

Figure 1 | Early events on a pathway towards the formation of a pancreatic tumour. Neuhöfer *et al.*² report using a mouse model to shed light on factors that might initiate the formation of cancer in the pancreas. The pancreas contains acinar and ductal cells, and the authors developed a system to study the pattern of expression of the enzyme Tert in the pancreas. Tert can enable dividing cells to avoid genomic damage, by aiding in the maintenance of telomere structures (not

shown) at the ends of chromosomes. The authors report that a small subset of acinar cells express Tert. If such cells also gain a mutation in the gene *Kras*, their division is promoted (clonal expansion) compared with that of other acinar cells. Such a cell lineage further expands in cell number in response to inflammation. The authors suggest that the formation of this type of cellular lineage might set the stage for other molecular changes that lead to the formation of a precancer.

groups of cells, which recapitulates the pattern of sporadic *KRAS* mutation found in human pancreatic cells. However, a caveat to this mouse system is that the effect of telomere maintenance on cancer might differ between mice and humans, given that inbred mouse strains have considerably longer telomeres than do humans⁴. Nevertheless, the concept that Tert expression is an early event in the formation of pancreatic tumours is consistent with results in humans showing that telomere shortening is a nearly universal event even in the earliest human pancreatic precancers, and might be the prelude to TERT activation⁵.

The identification of *KRAS* mutations in populations of human acinar cells by Neuhöfer *et al.* also provides indirect support for the hypothesis of an acinar cell of origin. That said, the hypothesis that TERT-expressing human acinar cells acquire *KRAS* mutations and then give rise to precancer is not testable with existing technologies, given the lack of a reliable way to visualize TERT expression in individual cells. Moreover, the role of *KRAS*-mutant acinar cells as a possible source of human precancers remains to be defined more clearly. Nevertheless, these manipulations of a mouse-model system provide an important foundation on which to design the analyses of human tissue that are needed to confirm or refute the hypotheses put forward by Neuhöfer and colleagues.

Understanding the origin of pancreatic cancer is crucial for the design of data-driven screening and cancer-prevention strategies. If the authors' results are validated in human samples, further characterization of TERT-expressing acinar cells might point to new strategies to intercept early stages of pancreatic tumour formation in high-risk individuals through depletion of the cells of origin.

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Molecular biology

Protein condensation enables chromatin control

David Lara-Astiaso & Brian J. P. Huntly

The protein UTX regulates the DNA–protein complex chromatin to suppress tumour growth. Data suggest that the ability of UTX to condense into liquid-like droplets underlies its chromatin-regulating ability. **See p.726**

In a process called liquid–liquid phase separation, proteins and nucleic acids self-organize into liquid-like droplets called condensates¹. These dynamic, membraneless compartments enable molecules to co-localize at the optimal concentrations needed for different reactions, excluding undesired molecules, and thereby controlling complex biochemical processes in space and time². A growing number of proteins have been described that contain intrinsically disordered regions (IDRs) and can therefore form condensates, and an increasing number of processes have been reported to be controlled by liquid–liquid phase separation. On page 726, Shi *et al.*³ add UTX to this list of proteins, and tumour suppression to the processes controlled by liquid–liquid phase separation.

In cells, DNA is wrapped around histone proteins to form a complex called chromatin.

UTX is a chromatin regulator, and controls diverse processes including development, cell differentiation and cancer suppression^{4,5}. It catalyses the removal of transcriptionally repressive dimethyl and trimethyl groups from lysine amino-acid residue 27 of the H3 histone protein (an amino acid dubbed H3K27), although many of its functions seem to be independent of this demethylase activity⁶.

UTX also binds to various proteins through its tetratricopeptide repeat domains, including: MLL3 and MLL4, which are the catalytic components of larger complexes⁴; the lysine acetyltransferase enzymes CREBBP and p300; and several proteins that directly remodel chromatin^{4–6}, such as CHD4 and SMARCA4. MLL3- and MLL4-containing complexes add monomethyl and dimethyl groups to lysine 4 of H3 histones (H3K4),

whereas CREBBP and p300 add acetyl groups to H3K27. These histone modifications have an activating effect: they help to specify and activate stretches of regulatory DNA called enhancer elements that, by interacting with gene-promoter sequences in DNA, stimulate gene expression (Fig. 1).

