Anatomy of a Viral Hijacking

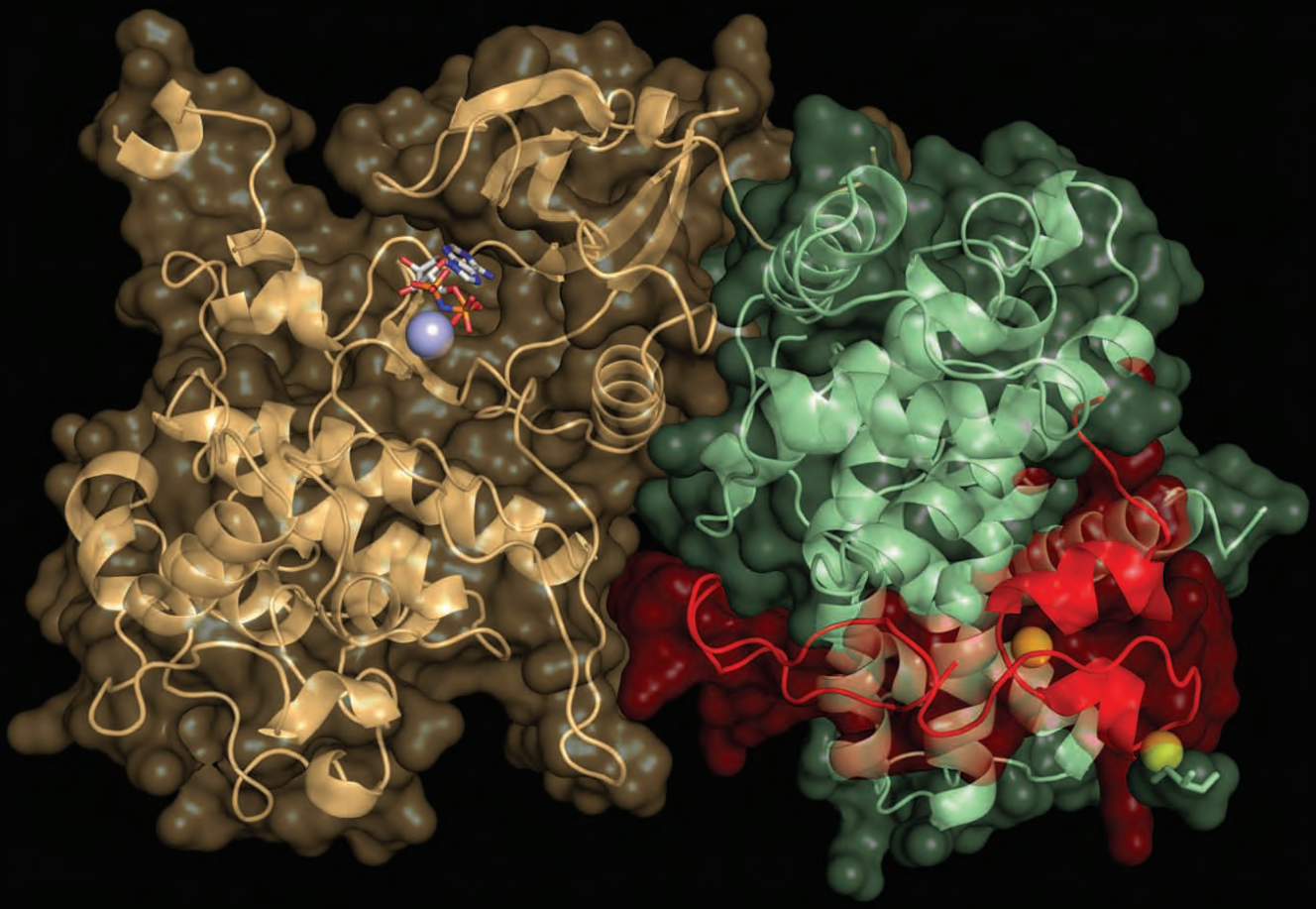

Fig. 1. Overall view of Tat•P-TEFb•ATP complex. The subunits are represented as cartoons and transparent surfaces. HIV Tat is red and Cdk9 and Cyclin T1 subunits of P-TEFb are in light orange and pale green, respectively. The ATP molecule and a bound magnesium ion are shown as sticks and a light blue ball. The Tat-bound zinc ions are shown as yellow balls. The figure was prepared with PyMOL.

