Kaufman and colleagues. Although \textit{Antennapedia} (\textit{Antp}) mutations had been known for many years (having first been described in the 1940s) the function of the gene identified by these mutations had remained enigmatic—certainly it had not been considered to be analogous to the genes of the BX-C. Perhaps part of the reason for this was that all of the \textit{Antp} mutations were dominant gain of function alleles; the transformation of antenna to leg caused by these mutations, while dramatic could in isolation give no clear indication of the normal function of the gene. Moreover, although dominant mutations in other members of the ANT-C had been described, these had been erroneously mapped to the left arm of chromosome three, thus obscuring their clustering with \textit{Antp} in a single complex. Through careful genetic and cytological analysis, Kaufman established that \textit{Antp} is one of a complex of homoeotic genes, including the previously described \textit{proboscipedia} and a new locus named \textit{Sex combs reduced} (\textit{Scr}), required for the development of the thoracic and gnathal segments (Lewis \textit{et al.}, 1980a,b; Denell \textit{et al.}, 1981; Wakimoto and Kaufman, 1981). The discovery of \textit{Scr} was particularly significant since, as its name implied, reduction in function of the gene leads to a partial transformation of the prothoracic leg towards its mesothoracic equivalent, precisely the phenotype seen in \textit{trx}$^1$ homozygotes. The \textit{trx} phenotype thus suggested a link between the regulation of the BX-C and the newly defined ANT-C, the inactivation of \textit{trx} apparently resulting in a loss of function not only of BX-C genes but also of at least one ANT-C gene. In terms of the Capdevila and García-Bellido model however, this presented something of a problem, since it was not clear how a simple anterior to posterior gradient of \textit{trx} could accomplish the activation of BX-C genes posterior to the mesothorax while at the same time activating ANT-C genes in segments anterior to the mesothorax.

Moreover, the inducer model suffered from another more serious conceptual flaw. The specification of segmental fate must somehow be closely co-ordinated with the subdivision of the embryo into segmental units and it was difficult to see how the graded activity of an inducer could activate the ANT-C and the BX-C with the precision needed if segmental units and segmental identity are established by independent mechanisms. To achieve such precision, the activation of the homoeotic complexes needed to be integrated with the activation of genes that define the segmental units themselves. As it happened, such “segmentation” genes had just been discovered in the saturation mutagenesis screen of Nüsslein-Volhard and Wieschaus (1980) and their subsequent analysis established how the co-ordination of segmental sub-division and specification of segmental identity is achieved. We now know that a regulatory hierarchy between the gap and pair-rule genes establishes a series of positional cues in the blastoderm.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig4.png}
\caption{Thoracic segments of wild-type, \textit{esc} and \textit{esc; trx} mutant larvae. In the \textit{esc} mutant, all the segments are transformed to eighth abdominal character, a transformation that is completely suppressed by the removal of \textit{trx} activity.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig5.png}
\caption{Transformation of clones of cells lacking \textit{trx} activity in the eye (a), posterior wing (b) antenna (c) and female genitalia (d). The clonal tissue is indicated by the boxes.}
\end{figure}
embryo (Ingham, 1988); these cues serve to activate expression both of the BX-C and ANT-C genes (Ingham and Martinez-Arias, 1986) and of genes such as wingless (wg) and engrailed (en) (Ingham et al., 1988), whose activities define and maintain segmental borders.

