Structural gymnastics of a bacterial transcription factor: *E. coli* NrdR

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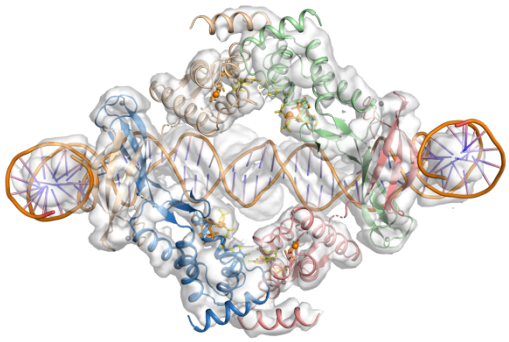
NrdR is a bacterial transcriptional repressor that controls expression of ribonucleotide reductase (RNR) genes in response to cellular levels of ATP and dATP. In all organisms studied so far, it governs the expression of all RNR genes (aerobic, anaerobic or indifferent to oxygen). As RNRs are essential for the survival of almost all living organisms due to their roles in generating the building blocks for DNA synthesis and repair, NrdR is a promising target for the development of novel antibiotics.

NrdR consists of a Zn-ribbon domain followed by an ATP-cone that binds ATP and dATP simultaneously in its repressor form, or two ATP molecules in its inactive form[1]. NrdR binds tightly and specifically upstream of RNR operons, of which *Escherichia coli* has three (*nrdAB, nrdHIEF, nrdDG*), all with 16 bp between the two "NrdR boxes" constituting the binding site.

We present crystal structures of *E. coli* NrdR in complexes with ATP-dATP and ADP-dATP, as well as cryo-EM structures of DNA-bound NrdR-ATP-dATP and novel filaments of the ATP-bound form[2]. All but the ATP-only form are tetramers formed by alternate interactions between pairs of Zn-ribbon domains and ATP-cones, respectively. However, there is considerable flexibility in orientation between the ATP-cones and Zn-ribbons. DNA-bound EcoNrdR-ATP-dATP reveals that significant conformational rearrangements accompany DNA binding while the ATP-cones retain the same relative orientation. In contrast, the ATP-loaded EcoNrdR filaments show rearrangements of the ATP-cone pairs and sequester the DNA-binding residues of NrdR in an inaccessible state. Our results point to a highly flexible transcription factor that when loaded with the correct nucleotides adapts to an optimal promoter binding conformation. Comparison with previously determined structures of NrdR from *Streptomyces coelicolor*[1] reveals species-specific mechanisms of downregulation of repressor activity by ATP.



References

1. Rozman Grinberg I, Martínez-Carranza M, Bimai O, Nouairia G, Shahid S, Lundin D, Logan DT, Sjöberg BM, Stenmark P (2022) A nucleotide-sensing oligomerization mechanism that controls NrdR-dependent transcription of ribonucleotide reductases. *Nat Commun* 13: 2700. doi: 10.1038/s41467-022-30328-1
2. Rozman Grinberg I, Bimaï O, Shahid S, Phillip L, Martínez Carranza M, Banerjee I, Lundin D, Stenmark P, Sjöberg BM & Logan DT (2024) Ribonucleotide reductase specific repressor NrdR – a multifactorial nucleotide sensor. Submitted.