The *UTX* gene is mutated in various cancers⁷. It resides on the X chromosome, one of the sex chromosomes: female cells carry two X chromosomes, whereas male cells carry only one. A process called X-linked inactivation silences one of the two X chromosomes in female cells; however, the *UTX* gene is in a region of the X chromosome that escapes such inactivation. As a result, *UTX* has been implicated, with other genes on the X chromosome that encode tumour suppressors, in the preponderance of cancer in males⁸.

The *UTY* gene is a counterpart of *UTX* that resides on the Y chromosome (the sex chromosome typically found in male but not female cells). *UTY* is weakly tumour-suppressive⁶, but lacks almost all demethylase activity, and it is mutated less frequently in cancers⁴ than is *UTX*.

Mutations can be missense (leading to a change in the amino-acid sequence of the protein) or, more commonly, nonsense (resulting in a truncated protein). The most common *UTX* mutation, Q555*, leads to truncation of the *UTX* protein, and a loss of its central IDR and its demethylase domain. However, mystery surrounds the mechanisms by which *UTX* and *UTY* suppress tumours. The mechanisms have been broadly linked to aberrant regulation of transcription by *UTX* and *UTY*, and variously

seem to require or be independent of the proteins' catalytic activity⁴. Shi *et al.* demonstrate that the interaction properties and catalytic activity of *UTX* depend, at least in part, on its ability to form liquid condensates.

The authors used a sophisticated series of biochemical, biophysical, genomic and functional experiments in cell culture and in mice to demonstrate that the *UTX* IDR is necessary for the formation of liquid condensates, for functional tumour suppression and for the differentiation of embryonic stem cells. In cancer cells lacking the *UTX* gene, for example, and in which the *UTY* gene is also silenced, reintroducing forms of *UTX* containing its IDR stopped the cells from growing and dividing, but this outcome did not occur when *UTX* forms lacking the IDR were reintroduced.

UTX containing the IDR of another phase-separating protein in cancer cells could also suppress tumour growth and partially restore gene-expression patterns to those of normal, non-cancerous cells. Notably, the tumour-suppressive effect of *UTX* containing an IDR from another condensate-forming protein varied depending on the IDR and the tumour cell type. This suggests that the sequence of the IDR, perhaps together with the complement of proteins specific to a given cell type, might further fine-tune liquid-liquid phase separation. Further experiments to investigate this are warranted.

The authors found that the ability of *UTX* to bind to its partners depends on its tetratricopeptide repeat and IDR, which were both required for *UTX* to co-condense with

From the archive

A report from a conference on the search for extraterrestrial life, and a reflection on scientific books.

50 years ago

The first international conference on Communication with Extraterrestrial Intelligence on this planet was held at the Byurakan Observatory in Soviet Armenia from September 5 to 11 ... There were present not only astronomers and communications experts, but biologists, historians, anthropologists, linguists and others, including two Nobel laureates, Charles Townes and Francis Crick. The subject, once treated as a bemusing speculation, is increasingly respectable ... The abundance of detectable civilizations should be proportional to their longevity as power emitting entities. Fears have grown that civilizations only slightly ahead of those on this Earth will be so good at conserving energy that there is none wasted for us to detect. Indeed, it may be possible to detect only those that want to help us, and even those may be few; as Carl Sagan put it, they may have little interest in conversing with a species as antique, in their view, as we are.

From *Nature* 1 October 1971

100 years ago

History and Bibliography of Anatomic Illustration in its Relation to Anatomic Science and the Graphic Arts. By Ludwig Choulant — Scientific books have short lives ... [W]orks containing new and original contributions are eagerly read for a short time, and their results rapidly absorbed into the pages of their successors. The older work then takes its place on the less accessible shelves of the library ... The ecological relationships of living and of dead literature may be compared to that of certain plant masses in which the upper surface alone is living and growth takes place on the hidden mass of dead vegetation. It is the special ... distinction of Ludwig Choulant (professor of medicine at Dresden, 1823–60) that he was the author of two works of reference that have remained in continuous ... use.