Apart from these theoretical considerations, it was in any case evident from the analysis of larvae homozygous for amorphic alleles of trx that its activity cannot be essential for initiating the differential expression of the two gene complexes. In contrast to the major transformations of the larval cuticle associated with complete loss of the BX-C or ANT-C, larvae homozygous for either amorphic point mutations of trx (Ingham, 1983) or for Di(3)red (Capdevila and García-Bellido, 1978) exhibit relatively minor modifications of their segmental pattern. Even if all maternal trx activity is also eliminated from such larvae, the pattern remains remarkably unaffected, with a clear distinction between thoracic and different abdominal segments easily discernible (Ingham, 1983). By contrast, mutations in putative repressors of the BX-C and ANT-C, such as Polycomb (Pc) (Lewis, 1978) or extra sex combs (esc) (Struhl, 1981) do have major effects on the larval pattern, even head and thoracic segments exhibiting a transformation towards the eighth abdominal segment (see Fig. 4), a phenotype predicted to result from the complete de-repression of both gene complexes. From this point of view, both Pc and esc seemed much better candidates for genes involved in initiating the differential expression of the homoeotic gene complexes. But one important finding ruled out such a role for both genes: despite the relatively mild effects of trx mutations on normal larval development, the same mutations act as potent suppressors of both the Pc and esc phenotypes (Capdevila and García-Bellido, 1981; Ingham, 1983). Thus in either Pc trx or esc; trx double mutants the transformation of head and thoracic segments towards the eighth abdominal is completely suppressed (see Fig. 4); so it is clear that the differential activation of ANT-C and BX-C genes is independent of all three genes.

This conclusion has since been confirmed by the direct visualization of BX-C and ANT-C gene expression in embryos mutant fortrx, esc and PC. In all cases, the initial patterns of expression in gastrulating embryo are indistinguishable from wild-type; however, as embryogenesis proceeds changes in the expression of both complexes become apparent. While in the case of Pc and esc mutant embryos, genes of the BX-C become ectopically expressed in anterior segments (Struhl and Akam, 1985; Simon et al., 1992), the effects of trx are more subtle. In general, all of the ANT-C and BX-C genes are expressed in their normal domains but in most cases the levels of expression appear reduced (Breen and Harte, 1993; Sedkov et al., 1994). The effect is most pronounced in the case of the BX-C genes, each of which shows a significant reduction in its transcript level from about stage 10. Effects on expression ofScr, Antp and Dfd, by contrast are much weaker and are first detectable only at around stage 16 of embryogenesis. Thus trx function seems to be necessary to maintain the appropriate levels of ANT-C and BX-C gene expression within their normal domains, a function that persists well beyond the completion of embryogenesis.

To establish exactly where and for how long trx function is required, clones of cells homozygous for null alleles of the locus were induced in the imaginal discs at successively later stages of development (Ingham, 1985). The initially surprising finding was that trx is required in every disc until very late in development to maintain the appropriate identity of each segment. In the absence oftrx activity, cells are autonomously transformed to a mesothoracic identity (Ingham, 1985)—thus clones in dorsal structures, such as the eye or haltere differentiate notal or wing tissue whereas clones in ventral structures, such as the proboscis, antenna or genitalia are transformed into mesothoracic leg (see Fig. 5). While incompatible with a role for trx as the embryonic inducer of ANT-C and BX-C expression, these transformations are perfectly consistent with a role for trx in the cell heredity mechanism postulated to maintain the appropriate state of homoeotic complex activation during successive cell divisions. But the clonal analysis revealed that trx function is not restricted to the regulation of just the ANT-C and BX-C: even in the wing trx clones exhibited a mutant phenotype. In the posterior compartment, clones including the wing margin differentiated socketed bristles, indicative of a transformation to anterior compartment identity (Ingham, 1985), a transformation previously only associated with mutations at theengrailed locus (Morata and Lawrence, 1975). This was intriguing since although not a member of either the BX-C or ANT-C, en had been classified with the latter as a selector gene, that is a gene that controls the identity of a specific developmental compartment. Like the ANT-C and BX-C genes, en expression was postulated to be initiated at the blastoderm stage and subsequently maintained in each posterior compartment by cell heredity (Lawrence and Morata, 1976). Thus the finding that trx clones have an en-like phenotype strongly suggested that the maintenance of expression of all selector genes is controlled by the same trx-dependent mechanism. Subsequent molecular studies have confirmed that en expression does indeed depend upon trx activity at least in the embryo (Breen et al., 1995), though this has yet to be confirmed in the imaginal discs. In addition trx clones in the anterior compartment of the wing also exhibit a mutant phenotype: in this case, clones including the distal wing margin bear bristles characteristic of more proximal regions (Ingham, 1981; Ingham et al., 1985). Unlike the posterior to anterior transformation, this phenotype does not correspond to that of any previously described mutation; however, it seems likely that this represents the loss of activity of some other selector gene that specifies distal versus proximal development, a function that in the ventral appendages at least is executed by the homoeobox geneDistalless.

