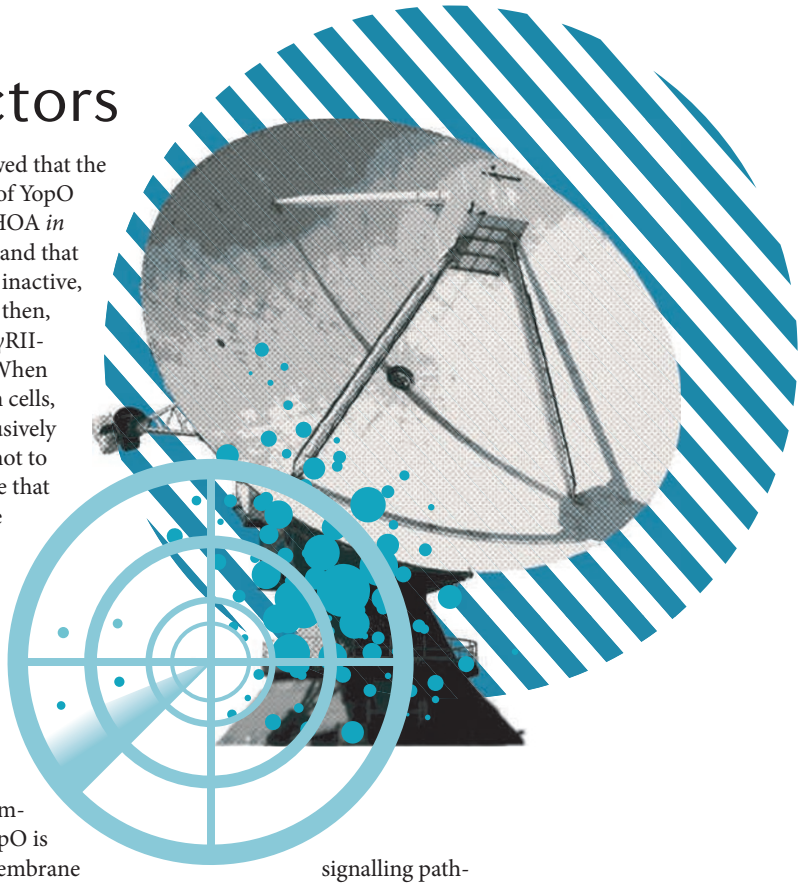
BACTERIAL PATHOGENESIS

Position effect of effectors



Many pathogens survive inside the host by injecting effector proteins into host cells. Secreted effectors can have various functions that facilitate bacterial survival, including prevention of phagocytosis. Writing in a recent issue of the *Journal of Biological Chemistry,* Groves and colleagues now show that the *Yersinia* effector YopO blocks phagocytosis through Fcγ receptor II (FcγRII), but not through complement receptor 3 (CR3), by taking advantage of the localization of a key host protein.

There are two main phagocytosis pathways in human cells, both of which rely on small monomeric GTPases. The FcγR-mediated pathway relies on Rac proteins, whereas the CR3-mediated pathway relies on RHOA. To understand how YopO inhibits phagocytosis, the authors measured inhibition of the two different pathways. Using a transfection assay, they found that YopO inhibits only phagocytosis that is mediated by FcγRII. YopO was recruited to many of the phagocytic cups that are induced after binding of an FcγRII ligand, but it had no effect on the binding of ligand to FcγRII. Interestingly, Rac was still recruited to these cups but was not activated after receptor stimulation in the presence of YopO.

The authors then showed that the carboxy-terminal region of YopO can bind to RAC1 and RHOA *in vitro* with similar affinity and that it has a preference for the inactive, GDP-bound forms. Why, then, does YopO affect only FcγRII-mediated phagocytosis? When YopO was recovered from cells, it was bound almost exclusively to RAC1 and RAC2 and not to RHOA. The authors argue that this reflects the difference in localization of these GTPases: RHOA is primarily detected in the cytosol, where it is bound with high affinity to the Rho GDP-dissociation inhibitor, whereas RAC1 and RAC2 are detected partly and completely in the membrane, respectively. As YopO is also sequestered in the membrane through its amino-terminal region, it can interact with RAC1 and RAC2 but not with RHOA, thus acquiring a specificity for FcγRII-mediated phagocytosis. This membrane localization is required, as removal of the membrane-targeting domain abrogates the function of YopO.

Thus, the targeting of an effector to a particular cellular location confers specificity for a particular host signalling pathway. As other effectors in different bacteria can also have defined distributions, it is possible that they derive a similar specificity from their targeting.

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ORIGINAL RESEARCH PAPER Groves, E. *et al.* Sequestering of RAC by the *Yersinia* effector YopO blocks Fcγ receptor-mediated phagocytosis. *J. Biol. Chem.* 19 Nov 2009 (doi: 10.1074/jbc.M109.071035)