tumour establishment and cell proliferation at a secondary site. Thus, with regard to the metastasis of invasive ductal breast carcinoma, the pro-survival contribution of E-cadherin outweighs the advantage of E-cadherin loss boosting invasiveness.

A future research direction worth pursuing would be to determine whether there are any differences in the expression of the gene that encodes E-cadherin in cells from primary tumours, CTCs and metastatic sites. During EMT, cells are thought to go through distinct states[18], but the cell-fate transitions that occur in tumours undergoing EMT are still unknown, and might vary depending on the tumour type. It is therefore unclear whether invasive ductal breast carcinoma cells that express E-cadherin, even at low levels, are in an EMT state or are a specific cellular lineage that is not undergoing EMT. Single-cell RNA sequencing could shed light on this by revealing whether there are distinct cell populations (clones) in primary tumours or metastatic cells that do not show signs of transitioning through EMT states.

Collective dissemination, in which different types of cell migrate together in a cluster, boosts a tumour's ability to colonize distant sites[19]. If such tumour co-dependencies occur between stress-resistant cells that have high levels of E-cadherin and invasive cells that have low E-cadherin levels, collective dissemination might aid metastasis after a person's tumour has been treated by, for example, chemotherapy, causing cellular stress. Examining the patterns of such tumour evolution, as well as analysing the mechanisms of therapy failure and pathways of cancer-cell growth, particularly of treatment-resistant cancer cells, will be crucial for the development of new clinical targets, treatments and therapeutic windows of opportunity. Whether E-cadherin expression has a key role in the survival of different types of tumour or in different forms of metastasis should also be explored.

The general factors that affect tumour growth provide clues to why cellular adaptations occur during metastasis. In-depth analyses are nevertheless needed, because the genetic background of a given type of tumour might affect the requirements for metastasis to occur. Padmanaban *et al.* have shown how E-cadherin is needed for metastasis of invasive ductal carcinoma, but other types of cancer might use alternative mechanisms to manage stress, perhaps generating different tumour vulnerabilities that could be exploited therapeutically.

It would be better to prevent metastasis than to have to treat cells that have metastasized. Understanding how E-cadherin expression is stabilized might reveal a vulnerability of cancer cells on a path towards metastasis. Developing tailored treatments to tackle or prevent metastasis should be a goal of cancer research, and we are headed in the right direction to make progress on this front. ■

Roger R. Gomis *is in the Oncology Program, Institute for Research in Biomedicine, Barcelona Institute of Science and Technology, Barcelona 08028, Spain, and at CIBERONC, Barcelona, Spain, at the University of Barcelona, and at the Catalan Institution for Research and Advanced Studies, Barcelona.*
e-mail: roger.gomis@irbbarcelona.org

1. Kennecke, H. *et al. J. Clin. Oncol.* **28**, 3271–3277 (2010).
2. Bogenrieder, T. & Herlyn, M. *Oncogene* **22**, 6524–6536 (2003).
3. Padmanaban, V. *et al. Nature* **573**, 439–444 (2019).
4. Yang, J. & Weinberg, R. A. *Dev. Cell* **14**, 818–829 (2008).
5. Nakaya, Y. & Sheng, G. *Dev. Growth Differ.* **50**, 755–766 (2008).
6. Haensel, D. & Dai, X. *Dev. Dyn.* **247**, 473–480 (2018).
7. Aiello, N. M. & Kang, Y. *J. Exp. Med.* **216**, 1016–1026 (2019).
8. Onder, T. T. *et al. Cancer Res.* **68**, 3645–3654 (2008).
9. Frixen, U. H. *et al. J. Cell Biol.* **113**, 173–185 (1991).
10. Derksen, P. W. B. *et al. Cancer Cell* **10**, 437–449 (2006).
11. Ciriello, G. *et al. Cell* **163**, 506–519 (2015).
12. Onder, T. T. *et al. Cancer Res.* **68**, 3645–3654 (2008).
13. Chaffer, C. L. *et al. Cancer Res.* **66**, 11271–11287 (2006).
14. Acs, G., Lawton, T. J., Rebbeck, T. R., LiVolsi, V. A. & Zhang, P. J. *Am. J. Clin. Pathol.* **115**, 85–98 (2001).
15. Kowalski, P. J., Rubin, M. A. & Kleer, C. G. *Breast Cancer Res.* **5**, R217–R222 (2003).
16. Pastushenko, I. & Blanpain, C. *Trends Cell Biol.* **29**, 212–226 (2019).
17. Zhang, Z. *et al. Cell Death Dis.* **9**, 83 (2018).
18. Pastushenko, I. *et al. Nature* **556**, 463–468 (2018).
19. Aceto, N. *et al. Cell* **158**, 1110–1122 (2014).

This article was published online on 4 September 2019.

ASTROPHYSICS

A galaxy with hiccups

A galaxy has been seen producing strong, regular bursts of X-rays that recur on timescales of hours. The eruptions imply that the matter flowing onto the galaxy's central black hole undergoes repeated restructuring. **SEE LETTER P.381**

BOŻENA CZERNY

On page 381, Miniutti *et al.*[1] report a stunning phenomenon unlike anything observed before in a galaxy: almost-periodic eruptions that increase the X-ray emission from the host galaxy by a factor of up to 100, and which last only about an hour. Even more remarkably, these galactic hiccups recur on timescales of hours — raising questions about the mechanism that could produce such rapidly repeating events.

