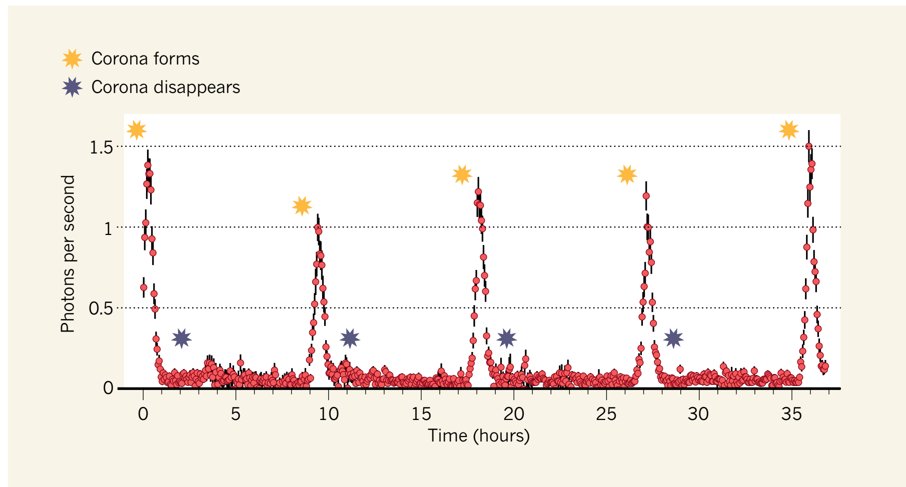

Figure 1 | Quasi-periodic X-ray eruptions from the galaxy GSN 069. Miniutti *et al.*[1] recorded the number of photons coming from GSN 069 per second, for X-ray photons that have energies in the range of 0.4 to 2 kiloelectronvolts. These data were acquired by the XMM-Newton space telescope during 16 and 17 January 2019. Each eruption lasted about an hour, and the eruptions recurred on timescales of hours. The X-ray emission is produced by the inflow of matter from a disk of material onto the supermassive black hole at the centre of GSN 069. The brightening and dimming probably occur as a result of the formation and disappearance of a warm corona of matter around the disk.

biggest variations in emission (up to 100-fold increases of amplitude) were observed at frequencies that correspond to the highest-energy photons, whereas little variation was observed for low-energy frequencies. From their spectral analysis, the authors conclude that the quasi-periodic eruptions of GSN 069 are probably associated with the transient formation and disappearance of a warm corona around a disk (Fig. 1).

In most active galaxies, however, such a corona would not form transiently — it would either be permanent or would not form at all[5]. In rare cases, known as changing-look active galaxies[6], coronas have disappeared, but the disappearance process was not followed over time[7]. The physics that underlies corona formation and eruptions is not well established, but might involve overheating associated with the presence of strong radiation in the disk.

The quasi-periodic eruptions of GSN 069 also bear some similarity to the 'heartbeat' states[8] that occasionally occur in micro-quasars — binary systems consisting of a Sun-like star and a black hole about ten times the mass of our Sun. However, the duration and recurrence of heartbeat states are on timescales of seconds.

Could the regular events that underpin the eruptions in GSN 069 occur in other active galaxies? Perhaps, but they might be more difficult to observe. The black hole at the centre of GSN 069 has a relatively small mass (about 400,000 times that of our Sun) whereas bright active galaxies can contain central black holes with a mass greater than 1 billion solar masses[9]. This means that the timescales of the eruptions in GSN 069 might be relatively short, which makes it possible for them to be seen by humans.

It should be noted that the periodic eruptions of GSN 069 only began once the initial X-ray outburst recorded in 2010 had dimmed to moderate levels — none were seen immediately after the outburst, or in observations made in 2014. Miniutti *et al.* report that the amplitude of the eruptions was decreasing over time, which means that the eruptions probably ended around late June this year, when the source finally became quite dim.

