Epigenetics

SARS-CoV-2 mimics a host protein to bypass defences

Lisa Thomann & Volker Thiel

It emerges that the SARS-CoV-2 virus has evolved to mimic one of the histone proteins that package DNA in the cell nucleus. This mimicry leads to disrupted gene transcription and a diminished antiviral response. **See p.381**

Our cells must react swiftly and efficiently to combat viral infections. In retaliation, viruses have evolved cunning strategies to interfere with or bypass the defence machinery of host cells. On page 381, Kee *et al.*[1] reveal one such strategy for SARS-CoV-2 — mimicking the histone proteins around which DNA is packaged in the cell nucleus as chromatin. This mimicry disrupts the host cell's ability to regulate gene expression and respond to infection effectively. So far, histone mimicry has been demonstrated for a handful of viruses[2], but this is the first conclusive evidence of this strategy being used by a member of the coronavirus family.

Since the beginning of the pandemic, the race has been on to understand why SARS-CoV-2 is so good at replicating in humans, and how it causes disease. The virus's genome encodes non-structural proteins needed for viral replication, structural proteins and accessory proteins; this third group is now of particular interest to researchers. Accessory proteins are less evolutionarily conserved than are other viral proteins; they have been described as having 'luxury' functions[3] that affect disease severity or virus–host interactions, or interfere with the host immune response, thus enabling the virus to replicate productively in its host[4,5].

SARS-CoV-2 can disrupt chromatin regulation[6,7] by promoting the formation of regions of densely packaged 'heterochromatin' in which gene expression is suppressed, thereby resulting in reduced antiviral responses[8,9]. Kee and colleagues set out to investigate whether histone mimicry by accessory proteins might have a role in this process. They began with a bioinformatic survey in which they compared the sequences of all SARS-CoV-2 proteins with those of all human histone proteins. They found that a sequence of six amino-acid residues was shared by the SARS-CoV-2 accessory protein Orf8 and the tail region of human histone H3. These six are alanine, arginine, lysine, serine, alanine and proline (here denoted collectively as ARKSAP, using their standard single-letter abbreviations).

The first four residues of ARKSAP, known as the ARKS motif, are also found a second time in the tail region of histone H3. Both ARKS motifs in H3 are sites commonly modified by enzymes that attach or remove molecular groups such as acetyl or methyl groups (a phenomenon known as post-translational modification). Moreover, they are crucial regulatory regions: the acetylation or methylation of lysine residues in ARKS motifs helps, respectively, to activate or repress expression of DNA in chromatin[10].

The authors speculated that the 'lookalike' ARKS motif in Orf8 might enable the viral protein to act as a histone mimic and thereby interfere with H3 functions. To provide evidence for this idea, the researchers introduced the gene that encodes Orf8 into human cells. They found that Orf8 could be detected in the nucleus (which is unusual for most coronavirus proteins). There, it interacted with chromatin and H3-containing protein complexes involved in maintaining nuclear and chromatin structure. By contrast, a version of the protein lacking the ARKS motif showed reduced binding to chromatin in the nucleus.

Kee *et al.* found that the ARKS motif of Orf8, like that of H3, was modified through acetylation (Fig. 1). Levels of the enzyme KAT2A, which is responsible for this post-translational modification, decreased markedly after Orf8 was expressed in cells. These data suggest that Orf8 can interfere with histone post-translational modifications, perhaps by triggering degradation of KAT2A, as it does with other proteins to which it binds[11]. Furthermore, histone modifications associated with active gene expression (on H3 and other histones) were reduced after Orf8 expression, and modifications associated with chromatin compaction and transcriptional repression increased. Perhaps this is a result of the reduced KAT2A levels — although it's also possible that other enzymes that mediate histone modification are directly or indirectly affected by Orf8.

Next, the authors asked whether Orf8 has the same effects on chromatin and histone regulation in cells infected with SARS-CoV-2. They generated versions of SARS-CoV-2 that either lacked the entire gene encoding Orf8 or expressed a version of the protein that lacked only the ARKSAP sequence. Unlike the wild-type virus, both modified Orf8 mutant viruses lacked the ability to disrupt host-cell chromatin, indicating that the ARKSAP sequence was responsible for this effect.

What about other viral characteristics? Kee *et al.* found that viral replication was only marginally affected by the deletions, but that transcription in the host cell was altered. Transcriptional responses to infection differed between cells infected with the wild-type virus and virus lacking Orf8 — but they also differed between cells infected with virus lacking Orf8 and virus lacking only ARKSAP. This indicates that other domains of Orf8 have functions that ultimately produce changes in gene transcription, too. Previous work supports this idea, showing that Orf8 alters the activity of certain immune pathways[12], decreases translocation

