STRUCTURAL BIOLOGY

Building a super elongation complex for HIV

A better understanding of the host cell protein complex that helps HIV replicate inside cells offers the possibility of new therapeutic targets.

CHRISTOPHER P HILL AND WESLEY I SUNDQUIST

IDS, which is estimated to have claimed the lives of more than 30 million people worldwide, is caused by HIV, a member of the lentivirus family of single-stranded RNA viruses. HIV infects cells that belong to the immune system; when the virus enters a cell, a viral enzyme converts HIV RNA into double-stranded DNA through a process called reverse transcription. The viral DNA then moves to the nucleus, where another viral enzyme integrates it into the host cell’s own DNA. From this point onwards, the virus can either remain latent (and invisible to the host immune system) or it can begin to replicate to produce more virus particles. To produce its genetic material, HIV ‘hijacks’ the cell’s gene expression machinery, forcing a cellular enzyme called RNA polymerase II to transcribe viral DNA along with the cell’s own DNA.

The HIV genome encodes a protein called Tat that promotes the transcription of viral DNA (Ott et al., 2011; Razooky and Weinberger, 2011). In the absence of Tat, RNA polymerase II begins to transcribe viral DNA into RNA, but typically pauses after copying fewer than 50 nucleotides. Tat stimulates HIV transcription by binding to newly formed viral transcripts at a hairpin-shaped—or stem-loop—structure called TAR. The Tat:TAR complex then binds an enzyme called positive transcription elongation factor b (P-TEFb), which itself is a complex of two proteins, CDK9 and cyclin T1. P-TEFb releases the paused RNA polymerase II by phosphorylating cellular proteins that would otherwise inhibit transcriptional elongation, and the polymerase tail, which is then able to recruit proteins important for elongation. P-TEFb also promotes the binding of additional elongation factors to form an assembly called the ‘super elongation complex’, which is organized by highly flexible scaffolding proteins, such as AFF4 (Figure 1) (He et al., 2010; Sobhian et al., 2010; Luo et al., 2012; Chou et al., 2013).

Now, writing in eLife, Tom Alber of the University of California at Berkeley and colleagues—including Ursula Schulze-Gahmen as first author—report a crystal structure that reveals the molecular basis for the interactions between P-TEFb and AFF4, helps to reveal how this complex is bound by the viral Tat protein, and suggests new strategies for therapeutic intervention (Schulze-Gahmen et al., 2013). The crystal structure reveals that part of the polypeptide chain of the AFF4 scaffolding protein (specifically residues 34–66) snakes across the surface of cyclin T1, some distance from CDK9 (Figure 1). The AFF4 polypeptide conformation lacks contacts between regions of AFF4 that are separated by more than a few residues in the amino acid sequence, consistent with the idea that AFF4 becomes well-ordered only...
The mechanisms by which super elongation complexes assemble and function are of general interest because these complexes also help regulate cellular gene expression at the level of transcriptional elongation (Luo et al., 2012). The coupling of multiple transcription factors into a single complex allows for signals such as HIV Tat:TAR or cellular DNA-binding proteins to trigger the rapid, synchronous activation of RNA polymerase complexes that have already been reeled in or reconfigured as transcription progresses.
recruited, and which are poised to complete transcription once the brakes are removed.

Obtaining a detailed structural and mechanistic understanding of the entire Tat:TAR:pTEFb:AFF4 network is also of considerable interest for the development of HIV therapeutics. To this end, it will be important to understand precisely how the HIV Tat:TAR complex contacts pTEFb, particularly through the TAR RNA loop. Our knowledge of the structure of the Tat:TAR:cyclin T1 complex in a related virus that afflicts horses may offer some clues (Anand et al., 2008), but detailed analyses of the HIV system would help in developing therapeutically useful small molecules. Indeed, the pTEFb:AFF4 analyses already make it clear that the scaffold should be taken into account when screening for small molecules that inhibit the activation of Tat. Indeed, the structure itself inspires hope because the cyclin T1:AFF4 interface creates a pronounced Tat-binding groove that may be targetable.

Paradoxically, there is also interest in identifying small molecules that can stimulate HIV transcription. This is to facilitate immune recognition and destruction of the otherwise undetectable quiescent T cells that confound efforts to eradicate HIV by allowing the virus to remain invisible to the immune system (Mbonye and Karn, 2011). Hence, the quest to uncover fundamental biological principles and identify new therapeutic strategies should continue to fuel detailed structural and mechanistic studies of the elaborate mechanism of HIV transcriptional control.

Christopher P Hill is at the Department of Biochemistry, University of Utah School of Medicine, Salt Lake City, United States
cris@biochem.utah.edu

Wesley I Sundquist is an eLife reviewing editor, and is at the Department of Biochemistry, University of Utah School of Medicine, Salt Lake City, United States
wes@biochem.utah.edu

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