# Stop and go: How the cell deals with transcriptional roadblocks

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Gene transcription is central to cell function, as it converts the information stored in the DNA into RNA molecules of defined sequence, which then program protein synthesis. The enzyme RNA polymerase II (Pol II) is responsible for this genetic readout, but is prone to transcriptional arrest.

The biochemist Professor Patrick Cramer, Director of LMU's Genzentrum, and his research associate Dr. Alan Cheung have now shown for the first time – and captured on film -- what happens when Pol II arrests at a "roadblock". They were even able to observe how transcript is reactivated. Reactivation of arrested transcriptional complexes is a normal part of the readout process, and is therefore of fundamental significance in all cells. Indeed, as Patrick Cramer points out, "It is also utilized to regulate gene activity in stem and tumor cells." (*Nature* online, 23 February 2011)

According to Patrick Cramer, "DNA itself is a silent molecule". It takes the enzyme RNA polymerase II to bring it to life. Pol II is the molecular machine that transcribes the genetic information encoded in the DNA into molecules of messenger RNA (mRNA). These in turn act as blueprints for the synthesis of proteins, whose structures are specified by the nucleotide sequences of the mRNAs. Since proteins, which include enzymes like Pol II, carry out most functions in cells, the process of transcription is essential for life.

Transcription is highly complex and easily perturbed. Misincorporated

nucleotides and other errors are quite frequent and can cause the enzyme to arrest. In such a case, Pol II often moves in retrograde, sliding a short distance in the opposite direction along the DNA, so that the defect can be repaired. As soon as such proofreading takes place, the enzyme restarts. Sometimes, however, the enzyme moves too far backwards, and the RNA it has just synthesized gets jammed in a binding pocket.

This brings the transcription process to a complete halt, and Pol II then requires the transcription factor TFIIS to get it moving again. TFIIS alters the shape of the active center of the enzyme, so that the tangled stretch of RNA can be excised, and transcription then resumes, with Pol II synthesizing that segment again. Cramer and Cheung have dissected the mechanism of blockade and reactivation in molecular detail -- and recorded it on film.

Among other insights, it emerged that TFIIS not only displaces the trapped segment of mRNA, it also facilitates its excision. "This process occurs in all cells all the time, and is essential for their survival", says Cramer. "In addition, in higher organisms, it is utilized to regulate gene activity, particularly in stem cells and tumor cells. Pol II performs a central function in cells, and is therefore the focus of my research. My approach is increasingly influenced by systems biology, and aims to elucidate the transcriptional network of the cell and describe it in molecular and mechanistic terms".

**More information:** Structural basis of RNA polymerase II backtracking, arrest, and reactivation; Alan C.M. Cheung and Patrick Cramer, *Nature* online, February 23, 2011.

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