cannot be achieved if the system has only one dimension.

A superfluid can be rotated only by twisting its corresponding wave in such a way that the superfluid hosts a vortex, similar to a whirlpool in water. The formation of this vortex requires a certain amount of energy, so that, in practice, the superfluid does not rotate until a sufficiently large rotational force is applied to the system. This peculiar behaviour causes the superfluid to have an unconventional moment of inertia — a quantity that measures the extent to which an object resists rotational acceleration. For a supersolid, it is qualitatively expected that the crystal component will rotate like a rigid body, whereas the background gas will not[1]. Comparing the moment of inertia of the authors' supersolid with that of an ordinary solid would be one way to determine the fraction of the supersolid that exhibits superfluidity.

Another question still to be addressed is to what extent the properties of the supersolid are driven by its limited size. The properties of systems that have long-range interactions, such as the magnetic interactions in the present case, are often driven by the structure of the system's outer edges. In Norcia and colleagues' experiment, the droplet array has a structure that is extremely sensitive to the trap, indicating a high sensitivity to such boundary effects[9]. It remains to be seen whether systems larger than the authors' supersolid can be made.

In the present experiment, the background gas of the supersolid has a healing length (a quantity that, for example, determines the size of a vortex core) that is probably much smaller than the material. This observation indicates that the system is already large enough to host vortex arrays[10] and other excitations associated with the symmetries and structure of a supersolid. The full study of the dynamical properties of this phase of matter will be an exciting research topic in the next few years.

Bruno Laburthe-Tolra is at the Laser Physics Laboratory, Paris North University, 93430 Villetaneuse, France.
e-mail: laburthe-tolra@univ-paris13.fr

1. Leggett, A. J. *Phys. Rev. Lett.* **25**, 1543–1546 (1970).
2. Tanzi, L. *et al. Phys. Rev. Lett.* **122**, 130405 (2019).
3. Böttcher, F. *et al. Phys. Rev. X* **9**, 011051 (2019).
4. Chomaz, L. *et al. Phys. Rev. X* **9**, 021012 (2019).
5. Norcia, M. A. *et al. Nature* **596**, 357–361 (2021).
6. Chan, M. H. W., Hallock, R. B. & Reatto, L. *J. Low Temp. Phys.* **172**, 317–363 (2013).
7. Li, J.-R. *et al. Nature* **543**, 91–94 (2017).
8. Léonard, J., Morales, A., Zupancic, P., Esslinger, T. & Donner, T. *Nature* **543**, 87–90 (2017).
9. Roccuzzo, S. M., Stringari, S. & Recati, A. Preprint at https://arxiv.org/abs/2104.01068 (2021).
10. Gallemí, A., Roccuzzo, S. M., Stringari, S. & Recati, A. *Phys. Rev. A* **102**, 023322 (2020).

The author declares no conflicts of interest.

Women's health

An epigenetic origin for uterine fibroid tumours

Zehra Ordulu

A previously unknown subgroup of uterine fibroid tumours is driven by mutations that result in disruption of the DNA–protein complex chromatin. The findings could inform the management of this common condition. **See p.398**

More than 70% of women are at risk of developing benign tumours of the uterus wall called uterine leiomyomas (ULs) by the age of 50 (ref. 1). These tumours, which are also known as fibroids or myomas, can cause debilitating symptoms in women such as excessive bleeding, and even infertility, with surgery being the only curative treatment. ULs therefore remain the leading cause of hysterectomies in the United States[2]. Understanding the molecular mechanisms that result in UL development could assist in the discovery of new approaches to clinical care. On page 398, Berta *et al.*[3] provide insights into the molecular basis of UL formation.

Previous work has identified at least three mutually exclusive categories of UL, defined according to the genetic alterations they show: those with mutations in the gene *MED12* (70%); those in which *HMGA2* is activated (15%); and tumours in which *FH* is mutated (1%)[4]. However, a subset of ULs do not harbour any of these alterations. To characterize the molecular subgroups of ULs more comprehensively, Berta *et al.* used various molecular techniques to study the genomes of 2,263 tumours from 728 women.