From *Nature* 29 September 1921

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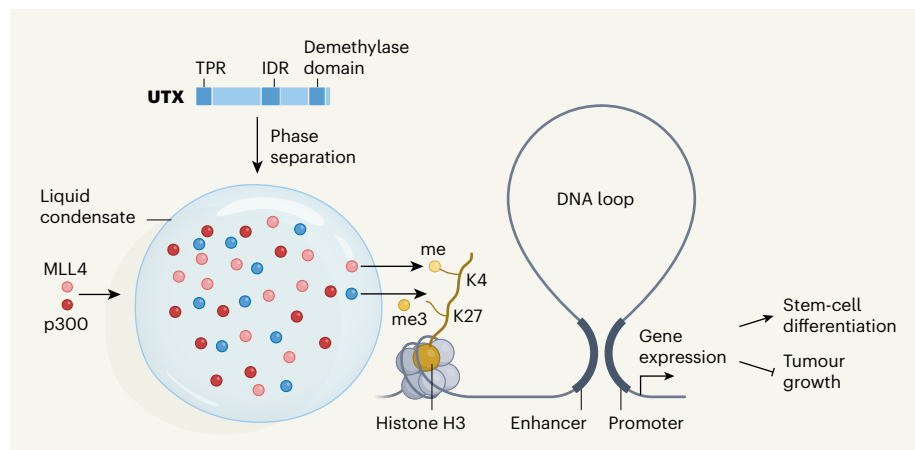


Figure 1 | The tumour-suppressive function of *UTX* protein depends on its condensation. The protein *UTX* regulates chromatin, the complex formed of DNA wrapped around histone proteins. *UTX* contains a tetratricopeptide repeat domain (TPR) that binds to other proteins, and an intrinsically disordered region (IDR) that is needed to enable the protein to undergo phase separation, whereby it condenses into a liquid-like droplet. Its catalytic demethylase domain removes trimethyl groups (me3) from the amino-acid residue lysine 27 (K27) of the histone H3 protein. Shi *et al.*³ show that phase separation of *UTX* also promotes co-condensation of its binding partners MLL4 and p300 at key regulatory regions of chromatin. This enhances the catalytic activity of *UTX* and of MLL4, which adds a methyl group (me) to lysine 4 (K4) of histone H3. Overall, this results in increases in the activity of stretches of DNA called enhancers that stimulate gene expression, together with increases in contacts between enhancers and gene promoters enabled by DNA looping, and in the expression of genes that suppress cancer and facilitate embryonic-stem-cell differentiation.

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MLL4 or p300 in cells. Shi *et al.* also show that co-condensation of UTX with MLL4 enhances the enzymatic functions of these proteins in demethylating H3K27 and methylating H3K4, respectively (Fig. 1).

Next, the authors showed that condensation affects UTX and MLL4 binding to the genome, together with the pattern of histone modifications, gene expression and the looping of DNA to allow interactions between enhancers and gene promoters. Unexpectedly, reintroducing IDR-containing UTX in the cancer cells both positively and negatively affected the binding of UTX and MLL4 to the genome, histone modifications, DNA-loop interactions and the expression of certain genes. When IDR-containing UTX was reintroduced, many of the genes that were expressed more strongly and many of the DNA-binding events that were gained were those associated with cancer inhibition, with very few associated with cell proliferation, in keeping with the restoration of tumour suppression. Lastly, the authors found that UTY was slower to form condensates than was UTX, and they speculate that this might explain why UTY suppresses tumour growth only weakly compared with UTX.

The role of phase separation in gene transcription is well described⁹. However, its role in chromatin regulation is less well studied.

This and other studies (see, for example, ref. 10) suggest that liquid condensates act as a platform to coordinate the regulation of chromatin, by bringing together protein members of specific complexes at key regulatory sites. Moreover, Shi and co-workers' study further confirms previous evidence that condensation can facilitate the catalytic activity of enzymes¹¹. It remains to be shown whether this effect reflects the concentrations of enzymes, substrates and any cofactors in the condensates (and, if so, which ones), or other properties, such as condensate-induced changes in the conformation of enzymes.

The observation that restoring the ability of UTX to form condensates has a variable effect on chromatin and gene expression suggests that this protein has a more complex role than just activating transcription, as has been suggested previously^{4,6}. However, a more detailed understanding is required of the direct or indirect nature of UTX-mediated gene repression, its possible links to liquid–liquid phase separation and the nature of possible co-condensing proteins in this process.

Together, Shi and colleagues' findings add tumour suppression to the list of cellular functions associated with phase separation, and suggest that condensates are a key physical platform for facilitating the regulation of

chromatin. The findings therefore reinforce the role of liquid–liquid phase separation as a dynamic means of functionally compartmentalizing the nucleus.

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