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Crystallographic snapshots of DesK and DesR: two component systems on the move

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Two-component systems (TCSs) are key players in bacterial signaling, to better understand signal-transmission with molecular detail. The TCS DesK/DesR controls fatty acid desaturation in Bacillus subtilis in response to cold shock and other membrane-altering effectors. We had previously put forward a model of signal-dependent allosteric control of the sensor kinase catalytic activity [1,2]. We have now turned our attention to the response regulator DesR. A canonical activation pathway has been widely accepted to explain phosphorylation-mediated control of response regulator function, allosterically coupling the phosphorylation site to the α4β5α5 surface. However, the structural evidence supporting the main hypotheses is still highly fragmentary. We are now reporting the crystal structure of full-length DesR, in complex with a phosphoryl-mimetic, showing the activated state [3]. Several crystal forms of the receiver domain were determined in the active and inactive configurations, revealing molecular details of the activation switch. Comparative small angle X ray scattering of full-length constructs, structure-guided point mutagenesis, as well as in vitro and in vivo functional analyses, allow us to propose an integral model of DesR activation. The phosphorylation of the receiver domain is allosterically coupled not to one, but two exposed surfaces, independently controlling its dimerization and tetramerization. Notably, a novel surface is shown to be essential for a non-canonical dimerization and activation mechanism. Direct coupling analysis highlights this interface as a shared feature of all NarL/LuxR regulators. This surface is further involved in cognate histidine kinase binding, disclosing a novel view of response regulator allosteric control. With the data we are now reporting, the DesK/DesR signaling pathway becomes, to the best of our knowledge, one of the most thoroughly studied examples of a thermosensor TCS at the molecular and biological levels.

[1] *D. Albanesi , M. Martin, F. Trajtenberg, et al, Proc Natl Acad Sci U S A, 2009, 106, 16185-16190,* ***[2]*** *F. Trajtenberg, M. Graña, N. Ruetalo, et al, J Biol Chem, 2010 285, 24892-24903,* ***[3]*** *F. Trajtenberg, D. Albanesi, N. Ruetalo, et al, submitted, 2014.*

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