The authors identified the previously known molecular subgroups in the sampled tumours, and used RNA sequencing to assess gene expression in subgroup-representative tumours and in all available tumours with unknown drivers. Nearly 40% of the tumours from the latter group showed high expression of *HMGA1* — perhaps not surprisingly, given earlier work[5] implicating *HMGA1* alterations in UL. More interestingly, the authors also identified a previously uncharacterized subclass of UL in this 'unknown driver' category. Tumours in this subclass carried alterations in the genes encoding proteins that make up the SRCAP complex, which is involved in remodelling of the genetic material in the nucleus.

DNA is packaged up in the nucleus in the form of chromatin. The DNA strand is wrapped around protein cores, each consisting of eight histone subunits, to form structural units of chromatin called nucleosomes. The SRCAP complex is an epigenetic remodeller: it regulates the structure of chromatin without altering the sequence of DNA bases. Specifically, it catalyses the incorporation of the histone variant H2A.Z into chromatin[6]. H2A.Z is involved in the regulation of gene transcription, the maintenance of genome integrity and DNA repair. Overexpression of H2A.Z is implicated in several types of cancer[6].

Berta *et al.* found alterations in six of the nine genes that encode proteins in the SRCAP complex, with *YEATS4* being the most commonly altered gene. Inactivation of both copies of SRCAP-complex genes was a common finding (Fig. 1). This inactivation was caused either by loss of the non-mutated copy of the gene or, in the case of *YEATS4* alterations, by epigenetic silencing of the remaining copy of the gene. Moreover, the authors identified six individuals who had at least two tumours with mutations in SRCAP-complex genes, suggesting that certain individuals might be particularly predisposed to such alterations, perhaps because of environmental factors or because of inherited genetic variants, known as germline alterations.

The authors therefore studied germline alterations in the protein-coding portion of the genomes of 25,506 women, stored in the UK Biobank. They found that mutations predicted to reduce the function of the proteins encoded by *YEATS4* and another SRCAP-complex gene, *ZNHIT1*, were strong candidates for an increased risk of UL. The authors validated the UL risk associated with such mutations in a replication group of 78,905 women, obtained from the UK Biobank. Remarkably, in both groups overall, the number of these germline alterations in SRCAP genes was greater than the number of *FH* mutations, which are well known to predispose women to UL[7].

Given the role of the SRCAP complex in loading H2A.Z into chromatin, the authors examined H2A.Z status in samples of myometrium (normal uterine wall) and ULs. SRCAP-altered tumours showed a striking

