eliminated entirely, by laser ablation of the retinal ganglion cell axons within AF7. These data suggest that selectivity for prey-like stimuli is already present in retinal ganglion cell axons targeting AF7, and that AF7 plays a role in regulating hunting behaviour. Anatomical reconstruction of singly labelled cells showed that two morphological subtypes of retinal ganglion cell innervate AF7, and that these cells also send collateral branches to the superficial layer (*stratum opticum*) of the tectum, consistent with the fact that some responses to prey-like stimuli were also seen in RGCs innervating the tectum.

By labelling single neurons in the vicinity of AF7, Semmelhack *et al.* [3] reconstructed the anatomy of potential postsynaptic partners of retinal ganglion cell axons targeting AF7. They identified cells that projected to the optic tectum and a second type of neuron that projected to the nucleus of the medial longitudinal fasciculus (nMLF) and hindbrain, areas that are important for controlling swim direction and speed (Figure 1) [13–15]. In future studies, it will be important to establish that these cells are *bone fide* targets of retinal ganglion cells within AF7 and to determine their tuning properties and neurotransmitter identity. Addressing these questions will provide valuable insight into how retinally-derived information about the presence of prey is transformed by circuits within AF7 to modulate prey capture.

Bianco and Engert [2] and Semmelhack *et al.* [3] reach different conclusions about the optimal stimulus for triggering hunting. This may be because the two groups did not explore exactly the same stimulus space, or that important experimental conditions were not identical in each study. An alternative explanation is that the two studies focussed on different stages of the visual pathway, Semmelhack *et al.* [3] on retinal ganglion cells, and Bianco and Engert [2] on tectal neurons. The differences they see may reflect the different response properties of neurons at different stages of the sensorimotor pathway. The two studies may therefore be complementary rather than contradictory. Together they certainly provide significant new insight into the circuitry underlying a complex visually-driven behaviour and raise some fascinating questions for the future. How do the tectum and AF7 together coordinate the various aspects of prey capture, and how are prey capture circuits modulated by attention, motivational state and input from other sensory modalities are questions to keep the field busy for quite some time.

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Epithelial Cell Division: Keeping Aneuploidy Levels in Check

Marta Clemente-Ruiz[1] and Marco Milán[1,2,*]
[1]Institute for Research in Biomedicine, Parc Cientific de Barcelona, Baldiri Reixac, 10, 08028 Barcelona, Spain
[2]ICREA, Parc Cientific de Barcelona, Baldiri Reixac, 10-12, 08028 Barcelona, Spain
*Correspondence: marco.milan@irbbarcelona.org
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Aneuploidy is deleterious at the cellular and organismal level and can promote tumorigenesis. Two new studies in *Drosophila* imaginal discs underscore the cellular and tissue-wide mechanisms that prevent the accumulation of aneuploid cells in symmetrically dividing epithelial tissues upon changes in centrosome number.

Aneuploidy — an abnormal number of chromosomes or parts of chromosomes — is deleterious at the cellular and organismal level from yeast to man [1,2], and maintenance of highly aneuploid cells in a tissue can cause