The mechanism that drives the quasi-periodic eruptions of GSN 069 must now be determined, and an explanation found for why this previously dormant galaxy rapidly became active. Further information about this source is likely to be reported in the future. More broadly, Miniutti and colleagues' observations might provide clues about the processes that underpin similar eruptions that occur much more slowly in other active galaxies. Astronomers have occasionally caught sight of such events, such as the dimming and brightening of changing-look galaxies that occurs on a timescale of years[10,11] — which is still very sudden, in the context of galactic processes. More changing-look galaxies are being sought[12], and their observation might add to our knowledge of these fascinating regular eruptions. ■

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EPIGENETICS

A key to unlock chromatin

Histone proteins pack DNA into a condensed form called chromatin. Detailed structures of the MLL family of histone-modifying protein complexes have been defined, shedding light on how they operate. SEE LETTER P.455

STEVEN J. GAMBLIN & JON R. WILSON

Each human cell contains so much DNA — about 2 metres if extended — that it must be tightly wrapped around specialized histone proteins to form spool-like structures called nucleosomes. Nucleosomes can then be packed together into dense strands called chromatin, in which the DNA is inaccessible, and must be unpacked for DNA to be accessible for transcription or replication. The dynamic conversion between inaccessible and accessible chromatin states is directed by protein complexes that write and read chemical marks on the chromatin called epigenetic modifications. On page 455, Xue *et al.*[1] describe the nucleosome-bound structure of members of the MLL family of proteins: complexes that add methyl groups to histone proteins. The new structures show how these protein complexes both write and read epigenetic modifications.

MLL complexes consist of five core proteins, including an MLL protein, which

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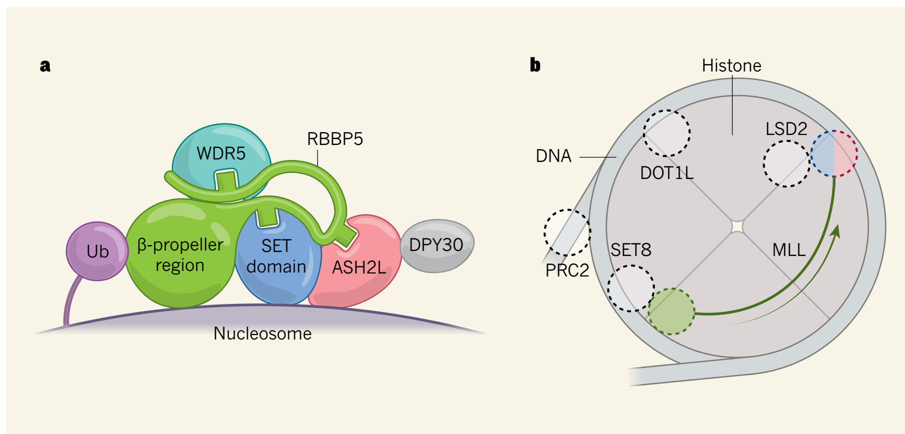

Figure 1 | How the MLL complex operates on histone proteins. DNA is wrapped around complexes of histone proteins that are called nucleosomes. **a,** The β-propeller region of the protein RBBP5, which is a subunit in the MLL family of histone-modifying complexes, recognizes a ubiquitin group (Ub) on a lysine amino-acid residue in an H2B histone. Xue *et al.*[1] used cryo-electron microscopy to determine the structure of the MLL complex. This revealed that, when RBBP5 is bound to the H2B Ub group and the nucleosome, it acts as a key to arrange the other subunits of the MLL complex, including ASH2L, DPY30, WDR5 and MLL (only the SET domain of MLL is visible in this view). This arrangement activates the SET domain, which then adds methyl groups to a lysine residue in an H3 histone (not shown). **b,** Other characterized histone-modifying complexes, including PRC2, DOT1L, SET8 and LSD2, target distinct sites (broken circles) on the nucleosome (seen here with four histone proteins wrapped in DNA) from those targeted by the MLL complex. The target of RBBP5 is depicted by the green broken circle; the methylation target is shown in blue and pink.

has a SET domain that contains the catalytic site of the complex. The organization of the human MLL complex is consistent with that observed in analyses of structures of the yeast-cell equivalent[2,3] and methylates the same lysine amino-acid residue (lysine 4, abbreviated as K4) of the H3 histone (H3K4)[4]. This implies that a version of this complex has carried out this role throughout a long evolutionary period. Another part of the MLL complex (the protein RBBP5) reads a ubiquitin group on the lysine 120 residue of the H2B histone (H2BK120ub), which promotes H3K4 methylation activity[5].

