Invited Lecture

Metal ion activation and DNA recognition by DR2539, the manganese sensor in *Deinococcus radiodurans*

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Deinococcus radiodurans (*Dr*) is a Gram-positive bacterium highly resistant to stress conditions. The molecular basis of its resistance has been the subject of several studies [1]. A *Dr* cell harbours multiple copies of its genome and is equipped with an efficient DNA repair system capable of repairing the entire genome through homologous recombination [1]. Additionally, its capacity to protect the proteome against Reactive Oxygen Species (ROS) enables proteins to remain fully functional after exposure to stress conditions, facilitating the recovery of bacterial DNA [2,3]. ROS scavenging is mediated by enzymatic and non-enzymatic scavengers, with manganese ions complexed with phosphates, nucleotides, or amino acids identified as the most powerful ROS scavenger in this bacterium [2,3].

The accumulation of manganese ions is pivotal for ROS scavenging and proteome protection in *Dr*. However, maintaining a balanced metal homeostasis is also essential to prevent toxicity. DR2539, a transcription regulator, plays a critical role in *Dr* manganese homeostasis [4,5]. Biophysical studies, along with crystal structures of DR2539 (dimerization and DNA binding domains) in its holo form and in complex with the 21 bp pseudo-palindromic repeat of the *dr1709* promoter region (DR1709 is a manganese transporter), provide insights into the protein activation mechanism through metal binding and DNA recognition [6].

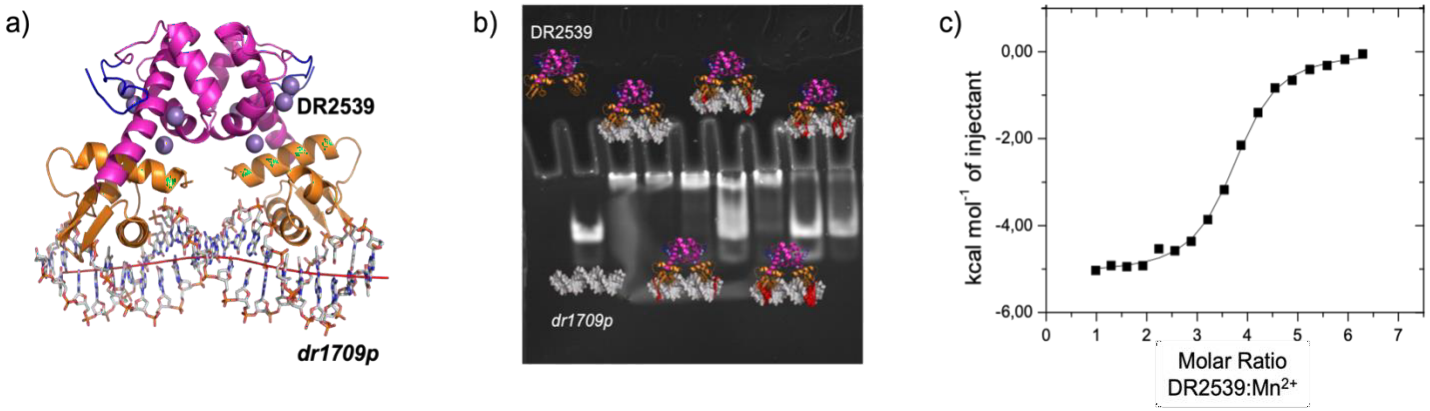

Figure 1. The manganese sensor DR2539 recognizes the *dr1709* promoter region in the presence of manganese ions. a) Structure of the ternary complex D2539:*dr1709*:Mn (PDB:8PW0). DNA binding domains in orange, dimerization domains in magenta, ancillary domains in blue and manganese ions as purple spheres; b) Protein-DNA interactions were investigated by EMSA; c) ITC assays show the binding of four manganese ions per monomer of DR2539 in solution.

[1] Slade D & Radman M (2011) Microbiol Mol Biol Rev 75, 133–191.

[2] Daly et al. (2007) PLoS Biol 5, e92.

[3] Daly MJ (2009) Nat Rev Microbiol 7, 237–245.

[4] Chen et al. (2010) Biochem Biophys Res Commun 396, 413–418.

[5] Sun et al. (2012) PLoS One 7, e35057.

[6] Mota et al. (2024) The FEBS Journal, (in press).

CM acknowledges the 'Fundação para a Ciência e Tecnologia' (FCT) for a postdoctoral contract SFRH/BEST/51724/2011. DdS and CM acknowledge Programa Pessoa from FCT and Campus France ref. 35797UH. The authors also thank the Partnership for Structural Biology, Grenoble (France) for an integrated structural biology environment and the ESRF Structural Biology Group for continuous support.