allowing the collapsing part of the structure to break away so as to isolate the failure and prevent it from propagating.

This is a clever idea, but the design of the fuse is key. Too weak and the building could turn into a house of cards; too strong and the collapsing part of the structure could pull down the entire building. Makoond and colleagues therefore developed the concept of hierarchy-based-collapse isolation, which essentially limits the extent of the collapse. When the initial area of damage is small (for example, affecting a single column), the building should be able to redistribute the load, and the fuse is just strong enough to prevent further collapse. The idea is that, in practice, the single damaged column would be noticed and repaired before more damage could occur. However, if the original area of damage spans several columns, the authors' fuses are weak enough to break, thereby stopping the whole building from collapsing.

Makoond *et al.* subjected their precast concrete building to two phases of testing. In the first phase, they removed two columns that were not adjacent to each other, one at a time. The fuses were strong enough to compensate for the missing columns and prevent collapse. In the second phase, the authors took out a corner column that was positioned between those removed in the first phase. This initiated a collapse in all of the areas directly supported by the missing columns, but not – thanks to the authors' fuses – in the rest of the building. These experiments also provided valuable data for Makoond and colleagues' computational models of collapsing buildings, which engineers can use to better understand how buildings fail.

This study shows that the hierarchy-based-collapse approach can work well in precast buildings. However, fuses will need to be custom designed for other building types, such as those for which the building frame is cast during construction, and those that contain concrete floor slabs with no beams. If such a system had been in place in Champlain Towers South (an example of the latter type of structure), it is possible that the initial collapse would not have propagated across almost half of the building. Although the details are a long way from being easily implemented, Makoond and colleagues' approach will ultimately make buildings more resilient. It therefore fulfils the main objective of structural engineering, which is to protect the safety of the public[4].

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Molecular biology

Tumours form without genetic mutations

Anne-Kathrin Classen

Researchers find that brief and reversible inhibition of a gene-silencing mechanism leads to irreversible tumour formation in fruit flies, challenging the idea that cancer is caused only by permanent changes to DNA. **See p.688**

The formation of tumours and progression to cancer are usually thought to be driven by the accumulation of permanent genetic mutations. Specific genetic mutations that have been linked to cancer often alter gene-expression programs, promoting changes in a host of cellular functions, including proliferation, differentiation, metabolism and survival[1,2]. On page 688, Parreno *et al.*[3] challenge the idea that tumours arise only from permanent genetic mutations. Using fruit flies (*Drosophila melanogaster*), they demonstrate that transiently disrupting mechanisms that regulate gene expression without making changes to the DNA sequence – a process known as epigenetic regulation – is sufficient to establish gene-expression programs that support tumour initiation and progression.

Epigenetic mechanisms maintain gene-expression patterns throughout a cell's divisions, even if the original environment in which these patterns were established changes. Biochemical modifications (such as the addition of a methyl group) to DNA or histone proteins (around which DNA is packaged as chromatin) allow genes to be activated or repressed in a heritable manner. Alterations to DNA-methylation and histone-modification patterns throughout the genome have been associated with various aspects of cancer, and so epigenetic modifications represent non-genetic but potentially heritable adaptations that promote tumour growth and progression. Beyond this, these modifications can be valuable biomarkers for the diagnosis of cancer, and potential therapeutic targets for its treatment[4,5].

However, epigenetic changes in tumours cannot always be attributed to permanent mutations in genes encoding proteins that carry out epigenetic modifications, such as histone modifiers, DNA-methylation enzymes and chromatin-remodelling proteins. In some cases, tumours can develop without any identifiable mutations being present[6]. These puzzling observations suggest that epigenetic alterations can function as crucial non-genetic drivers of disease, yet experimental evidence for this has been lacking.

Parreno and colleagues investigated whether tumours could arise from transient dysfunction of components of a family of gene-silencing proteins called the Polycomb group. Polycomb group proteins are essential for the determination of cell fate: they epigenetically repress genes that control differentiation by (among other things) methylating histones in patterns that are established during embryonic development. Mutations in Polycomb group proteins have been linked to various human cancers[7]. Because Polycomb group proteins are evolutionarily conserved from fruit flies to humans, it is not surprising that mutations in these proteins also promote tumour formation in fruit-fly tissues by deregulating genes that control cell fate and proliferation[8,9]. The simplicity of fruit-fly Polycomb group proteins and tumour-suppression mechanisms allowed Parreno *et al.* to test *in vivo* whether cellular reprogramming sufficient for tumour initiation can be driven by purely epigenetic mechanisms.

A gene-silencing technique called RNA interference allowed the authors to reversibly reduce the levels of two members of the Polycomb group, referred to as PH proteins, in a tissue of the developing fruit-fly larva called the imaginal disc. Strikingly, transient loss of PH proteins at an early stage of development induced the formation of tumours that were characterized by abnormal tissue architecture, excessive growth and loss of cell differentiation – but were not associated with any specific permanent mutations. Importantly, Parreno *et al.* saw that these tumours remained stable even though PH protein