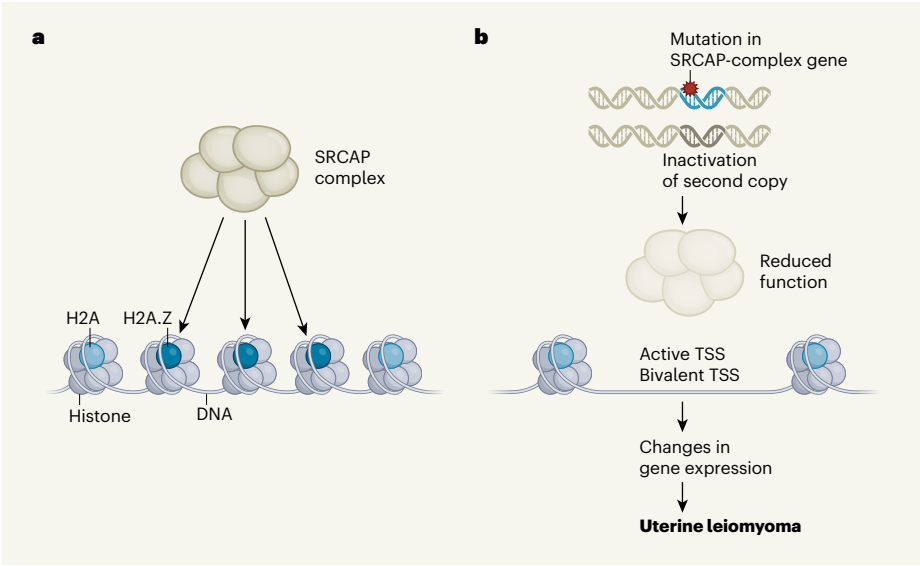

Figure 1 | A molecular mechanism underlying formation of uterine leiomyoma tumours. a, The SRCAP complex of proteins remodels chromatin (DNA wrapped around complexes of histone proteins) by loading it with the histone H2A variant H2A.Z, which regulates gene expression. **b**, Berta *et al.*[3] examined genomic alterations in 2,263 uterine leiomyoma tumours from 728 women. Some tumours were driven by mutations in genes encoding protein components of the SRCAP complex, combined with another 'second-hit' genetic alteration (such as a deletion). The resulting inactivation of both copies of a SRCAP-complex gene can reduce SRCAP-complex function. This leads to deficient loading of H2A.Z at exposed regions of chromatin that contain transcription start sites (TSSs) that are active and bivalent (that is, bearing repressive and activating regulators). Overall, this results in underexpression of some genes and overexpression of others – including certain genes involved in the spatial organization of growing tissue.

loss of H2A.Z, whereas myometrium, *MED12*-mutated tumours and *FH*-mutated tumours showed strong expression, and *HMGA1*- or *HMGA2*-altered tumours had moderate expression.

The authors then analysed H2A.Z binding to chromatin, making use of chromatin immunoprecipitation (ChIP) sequencing, a method that analyses protein–DNA interactions. Compared with myometrium, SRCAP-altered tumours showed reduced H2A.Z–chromatin binding, compatible with the loss of H2A.Z protein expression in this subgroup. Intriguingly, *MED12*-mutated tumours also had a global decrease in H2A.Z–chromatin binding, despite having strong H2A.Z expression. *HMGA2*-altered tumours that had lower H2A.Z protein expression than normal also showed decreased binding of H2A.Z.

Findings of a different assay evaluating chromatin organization were complementary to the ChIP-sequencing results. Overall, Berta *et al.* observed that chromatin activation (whereby the DNA is exposed) in *YEATS4*-mutated tumours preferentially occurred at transcription start sites (TSSs) that were active or bivalent (that is, bearing both repressive and activating epigenetic regulators). These activated chromatin regions showed reduced H2A.Z binding compared with that in myometrium. These findings are in line with previous animal studies reporting that the loss of SRCAP-complex function results in reduced H2A.Z–chromatin binding[6]. In association with this epigenetic modification at these TSSs, *YEATS4*-mutated tumours had changes in the expression of various genes (Fig. 1). Many of the genes showing increased expression were associated with the spatial organization of cells in growing tissues.

All UL subgroups exhibited increases in the expression of three sets of genes: those encoding the CBX2, CBX4 and CBX8 protein components of the canonical polycomb repressor complex 1 (cPRC1) that epigenetically silences genes to regulate development; genes encoding the developmental transcription factors SATB2 and HOXA13; and genes encoding the enzymes SRD5A2 and HSD17B6, which synthesize the sex hormone dihydrotestosterone. By contrast, expression of the gene encoding CBX7, also a component of cPRC1, was reduced. Given that mutations in *MED12* are the most common genomic alterations in UL, it is interesting that MED12 protein was previously shown to act with CBX7-containing PRC1 to repress the expression of genes involved in mouse cell differentiation[8]. Berta and colleagues' findings suggest that, regardless of the mutation status of the tumours, altered PRC1 function might lead to abnormal differentiation of cells that are encouraged to divide by overexpressed developmental transcription factors, potentially leading to UL formation. In addition, inhibiting the enzymes SRD5A2 and HSD17B6 might be a potential therapeutic strategy for treating some ULs.

"Uterine leiomyomas affect millions of women and cost more than US$1 billion in health care annually in the United States."

