34420-Bloom

**Manuscript**

Mapping mutational effects along the evolutionary landscape of HIV envelope

**Digest**

The virus that causes AIDS, known as HIV, has a protein on its surface called Env that is essential for the virus to infect cells. Env can also be recognised by the immune system, which then targets the virus for destruction or blocks it from infecting cells. Unfortunately, Env evolves very quickly, which means that HIV can evade our defences. However, there are limits to how much this protein can change, since it still needs to perform its essential role in helping viruses enter cells.

In the century since HIV first appeared in human populations, the virus has evolved considerably. There are now many HIV strains that infect people, and they bear Env proteins with substantially different sequences. However, it is not clear if these changes in sequence have resulted in Envs from distinct strains being able to tolerate different mutations.

To examine this question, Haddox et al. compared how the Envs from two strains of HIV react to modifications in their sequences. They created all possible individual mutations in the proteins, and the resulting collection of mutated viruses was then tested for their ability to infect cells in the laboratory.

Most mutations had similar effects in both Env proteins. This allowed Haddox et al. to identify portions of the protein that easily accommodate changes, and portions that must remain unchanged for viruses to remain infectious—at least in the laboratory.Some of these mutations are under different types of pressures when the virus faces the immune system, and those were identified using computational approaches.

However, some mutations were tolerated differently by the two Env proteins. Therefore, viral strains differ in how their Env proteins can evolve. The parts of Env that showed differences between the strains were not necessarily the sections that had been mutated. This showed that changes in sequence in one part of the protein can modify how other portions evolve.

It remains to be determined whether changes in tolerance to mutations translate into differences in how the virus can escape immunity. This is an important question given that the rapid evolution of Env is a major obstacle to creating a vaccine for HIV.