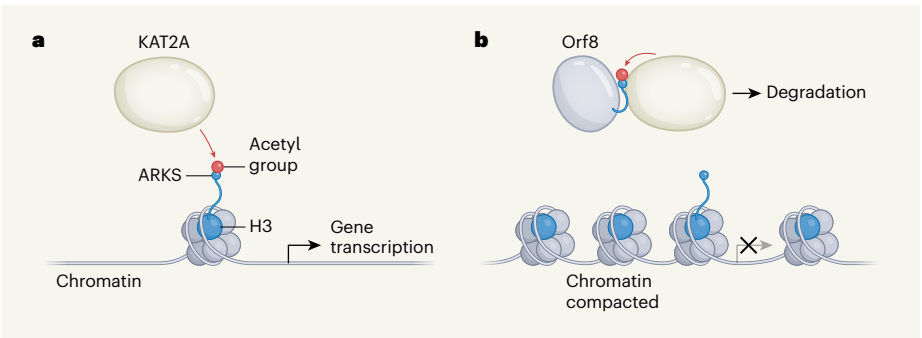

Figure 1 | Mimicking histone proteins to circumvent host defences. a, DNA is packaged around proteins such as histone H3 to form chromatin. The addition or removal of acetyl groups, among other modifications, can alter the compaction of chromatin and so lead to changes in gene expression. The enzyme KAT2A adds acetyl groups to an amino-acid sequence called the ARKS motif in H3 — a modification that promotes gene transcription. **b**, Kee *et al.*[1] report that a protein from the SARS-CoV-2 virus, Orf8, also contains an ARKS sequence. The protein binds to and is modified by KAT2A, and might trigger its degradation. Levels of H3 acetylation decrease, along with an increase in other histone modifications (not shown) that are associated with chromatin compaction and transcriptional repression.

of the immune protein interferon regulatory factor 3 to the nucleus[13], promotes stress responses in an organelle called the endoplasmic reticulum[13] and mediates degradation of immune proteins called MHC proteins[11].

Kee and colleagues' work adds another layer to our understanding of how SARS-CoV-2 interacts with host cells. It will be important to investigate further how Orf8 activity can alter virus infection and spread, and the development of disease in humans. A naturally occurring deletion in the SARS CoV-2 gene encoding Orf8 that was found in 2020 in Singapore was associated with less severe disease[14] and might provide the first hints. It remains unclear whether the decreased severity of this variant was directly linked to changes in histone mimicry, but the association shows that coronavirus accessory proteins can have roles in disease severity.

The study raises questions about virus evolution and adaptation to humans. Most of the proteins in SARS-CoV-2 and the related virus SARS-CoV, which was responsible for a smaller coronavirus pandemic in 2003, are highly evolutionarily conserved, except for Orf3b and Orf8, with the Orf8 protein of SARS-CoV lacking an ARKS motif. By contrast, some SARS-related coronaviruses in bats exhibit the motif. This might indicate that SARS-related coronaviruses are evolving to use an accessory protein and histone mimicry as part of their interference strategies.

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Physical chemistry

Secrets of light-activated catalyst particles revealed

Ulrich Aschauer

The movement of electric charges in light-activated catalyst particles is key to the water-splitting reaction, which could be used to generate hydrogen as a renewable fuel. Such movement has now been observed in exquisite detail. **See p.296**

Renewable energy sources are of great interest for reducing our dependence on fossil fuels. Light-activated catalysts — known as photocatalysts — are promising in this regard, because they convert solar energy to chemical energy that is stored in the bonds of fuel molecules. Progress in this field will require the development of new photocatalytic materials. But future advances will also hinge on an improved understanding of how electric charges are generated and transferred within photocatalyst particles, so that the particles can be rationally tuned for solar-to-fuel conversion. Such insight is challenging to obtain, given the extremely wide range of timescales and length scales involved. On page 296, Chen *et al.*[1] report an impressive advance in the spatio-temporal monitoring of excited charge carriers on single photocatalyst particles; the findings could provide much-needed detail on photocatalytic processes.

The Sun has great potential as a renewable energy source — the solar radiation that strikes Earth in just one hour is equivalent to the amount of energy currently used annually by humans[2]. The only requirement is that the radiation's energy must be converted to a usable form, such as electrical, chemical or thermal energy. Solar cells are commercially available to convert sunlight to electricity, but for some

From the archive

Detecting counterfeit whisky using nuclear technology, and the legendary origins of Scottish boulders.

50 years ago

Some of the most useful ... benefits of nuclear technology have come from the application of activation analysis to forensic problems ... The forensic uses of activation analysis depend mainly on the detection and estimation of trace elements in material gathered from the scene of a crime or from a suspect ... F. W. Lima ... told of studies on counterfeit whisky. The bottles, labels, corks — and even the contents — were not distinguishable chemically from the genuine articles, but the lead foil caps were found, by anomalies in tin and antimony content, to be of local manufacture. The object of the well-planned counterfeiting was to sell Brazilian whisky (of its kind, quite good) as a genuine Scottish product at an inflated price.

From *Nature* 13 October 1972

150 years ago

The first Report of the Committee appointed to collect statistics as to boulders ... contains much that is interesting both to the geologist and archaeologist ... Great numbers of boulders have legends attached to them, one of the commonest being that the boulder was thrown to the spot where it lies by some giant, demon, or even by "Auld Nickie Ben" himself ... [A]lmost invariably, the place from which the legend says the huge stone was thrown, is the nearest spot containing the formation to which the boulder belongs ... [B]oulders differ from the formation on or in which they are found, and in reference to what we have just mentioned, the place from which the giant or devil took his throw is often at a very considerable distance ... For example there is a large conglomerate boulder near the top of a hill, in the island of Edag, one of the Orkneys, which goes under the name of the "Giant's Stone." The legend says it was flung by a giant from the island of Stronsay; now there is no conglomerate rock which could have supplied the boulder in Edag, though there is in Stronsay.

From *Nature* 10 October 1872