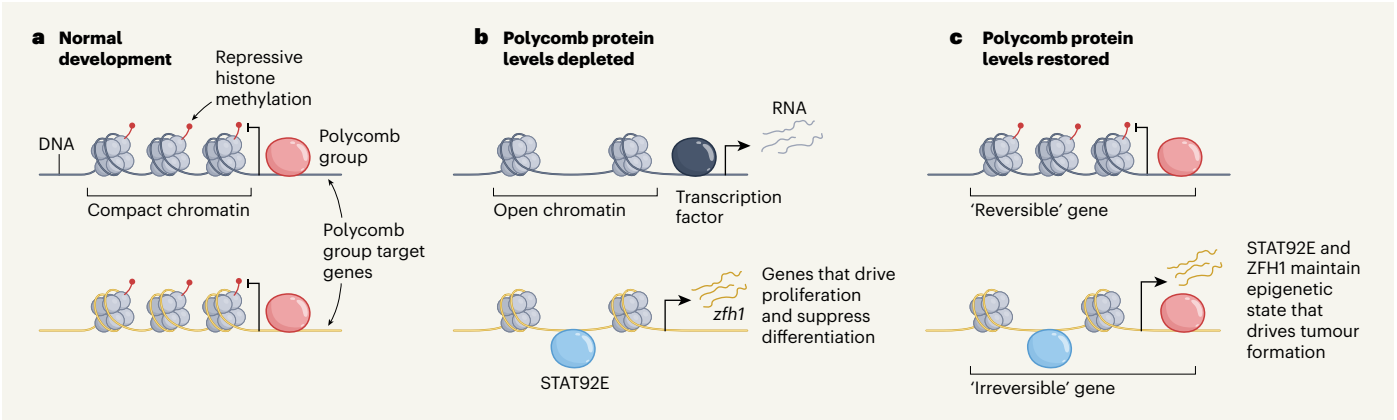

Figure 1 | Tumour initiation without permanent changes to DNA. **a**, During normal tissue development, the Polycomb group protein complex represses transcription of a set of target genes by way of epigenetic modifications: methylation of histone proteins (around which DNA is packaged to form chromatin) and compaction of chromatin. **b**, To investigate whether tumours can form as a result of changes to epigenetic regulation rather than permanent mutations, Parreno *et al.*[3] reversibly depleted levels of two Polycomb group proteins and observed tumour formation in tissue in developing fruit flies (*Drosophila melanogaster*). Loss of transcriptional repression results in chromatin becoming open and transcription of target genes, including genes that determine cell fate (top panel) and activators of the JAK–STAT signalling pathway (bottom panel). As a result, the protein STAT92E activates transcription of genes that promote cell proliferation, as well as *zfh1* (bottom panel). The ZFH1 protein (not shown) represses the transcription of genes that control cell differentiation. **c**, After Polycomb group protein levels return to normal, transcriptional repression is restored at 'reversible' target genes, but STAT92E continues to mediate transcription of 'irreversible' genes. This suggests that transient disruption of epigenetic silencing can initiate a self-perpetuating epigenetic state, sustained by STAT92E and ZFH1, that drives tumour formation.

levels returned to normal at later stages of development.

Genomic analysis of these tumours revealed that, for most of the genes that Polycomb group proteins act on, repressive histone modifications and transcriptional silencing were eventually restored. Many of these 'reversible' genes are well-known targets of the Polycomb group that encode proteins that determine developmental fate. Interestingly, the authors identified a smaller set of target genes whose upregulation was irreversible. These included genes that encode signalling proteins called cytokines, which activate an evolutionarily conserved signalling pathway called JAK–STAT that is essential for many cellular processes, including those involved in growth and development. Another affected gene was *zfh1*, which is activated by the transcription factor STAT92E, a key component of the fruit-fly JAK–STAT pathway. The ZFH1 protein, in turn, acts as a transcriptional repressor. Notably, mutations in the equivalent gene in humans, *ZEB1*, have been linked to cancer.

Transcriptional regulators such as STAT92E and ZFH1 bind to short DNA sequences called motifs to exert their effects. These motifs are often found in regions of the genome called regulatory sequences that control gene expression. The authors found that STAT92E and ZFH1 DNA-binding motifs were enriched in the regulatory sequences of genes that were activated or repressed (respectively) in stable tumours. Moreover, expression of both ZFH1 and STAT92E was required for tumour formation. This evidence suggests that these two proteins are central players in setting up a self-perpetuating epigenetic state that supports tumour growth (Fig. 1).

It is possible that the initial activation of another evolutionarily conserved signalling pathway called JNK–AP-1 could be an essential early trigger that facilitates epigenetic reprogramming. Some of Parreno and colleagues' data point to the involvement of this pathway, which is known to facilitate JAK–STAT activation. In fruit flies, JAK–STAT, ZFH1 and JNK–AP-1 are all considered to be potent regulators of cell proliferation and survival, and have been linked to stem-cell maintenance, tissue regeneration and metabolic reprogramming, as well as transdifferentiation (the process by which a cell switches from one cell-type fate to another) and tumour growth[10–14].

Parreno *et al.* shine a new light on the epigenetic plasticity of this central cellular signalling network, and show how transcriptional alterations driven by JAK–STAT, ZFH1 and perhaps JNK–AP-1 result in a self-reinforcing, abnormal epigenetic cell state that is sufficient to promote tumour initiation. The authors therefore expand on and challenge the conventional view that cancer development is caused solely by genetic mutations, and highlight the crucial role of temporary epigenetic dysregulation in mediating permanent changes that can drive tumour initiation and progression, and even different cell behaviours within tumours. Whether these findings hold true for more complex organisms such as mammals remains to be seen. Furthermore, the fruit-fly imaginal disc is a developing and therefore relatively 'plastic' tissue. It is currently unclear whether more-differentiated cell types in more mature tissues can be similarly reprogrammed through temporary disruption of epigenetic functions.

In people, temporary epigenetic changes might arise from environmental influences that are specific to an individual's life history, such as certain diets or medications, or exposure to chemical agents. Consequently, approaches to the experimental analyses of tumours need to take these transient events into account and consider their long-term consequences. This thinking underscores the importance of understanding that both the genetic and epigenetic landscapes of tumours will have implications for future clinical approaches to personalized diagnostics and treatment.

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