Berta and colleagues' study is a tour de force in the molecular subclassification of UL. Some questions remain, however. Although there are some hints of the presence of H2A.Z alterations in UL subgroups without SRCAP-complex mutations, the underlying mechanisms are still unknown. Even in SRCAP-altered tumours, a detailed understanding of how ULs might result from diminished H2A.Z–chromatin binding requires further study. The reasons why some individuals accumulate SRCAP-complex-deficient ULs are also not obvious, although the germline-alteration findings suggest a hereditary component. However, environmental factors, such as changes in an individual's hormonal milieu, might also affect the abnormal differentiation of the bivalent regions of the myometrium genome, and warrant further study. Moreover, SRCAP-complex genes are not currently targeted by clinical sequencing assays, so it might be challenging to translate these findings into routine clinical practice.

Uterine leiomyomas affect millions of women and cost more than US$1 billion in health care annually in the United States[2]. A comprehensive understanding of the genomic underpinnings of the distinct molecular subgroups of ULs might eventually inform clinical decision-making, from diagnosis to therapy. Berta and co-workers' study describes how SRCAP-complex alterations lead to decreased loading of H2A.Z into chromatin in UL, recapitulating observations in previous model systems[6]. The association of germline SRCAP-complex gene mutations with predisposition of women to develop ULs not only further supports the authors' genomic findings in the tumours, but also can have immediate clinical implications for the genetic counselling of affected women and their family members. Through multiple layers of '-omics' data, the authors suggest an epigenetic mechanism for UL development whereby deranged chromatin leads to the expression of genes involved in tumour formation.

Zehra Ordulu is in the Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114, USA, and the Department of Pathology, University of Florida, Gainesville.
e-mail: mordulusahin@ufl.edu

1. Baird, D. D., Dunson, D. B., Hill, M. C., Cousins, D. & Schectman, J. M. *Am. J. Obstet. Gynecol.* **188**, 100–107 (2003).
2. Morgan, D. M. *et al. Am. J. Obstet. Gynecol.* **218**, 425–425 (2018).
3. Berta, D. G. *et al. Nature* **596**, 398–403 (2021).
4. Mehine, M., Mäkinen, N., Heinonen, H.-R., Aaltonen, L. A. & Vahteristo, P. *Fertil. Steril.* **102**, 621–629 (2014).
5. Williams, A. J., Powell, W. L., Collins, T. & Morton, C. C. *Am. J. Pathol.* **150**, 911–918 (1997).
6. Giaimo, B. D., Ferrante, F., Herchenröther, A., Hake, S. B. & Borggrefe, T. *Epigenet. Chromatin* **12**, 37 (2019).
7. Tomlinson, I. P. M. *et al. Nature Genet.* **30**, 406–410 (2002).
8. Papadopoulou, T., Kaymak, A., Sayols, S. & Richly, H. *Cell Cycle* **15**, 1479–1493 (2016).

The author declares no competing interests.
This article was published online on 4 August 2021.

Ecology

A cocktail of pressures imperils bees

Adam J. Vanbergen

Pollinators are under threat. A meta-analysis reveals that the combination of agrochemicals, parasites and malnutrition has a cumulative negative effect on bees, and that pesticide–pesticide interactions increase bee mortality. **See p.389**

Worldwide, an estimated 20,000 species of wild and managed insects pollinate flowers, aiding plant reproduction[1]. In doing so, they form a key link in the tangled web of species interactions that support biodiverse and healthy ecosystems[1,2]. Moreover, humans enjoy a variety of sociocultural and economic benefits from pollinator biodiversity[2,3], and pollination secures crop yields that supply essential nutrients and healthy, diverse diets[1,4]. On page 389, Siviter *et al.*[5] report a pollinator threat that jeopardizes these benefits.

Pollinators and pollination are threatened by environmental pressures, including many that are a consequence of human activity (Fig. 1). These pressures include land-use and climate change[2,6], intensive agriculture[7], the spread of invasive alien species and problems with pests and disease-causing agents (pathogens)[2,8]. The individual effects of these pressures on pollinators are well established[1,2], raising the question of whether an interplay between these various pressures exacerbates the overall risk that they pose to pollinators and pollination[9–11]. This issue has been recognized by the Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services, which stated[2] in 2016 that "many drivers that directly impact the health, diversity and abundance of pollinators … can combine in their effects and thereby increase the overall pressure on pollinators".