The molecular characterization of trithorax

Molecular cloning and sequence analysis of trx has revealed that it encodes two large proteins of 365KDg and 405 KDg (Mazo et al., 1990; Sedkov et al., 1994). The most notable feature of these proteins—apart from their size—is the presence of novel zinc finger-like motifs, suggesting a possible interaction between the TRX proteins and DNA. Such an interaction would, of course, be consistent with the hypothesized role of trx in regulating the expression of ANT-C, BX-C and other genes. Indirect evidence that TRX protein binds to the regulatory regions of ANT-C and BX-C genes has come from various studies. In the case of the ANT-C, mutations in trx were found to enhance repression of transgenes by a putative cis-regulatory region of theScr gene (Gindhart and Kaufman, 1995), whereas in the case of the BX-C, mutations in cis-regulatory regions of theUbx gene were found to be enhanced by mutations in trx (Castelli-Gair and García-Bellido, 1990). More recently, a relatively small (440bp) fragment from the pbx/bxd regulatory region ofUbx has been shown to be sufficient to
mediate trx dependent activation of a reporter gene both in vivo and in transfected tissue culture cells (Chang et al., 1995). Activation of transcription via this so called TRE (trithorax response element) requires the zinc finger binding domain of the TRX protein (Chang et al., 1995). However, there is no evidence for a direct interaction between TRX and this DNA element. Interestingly, the same 440bp fragment also mediates repression of transcription by the PC protein (Chang et al., 1995). This protein is thought not to bind directly to DNA but rather to associate with chromatin via other proteins, some of which may have sequence specific DNA binding activity. Indirect immunofluorescence studies have revealed that both PC and TRX proteins bind to specific sites in the polytene chromosomes of larval salivary glands some of which are shared by the two proteins (Kuzin et al., 1994; Chinwalla et al., 1995); as expected, these sites include the ANT-C and BX-C the best characterized targets of both Pc and trx activity. These studies suggest that the proper regulation of the ANT-C, BX-C and other target genes may be achieved by a competition between PC and TRX for binding to chromatin sites around the target loci.

Analysis of trx transcription has revealed that the gene gives rise to multiple splice variants which unexpectedly are expressed in spatially and temporally distinct patterns in the embryo. Four different forms are expressed in the embryo prior to 7 h post fertilization, the predominant form of which is expressed both maternally and in the early zygote, peaking at around 2-4 h post fertilization (Sedkov et al., 1994), a period that corresponds approximately to the cellular blastoderm stage. Interestingly, expression is first detected at this stage in the posterior half of the embryo, resolving into four alternating stripes that correspond to the parasegments in which the Ubx gene is initially activated (Sedkov et al., 1994). This early phase of expression correlates with the relative temperature sensitive period of the early temperature sensitive period of the 1994). This early phase of expression correlates with the ANT-C, BX-C and other target genes may be achieved by a counteracting activity. These studies suggest that the proper regulation of the ANT-C, BX-C and other target genes may be achieved by a competition between PC and TRX for binding to chromatin sites around the target loci.

Finally, the molecular cloning of trx has led to the discovery that the gene has been conserved both structurally and functionally in the course of evolution. The vertebrate homolog of trx, the Mixed-lineage leukaemia (Mll) gene was, as its name suggests, initially identified as an oncogene (Djabali et al., 1992). Analysis of mice mutant for the murine Mll homolog however, has more recently shown that this gene, like its Drosophila counterpart, plays a crucial role in homoeotic gene regulation. As in flies, the murine trx gene is haplo-insufficient so that heterozygous animals display fusions of the sternal vertebrae as well as transformations of the cervical, thoracic and lumbar vertebrae in anterior and posterior directions (Yu et al., 1995). This is mirrored by shifts in the anterior limits of Hoxa7 and Hoxc9, while in homozygous Mll mutants, expression of both genes completely disappears (Yu et al., 1995). The continuing analysis of trx in Drosophila thus provides a powerful approach not only to understanding the development of the fly but also towards understanding the specification of the vertebrate body plan and of tumor progression. The field has certainly come a long way in the last twenty years!

References


