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Regulation of Pseudomonas aeruginosa virulence by the ExsACDE Signaling Cascade

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Pseudomonas aeruginosa requires its type III secretion system (T3SS) to facilitate acute infections. T3SS-related gene expression is controlled by the AraC-type transcriptional activator ExsA. A signaling cascade involving ExsA and three additional proteins -ExsC, ExsD, and ExsE directly ties the up-regulation of transcription to the activation of the type III secretion apparatus. In order to characterize the molecular interactions underlying the signaling process the crystal structures of the unique T3SS chaperone ExsC in complex with its cognate effector ExsE, the structure of the negative regulator ExsD and that of the regulatory domain of ExsA have been determined. The ExsC-ExsE structure revealed two Arg-X-Val-X-Arg motifs in ExsE that form identical interactions along opposite sides of the ExsC dimer. The structure of ExsD not only provided insights into the interactions of how ExsD is sequestered by ExsC but also revealed surprising similarities between ExsD and DNA binding proteins. Based on these findings, a new model for the ExsC-ExsD complex is proposed to explain its distinctive 2:2 stoichiometry and why ExsC displays a weaker affinity for ExsD than for ExsE. Lastly, we have determined the structure of ExsA regulatory domain revealing the protein's dimerization interface. The position of the interface appears to postulate interesting conformational changes upon binding of ExsA to DNA. The crystal structures of ExsD and the ExsA domain also serve as road maps for determining the interface for the critical interactions between these two proteins at the bottom of this unique signaling cascade.

[1] R. Bernhards, A. Marsden et al., 2013, FEBS Journal 280(4):1084-1094, [2] N. Vogelaar, X. Jing et al., 2010, Biochemistry 49: 5870-5879
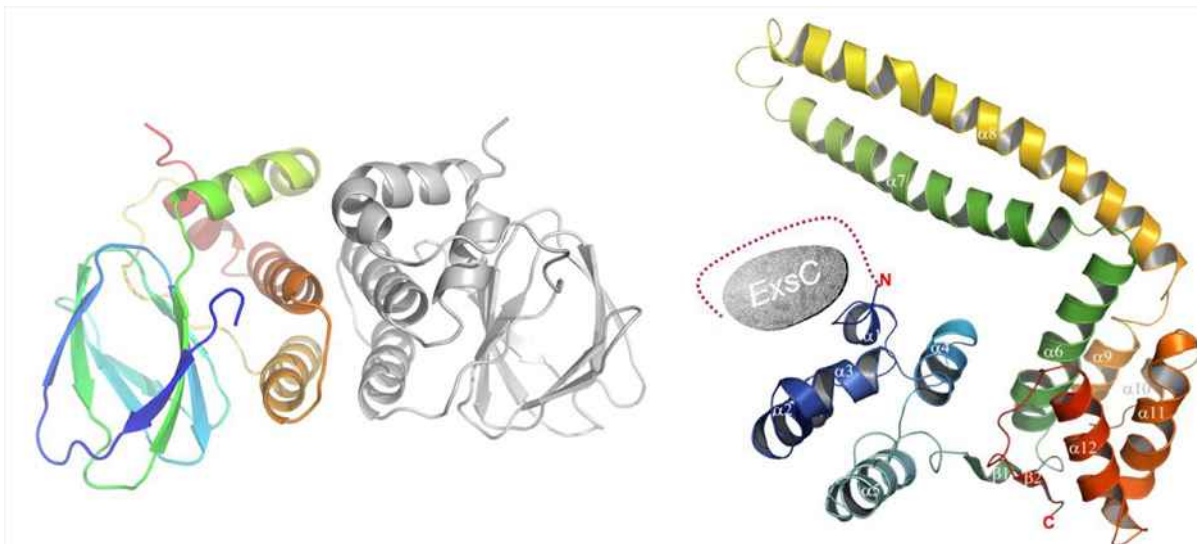
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