The galaxy in question is called GSN 069, and has a past record of surprising behaviour. It was initially classified as a field galaxy[2] (a galaxy that does not belong to a larger group or cluster of galaxies) in 1989, and at first was not observed to produce any unusual emission. But then, in 2010, its X-ray emission brightened[3] by a factor of at least 240.

This event identified GSN 069 as an 'active' galaxy, in which the efficient inflow of plasma onto a central supermassive black hole causes enormous amounts of energy to be dissipated as the material approaches the black hole's event horizon (the boundary beyond which nothing can escape the black hole's gravitational field). Some of the dissipated energy leads to the strong emission of electromagnetic radiation. Because the inflow is turbulent, the emission from the central regions of active galaxies is variable. The variability is usually stochastic, with continuous irregular increases and decreases in brightness at all timescales — which, in the case of GSN 069, were superimposed on an overall dimming trend[1].

However, in late 2018, Miniutti *et al.* observed variations in the emission from GSN 069 that were nothing like the pattern described above. They detected two X-ray eruptions by chance on 24 December 2018, during a half-day observation period using the XMM-Newton space telescope. The X-ray emission unexpectedly brightened by a factor of more than 30 over the course of about 30 minutes, returned to its previous state in about another 30 minutes, and then erupted again after a further 8 hours. The authors recorded five more eruptions during 16 and 17 January 2019, using the same instrument (Fig. 1), and three more during 14 and 15 February, using the space-based Chandra X-ray Observatory. These eruptions were extremely regular, separated in time by about 9 hours, and each lasted just over an hour.

What could the explanation be? The radiation spectra produced by many active galaxies have been interpreted as coming from a complex flow of material onto a black hole[4,5] — that is, a flow in which most of the material comes from a relatively cold (about 100,000 kelvin) disk of matter, but some of which comes from a corona of less-dense material that surrounds the disk and is about ten times warmer. In the case of the eruptions observed by Miniutti and co-workers, most of the energy must be released from a region close to a black hole that is compact enough to undergo coordinated changes of state.

Some hints about the eruption source in GSN 069 come from details of Miniutti and co-workers' analysis of how the amplitude of the outbursts depends on the range of energies of the studied photons. The

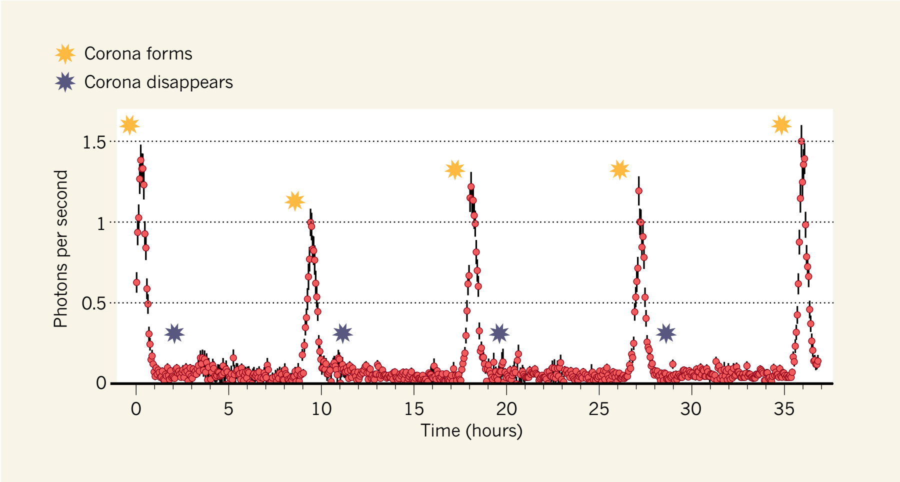

Figure 1 | Quasi-periodic X-ray eruptions from the galaxy GSN 069. Miniutti *et al.*[1] recorded the number of photons coming from GSN 069 per second, for X-ray photons that have energies in the range of 0.4 to 2 kiloelectronvolts. These data were acquired by the XMM-Newton space telescope during 16 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. ■

Bożena Czerny *is in the Center for Theoretical Physics, Polish Academy of Sciences, 02-668 Warsaw, Poland.*
e-mail: bcz@cft.edu.pl

1. Miniutti, G. *et al. Nature* **573**, 381–384 (2019).
2. Metcalfe, N., Fong, R., Shanks, T. & Kilkenny, D. *Mon. Not. R. Astron. Soc.* **236,** 207–234 (1989).
3. Miniutti, G. *et al. Mon. Not. R. Astron. Soc.* **433,** 1764–1777 (2013).
4. Czerny, B. *et al. Astron. Astrophys.* **412,** 317–329 (2003).
5. Done, C., Davis, S. W., Jin, C., Blaes, O. & Ward, M. *Mon. Not. R. Astron. Soc.* **420,** 1848–1860 (2012).
6. Trakhtenbrot, B. *et al.* Preprint at https://arxiv.org/abs/1903.11084 (2019).
7. Noda, H. & Done, C. *Mon. Not. R. Astron. Soc.* **480,** 3898–3906 (2018).
8. Belloni, T., Méndez, M., King, A. R., van der Klis, M. & van Paradijs, J. *Astrophys. J.* **488,** L109–L112 (1997).
9. Vestergaard, M. & Peterson, B. M. *Astrophysics J.* **641,** 689–709 (2006).
10. Alloin, D. *et al. Astrophys. J.* **308,** 23–36 (1986).
11. MacLeod, C. L. *et al. Mon. Not. R. Astron. Soc.* **457,** 389–404 (2016).
12. Frederick, S. *et al.* Preprint at https://arxiv.org/abs/1904.10973 (2019).

This article was published online on 11 September 2019.

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