Viruses are not capable of self-replication and they carry only a few genes essential to their infection cycle. They must take over their host's cellular machinery in order to transcribe their genes and translate them into proteins. These proteins are then used to build new viral particles that can spread to other cells. For the human immunodeficiency virus (HIV) this is achieved by hijacking a cellular transcription elongation factor called P-TEFb using the viral protein HIV-1 Tat. The intimate details of this hostile takeover have now been elucidated by researchers from the University of Nebraska Medical Center and the University of Iowa, who solved the structure of the P-TEFb•Tat complex utilizing the NE-CAT 24-ID-C and 24-ID-E x-ray beamlines. The work shows that Tat induces significant structural changes in P-TEFb and provides an opportunity for the design of targeted drugs that disrupt the complex and inhibit HIV replication but do not affect normal cellular functions.

Although drugs have been developed to treat HIV infection, drug resistance is common because of the rapid development of new strains of the virus that no longer respond to the drugs. Most current HIV therapies inhibit viral enzymes, but it might also be possible to block the interactions between viral proteins and host proteins that are hijacked as part of the infection process. One such interaction is that between the viral protein Tat and the positive elongation factor P-TEFb. P-TEFb functions in cells to regulate the activity of RNA polymerase II in the generation of mRNA. It consists of a cyclin-dependent kinase (Cdk9) and a cyclin subunit, cyclin T1. It is normally maintained in an inactive state by the protein HEXIM and, when activated, binds to genes and promotes transcription. However, when P-TEFb is bound to HIV Tat, it is recruited to promote the transcription of HIV genes and support HIV infection instead.

Tat proteins maintain a flexible structure and do not have much secondary structure when not bound to their target. Once bound, HIV Tat devotes a large proportion (37%) of its folded surface to interactions with P-TEFb, mainly through interactions with the cyclin T1 subunit (88%). Comparison of the structure of P-TEFb alone to that of P-TEFb•Tat revealed that HIV Tat induces significant conformational changes in P-TEFb that alter the surface that normally interacts with its inhibitor, HEXIM, as well as the substrate binding surface of its kinase subunit. This explains observations that the phosphorylation profile of the P-TEFb•Tat complex is different from that of P-TEFb alone. Alteration of the HEXIM binding surface suggests that Tat induces changes in P-TEFb that weaken HEXIM's inhibitory effect and facilitate P-TEFb extraction by HIV Tat.

In addition to increasing our understanding of the mechanism that HIV uses to take over cellular transcription for its own ends, this work provides a possible means for blocking this takeover. Comparison of sequence alignment data and the P-TEFb•Tat structure shows that HIV Tat amino acids that are crucial to P-TEFb binding are the most conserved and that those which are exposed on the protein surface are the least essential. This is important information for drug design projects that will be most effective if they target conserved amino acids that facilitate the binding interaction. Also, due to the fact that the structure of P-TEFb is very different when bound to HIV Tat, it might be possible to exploit these differences in order to design new drugs that could interfere with the interactions between P-TEFb and HIV Tat but would not inhibit normal gene transcription. This will be crucial to finding an effective treatment that can overcome the rapid evolution of HIV without harmful side effects. In fact, the research team will explore the structure of the P-TEFb•Tat complex for the design of a new generation of inhibitors called "Conditionally Anchored Smart Inhibitors," or CASIs, which will become active and inhibit P-TEFb only when it is "infected" with HIV Tat. — *Sandy Field*

See: Tahir H. Tahirov[1]*, Nigar D. Babayeva[1], Katayoun Varzavand[2], Jeffrey J. Cooper[2], Stanley C. Sedore[2], and David H. Price[2], "Crystal structure of HIV-1 Tat complexed with human P-TEFb," Nature **465**, 747 (10 June 2010). DOI:10.1038/nature09131

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