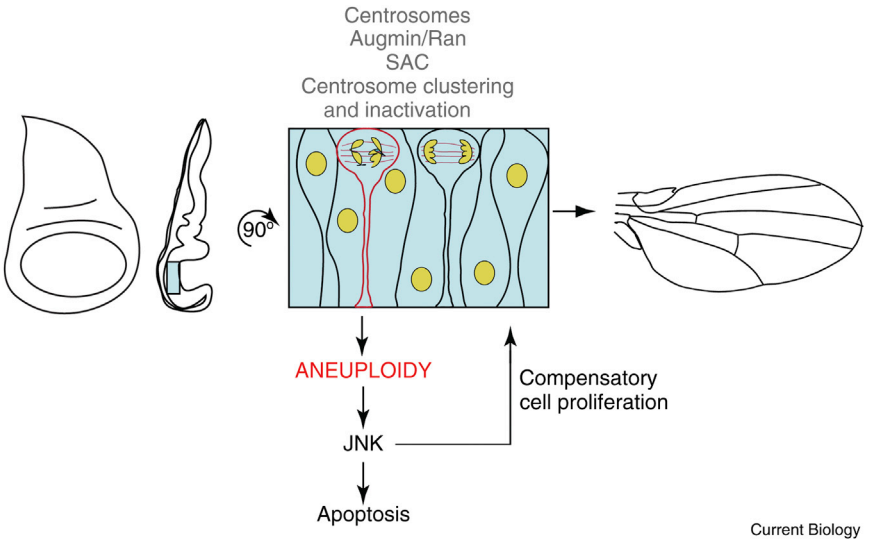

Figure 1. The cellular and tissue-wide mechanisms that keep aneuploidy levels in check in *Drosophila* wing epithelial cells.
Various mechanisms (in grey at the top of the figure) ensure the correct segregation of chromosomes in symmetrically dividing wing cells. Changes in centrosome number lead to chromosome segregation defects and aneuploidy, which induces activation of the JNK pathway to promote cell death and compensatory proliferation, thus giving rise to normal-looking adult wings.

tumorigenesis [3–5]. Aneuploidy results from defects in chromosome segregation during mitosis. The dysfunction or amplification of centrosomes — the major microtubule-organizing centers that play key roles in forming and orienting mitotic spindles — induces aneuploidy and may lead to tumorigenesis. Remarkably, flies that lack centrosomes or are subject to centrosome amplification are viable and do not show major developmental defects [6,7]. New studies by the labs of Mark Peifer and Renata Basto [8,9] use the *Drosophila* wing imaginal disc, a highly proliferative epithelium, to elucidate the consequences of changes in the number of centrosomes in symmetrically dividing cells. These two studies unravel the presence of robust compensatory mechanisms at the cellular and tissue-wide level that keep aneuploidy levels in check, thus allowing the development of morphologically normal adults.

Several years ago, the characterization of flies mutant for the centriole duplication protein DSas-4 that lack centrosomes in all cells gave rise to the unexpected observation that the resulting adults were morphologically normal [6]. Similar surprising results were obtained upon centrosome amplification in all cells by means of ubiquitous overexpression of Sak/Plk4, the master regulator of centriole duplication [7]. These findings suggested that centrosomes were dispensable in somatic tissues, thus contradicting the canonical view of the role of these organelles in ensuring the correct segregation of chromosomes. A subsequent analysis of the developing animals revealed an important consequence of centrosome dysfunction or amplification in neural tissues. Centrosomes ensured the asymmetric segregation of cell fate determinants and the orientation of the mitotic spindle in neuroblasts, and centrosome dysfunction led to the expansion of the stem cell population [7,10]. Most interestingly, this expansion gave rise to brain tumors. Remarkably, the levels of aneuploidy in the tissue were very low [7] and increased only after serial transplantation in adult hosts [10]. These observations opened up the possibility that multiple mechanisms buffer the effects of centrosome loss or amplification in somatic cells, thus maintaining low tissue-wide levels of aneuploidy.

Peifer and colleagues [8] selected the wing imaginal disc of *Drosophila* as a model system to study the consequences of centrosome loss in symmetrically dividing cells. They first found out that centrosomal loss is not without consequence in fly epithelial cells because it leads to high levels of apoptosis. This cell death process was largely a consequence of the generation of aneuploid cells, as these cells were not found in acentrosomal tissues unless programmed cell death was blocked. Inhibition of apoptosis also led to a dramatic overgrowth of the acentrosomal tissue, as previously shown in highly aneuploid wing primordia unable to activate the apoptotic program [5]. The authors unraveled a major role of the Augmin and Ran pathways of microtubule nucleation and spindle assembly in acentrosomal cells. However, the increased apoptosis and chromosome segregation errors observed in these cells suggested that Augmin- and Ran-mediated spindle assembly in acentrosomal cells is prone to errors. Interestingly, disruption of the spindle assembly checkpoint (SAC), which ensures that all kinetochores are attached to microtubules before anaphase onset, was lethal to the acentrosomal animal. This lethality resulted from a dramatic increase in the number of chromosome segregation errors, which led to the absence of proliferating epithelial tissues in the developing individuals. Thus, acentrosomal epithelial cells go through mitosis by using error-prone alternative microtubule-organizing mechanisms and have a robust checkpoint to prevent anaphase until the spindle assembles.

