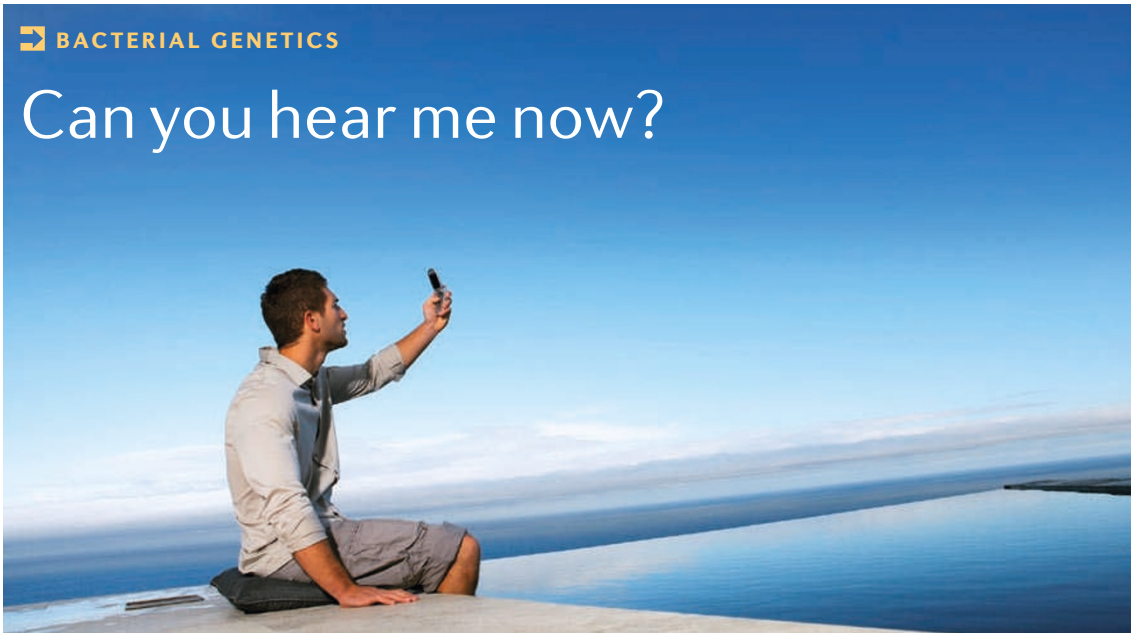
BACTERIAL GENETICS

Can you hear me now?



MACMILLAN

A bacterial two-component system consists of a sensor kinase that senses signals in the environment and transfers this information through phosphorylation and dephosphorylation of a response regulator that induces a transcriptional response when phosphorylated. In bacteria that contain multiple two-component systems, the interaction between the sensor kinase and the response regulator is very specific to ensure that the correct response is initiated. Siryaporn and colleagues now show that a robust signal transduction pathway can evolve between a sensor kinase and a response regulator that formerly interacted only weakly.

The authors investigated CpxA, a sensor kinase that phosphorylates CpxR in response to periplasmic stress, in wild-type cells. It had previously been shown that *Escherichia coli* CpxA can phosphorylate another response regulator, OmpR (which is normally regulated by the sensor kinase EnvZ) in a cell that lacks CpxR and EnvZ. However, this cross-phosphorylation of OmpR by CpxA is independent of stimulation of CpxA.

In a genetic screen, the authors identified four mutations in CpxA that increased its ability to activate OmpR. Interestingly, combining the four mutations in one protein, referred to as CpxAmut1, abolished this effect. Furthermore, CpxAmut1 decreased the levels of phosphorylated of OmpR in a strain that contained a version of EnvZ that can only phosphorylate, but not dephosphorylate, OmpR (normally leading to a high level of OmpR phosphorylation), indicating that CpxAmut1 can dephosphorylate OmpR. However, dephosphorylation of OmpR did not depend on activation of CpxAmut1, so the authors set up a screen to find activation-dependent versions of CpxA. This led to the identification of CpxAmut2, which phosphorylated OmpR in a signal-dependent manner, thus forming a rewired but functional two-component system.

Together, these results provide insight into how new connections can be forged between components of separate two-component systems. The authors propose a model in which the strength of the interaction between the sensor kinase and the response regulator sets the balance between phosphorylation and dephosphorylation activity and must be appropriately tuned for a signal-responsive interaction to be formed.

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ORIGINAL RESEARCH PAPER Siryaporn, A. *et al.* Evolving a robust signal transduction system from weak cross-talk. *Mol. Syst. Biol.* **6**, 452 (2010)