Intensive agriculture is a multifactorial source of stress on pollinator populations[1,7,10,11]. Pollinating insects, such as bees, face the physiological challenge of acute or chronic harm from exposure to various agrochemicals, including fungicides and pesticides, that are used to protect crop plants. They also face nutritional stress arising from the lack of pollen- and nectar-providing wild flowers in large-scale, intensive crop monocultures[1,2,7,12]. Moreover, the industrial transport and use of managed high-density colonies of honey bees (*Apis mellifera*) for crop pollination can increase pollinator exposure to parasites or pathogens[2], and might result in disease spillover to wild pollinators[13]. Over the past decade, the lethal or sublethal effect of combinations of agrochemical, pathogenic or nutritional stressors on bees has been tested in many individual experiments[2,9,10].

Siviter *et al.* advance this knowledge through a quantitative meta-analysis of the effect of interactions between agrochemical, pathogenic and nutritional stressors on multiple aspects of bee health and fitness. Their analysis is notable because of the breadth of bee responses considered (for example, foraging behaviour, memory, mortality and colony reproduction), and for comparisons of the interactions of multiple classes of stressor (for example, agrochemical–parasite, parasite–nutrition, agrochemical–agrochemical and parasite–parasite interactions).

The authors conducted a monumental literature search that yielded almost 15,000 relevant individual studies. Siviter and colleagues combed through these publications to focus on the experiments that investigated the combined effect of parasites (microorganisms and invertebrates), agrochemicals and nutritional stressors on bee health. The authors selected studies that used a balanced and replicated experimental design, and that provided accessible data (means, standard deviations and sample sizes) for each treatment. This rigorous focus and quality control resulted in a final set of 90 studies being selected for further analysis.

These studies provide a total of 356 effect sizes (measurements indicating the magnitude of a relationship between factors of interest and a particular outcome) for different stressor and bee-response combinations. The authors accounted for data issues that might have confounded their accurate detection of bee responses. Such challenges included those arising from statistical non-independence of multiple effects reported from a single study, publication biases (for example, the lack of negative results), species skews (honey bee data sets predominated), and how experimental treatments such as pesticide dose compare with what might be realistically encountered in the field (termed field realism).

Siviter and colleagues tested whether the stressor interactions were synergistic, meaning that their combined effect was greater than the sum of their individual effects, as would be the case if the effect of one stressor on a bee elevates the effect of another stressor. The authors also examined alternative scenarios in which the effects of multiple stressors were antagonistic (the effect of one stressor lessens the effect of another) or additive (the combined effect is equivalent to the sum of the individual effects).

A consistent message from their analysis is that bee mortality is increased by a synergistic interaction between multiple stressors — the worst-case scenario, indicating a disproportionate effect of multiple stressors on bee survival. Interactions between different agrochemicals, rather than other stressors, drove this overall effect, and this finding held true when accounting for the field realism of the agrochemical doses. This result confirms that the cocktail of agrochemicals that bees encounter in an intensively farmed environment can create a risk to bee populations[1,2,9,14]. Multi-stressor interactions involving parasites and nutritional stress (including in combination with agrochemicals) produced additive effects on bee mortality overall.

The authors' deeper analysis of the biological complexity, however, revealed large differences between particular parasite groups in terms of the full range of additive, antagonistic and synergistic effects on bee mortality, when considering interactions between different parasites or between different parasites and nutritional stress. This variability in response, together with the lower sample sizes for the interactions involving stressors other than agrochemicals, indicate a caveat to consider and also suggest a need for more research on the combined effects of biological sources of stress.

It is intriguing that Siviter and colleagues found that additive, not synergistic, effects predominated for the non-lethal effects of stressors on fitness proxies (such as