Lagging chromosomes produced by mitotic failure induce DNA damage, which activates the p53 tumor suppressor gene to cause programmed cell death. However, Peifer and colleagues [8] made two interesting observations that led to the proposal that the contribution of DNA damage to the death of acentrosomal wing epithelial cells was minor. First, the fraction of cells with DNA damage was smaller than the fraction of apoptotic cells and, second, the extent of cell death was unaffected by p53 depletion in acentrosomal tissues. In *Drosophila* epithelial cells, multiple cellular insults, including aneuploidy [5], can activate the Jun N-terminal kinase (JNK) signaling pathway, thus inducing the expression of pro-apoptotic genes and triggering the apoptotic

cascade. The authors presented evidence that this pathway mediates the apoptosis observed in acentrosomal cells in the wing, thus reinforcing the notion that cell death is mostly a consequence of chromosome segregation errors and the resulting aneuploidy.

How do tissues deal with cells having more than two centrosomes and how do they give rise to normal-looking animals? Neural tissues resolve this problem by inducing centrosome clustering, which ensures the generation of bipolar mitoses and impedes the production of aneuploid cells [7]. In a paper published in this issue of *Current Biology*, Basto and colleagues [9] use the wing imaginal disc to analyze how symmetrically dividing cells deal with supernumerary centrosomes. Interestingly, they discovered that the vast majority of wing disc cells overexpressing Sak/Plk4 also form a bipolar spindle and that they do so by inactivating supernumerary centrosomes and, to a lesser extent, by clustering them. However, these mechanisms were not as efficient as in neural stem cells because a considerable number of tripolar mitoses were observed, which led to the generation of aneuploid cells. As occurs in acentrosomal wings, apoptotic cell death was also used to remove aneuploid cells from the wing disc as blocking cell death dramatically increased aneuploidy levels in the tissue. Interestingly, centrosome amplification was able to drive tumor growth and cellular transformation, as previously shown in SAC-depleted (and highly aneuploid) wing primordia unable to activate the apoptotic program [5,11,12]. These results reveal two distinct mechanisms by which centrosome amplification drives tumorigenesis in symmetrically (epithelial) and asymmetrically (neural stem cell) dividing fly cells. Of course, the next issue was to find a mechanistic explanation for the differential behavior of supernumerary centrosomes in epithelial and neural stem cells. In this regard, Basto and colleagues [9] identified the FERM-domain protein Moesin as a centrosomally localized protein that is specifically enriched in Sak/Plk4-overexpressing epithelial cells but not in neural stem cells of the same genotype. The authors provided evidence that Moesin upregulation in epithelial cells sustains the microtubule-organizing activity of unclustered centrosomes, thus promoting the generation of multipolar mitoses and the induction of chromosome segregation errors and aneuploidy. The identification of Moesin may open up new avenues towards the pharmaceutical treatment of carcinomas in which centrosome amplification is a common trait.

Despite the dramatic levels of apoptosis observed in wing primordia with an altered number of centrosomes, the resulting adult structures were largely unaffected [6,7]. For Peifer and colleagues [8], these results were reminiscent of the classical experiment performed forty years ago in which at least 40–60% of cells in the *Drosophila* wing disc were lost by programmed cell death, yet these discs went on to give rise to normal-looking adult wings as a result of compensatory proliferation [13]. The signals driving this proliferation were subsequently demonstrated to be dependent on the activity of JNK [14,15]. Indeed, Peifer and colleagues [8] found that proliferation rates were increased in acentrosomal tissues and that JNK participated in this process because blocking JNK signaling gave rise to dysmorphic acentrosomal wings. Thus, JNK plays a tissue-wide role not only in removing aneuploid cells by apoptosis but also in inducing compensatory proliferation to counteract cell loss (Figure 1).

Taken together, the current reports on the fast-evolving *Drosophila* model [8,9] have unraveled a plethora of cellular and tissue-wide mechanisms at work in highly proliferative epithelial tissues that keep aneuploidy in check. These breakthroughs open up a promising direction for further research on the role of these mechanisms in dampening aneuploidy levels in mammals.

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