Snapshots of actively transcribing influenza polymerase

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The flu is caused by the highly infectious, rapidly evolving and potentially dangerous influenza virus. The genetic material of the influenza virus is single-stranded RNA. During an influenza infection, the viral RNA-dependent RNA polymerase uses the genomic RNA as a template firstly to synthesise viral messenger RNA, which is then translated into viral protein by the cellular protein synthesis machinery, and secondly, in a distinct process, to generate genome copies. The genome copies together with the newly synthesized viral proteins are then packaged into progeny virions that can go on to infect other cells and organisms. Our goal is to understand at atomic resolution the unique mechanisms whereby influenza polymerase performs transcription and replication of the viral genome. This is not only of fundamental interest but will also help understand avian to human interspecies transmission of the virus and promote development of new anti-influenza drugs targeting the polymerase.

To achieve this goal we have used a combination of the complementary methods of X-ray crystallography and single particle cryo-electron microscopy (cryoEM), most often performed at the ESRF, to determine structures of the polymerase in various functional states. In particular, recent advances in cryoEM have permitted a series of snapshots of transcribing polymerase to be obtained that, for this system, are superior in resolution to that previously obtained by X-ray crystallography. These structures constitute a molecular movie of the polymerase machine in action. In addition, structures will be presented showing the mode of action of the newly approved anti-influenza drug Xoflusa (baloxavir marboxil) that directly inhibits transcription by the polymerase and possible ways how the virus can become resistant to the drug.

References

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