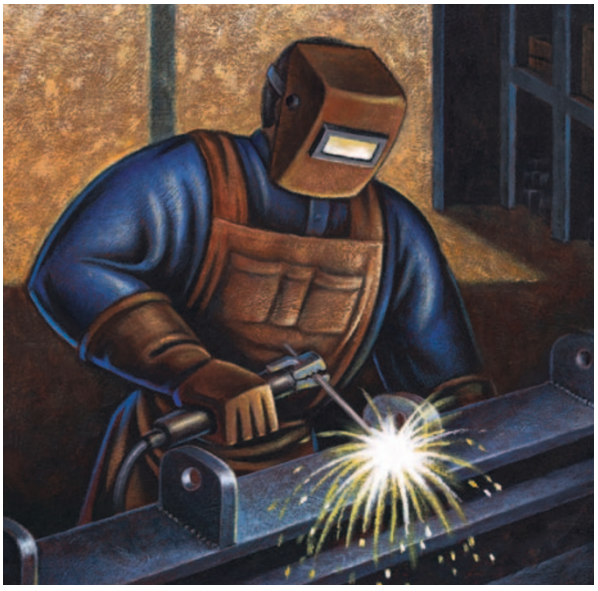
GENE REGULATION

Welded on the spot

> …determined the crystal structure of the human core EJC bound to RNA and ATP.

The exon junction complex (EJC) is loaded onto mRNA during pre-mRNA splicing and remains bound as the mature mRNA is transported to the cytoplasm, where it influences various post-transcriptional regulatory processes including mRNA surveillance, translation and localization of mature mRNAs. Andersen *et al.* and Bono *et al.* have now determined the crystal structure of the human core EJC bound to RNA and ATP.

Both groups crystallized a complex that consisted of four proteins (the DEAD-box ATPase eIF4AIII, Barentsz (Btz; also known as MLN51), Mago (or MAGOH) and Y14), an ATP analogue and RNA. The overall shape of the complex resembles an L-shaped molecule with the eIF4AIII–Btz heterodimer at the base and the Mago–Y14 heterodimer arranged almost perpendicularly to it.



eIF4AIII adopts a closed conformation with a deep interdomain cleft that buries ATP. It also binds to six RNA nucleotides on the opposite surface from the ATP-binding site, with the 3′ end interacting with domain 1 of eIF4AIII and the 5′ end interacting with domain 2. Btz also contacts the 5′ nucleotide.

Btz wraps around eIF4AIII, and a network of interactions between Btz, Mago, Y14 and eIF4AIII results in the insertion of two Mago loop regions into the interface between the two domains of eIF4AIII. This places eIF4AIII at the intersection with the other proteins of the complex.

The protein–RNA interactions and ATP-binding sites in the EJC are strikingly similar to those observed in another DEAD-box ATPase, VASA, in complex with ATP and RNA. However, the ATPase activity is inhibited in the EJC, whereas the ATPase activity of VASA is not. Both groups proposed that other components of the EJC might account for this functional difference. Andersen *et al.* showed that certain mutations in the eIF4AIII-binding region of Mago prevented EJC assembly and abolished ATPase inhibition, whereas others supported EJC assembly and only partially released ATPase inhibition. The two groups also suggested that the network of interactions that anchors Mago–Y14 and Btz at the interdomain crevice of eIF4AIII effectively locks eIF4AIII into the closed ATP-bound conformation.

Both teams showed that the structure of eIF4AIII — on its own or as part of the eIF4AIII–Btz subcomplex — had a strikingly different conformation compared with its structure when incorporated into the EJC. Domain 1 of eIF4AIII bends away from domain 2, which opens up the ATP-binding cleft and disrupts the RNA-binding site. Therefore, eIF4AIII must undergo large conformational changes upon its incorporation into the EJC.

In summary, the first three-dimensional structure of a DEAD-box ATPase associated with several regulatory partners has provided insights into their cooperative action that, in the case of the EJC, results in a stable complex that remains stably 'welded' on its spot on the mRNA.

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ORIGINAL RESEARCH PAPERS Andersen, C. B. F. *et al.* Structure of the exon junction core complex with a trapped DEAD-box ATPase bound to RNA. *Science* 24 Aug 2006 (doi:10.1126/science.1131981) | Bono, F. *et al.* The crystal structure of the exon junction complex reveals how it maintains a stable grip on mRNA. *Cell* **126**, 713–725 (2006)

FURTHER READING Maquat, L. E. Nonsense-mediated mRNA decay: splicing translation and mRNP dynamics. *Nature Rev. Mol. Cell Biol.* **5**, 89–99 (2004)