Using a technique called cryo-electron microscopy (cryo-EM), Xue *et al.* determined the structures of two MLL complexes (one containing MLL1 and the other containing MLL3) bound to their target nucleosome. The authors conducted structural and biochemical analyses to support their model of how the MLL complex operates. Altogether, they show that, analogous to a tumbler lock and key, several distinct parts of the complex must be slotted together in a particular configuration to 'switch on' the complex's methylation activity (Fig. 1a).

In the MLL complex, the otherwise unstructured region of RBBP5 called the post-β-propeller region becomes ordered, and aligns and activates the methylating subunit (Fig. 1a). Furthermore, the structures also revealed that the β-propeller domain of the RBBP5 subunit makes a major contact with the nucleosome, and with the H2BK120ub mark, which also acts to further stabilize and activate the complex. Thus, the protein subunits must be exactly organized in the complex to 'unlock' chromatin.

The structure established by Xue *et al.* reveals that the MLL complex recognizes features on the surface of the nucleosome that are different from those recognized by other characterized chromatin-modifying protein complexes (Fig. 1b). These complexes include DOT1L (refs 6, 7), SET8 (ref. 8) and LSD2 (ref. 9), which each bind different sites on the face of the nucleosome, as well as the PRC2 complex, which binds to the edge of its substrate nucleosome[10]. The differences in binding sites between these complexes can be attributed to the fact that they must each access different target residues while simultaneously reading other particular epigenetic marks. For example, whereas the MLL complex binds simultaneously to H3K4 and the H2BK120ub mark, PRC2 must bind to lysine 27 in an H3 histone (H3K27) with its active site while also binding to a K27 residue in another H3 molecule that has already been modified by trimethylation.

"A common myth is that the most functionally important parts of an examined structure tend to be the most difficult to define."

Previous insights into the structural and mechanistic bases of chromatin regulation have necessarily been restricted by the capabilities of existing methodologies. X-ray crystallography has often been used to focus on single proteins, typically achieving a resolution of 2.5 ångströms or better. More recently, cryo-EM analysis has enabled the visualization of much larger complexes, but at somewhat lower resolution (greater than 4 Å).

X-ray crystallography typically requires that the structure of the molecule studied is consistent throughout the sample. The structures that are being determined using EM can often exist in various conformations within the same sample. In both X-ray crystallography and EM, a common myth is that the most functionally important parts of an examined structure tend to be the most difficult to define, and both techniques are sensitive to the fact that some parts of proteins are intrinsically better ordered than others. However, in cryo-EM, weak molecular interactions that exist to varying extents within a sample can be stabilized, for example by introducing covalent cross-links, enabling the detection of multiple possible conformations of proteins or complexes. Thus, single-particle analysis can be used to exploit the differences between different conformations of a protein or complex to understand more about its biology.

Xue and colleagues' structures of multi-protein MLL complexes bound to nucleosomes reveal how a series of weak interactions within the complex and between the complex and the nucleosome act synergistically to turn on the activity of the enzymatic subunit of the complex. Thus, although the presence of the H2BK120ub mark does not noticeably affect the affinity of the MLL complex for the H3K4 residue, it doubles the methylation activity of the complex.

The existence of multiple structural conformations of a protein or a complex has been a confounding complication in EM studies[11]. However, the development of more-sophisticated analytical tools with which to interpret cryo-EM data means that different conformations can be described and examined to reveal a wealth of biological insights. Xue *et al.* describe several configurations of the MLL complex that interact with ubiquitin and the nucleosome in different ways. Future studies should reveal the biological relevance of the dynamic binding mode of this complex. ■

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