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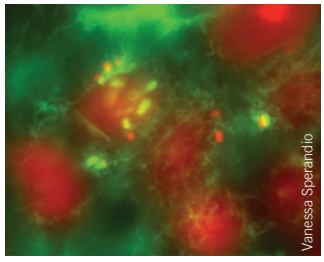
Fatty acid pools for PPARγ

Peroxisome proliferator-activated receptor-γ (PPARγ) is a member of the nuclear receptor transcription factor family and is critically important in human metabolism. Several synthetic agonists of PPARγ are known, but the identity of bona fide *in vivo* ligands has remained elusive. To shed light on this, Itoh *et al.* solved the X-ray crystal structure of PPARγ with eight putative fatty acid ligands. Similar to structures between PPARγ and synthetic ligands, a single fatty acid molecule generally contacted two clusters of polar amino acids at either end of PPARγ's unusually large ligand binding pocket. Surprisingly, the specific architecture of the interaction between the binding cleft and different fatty acids differed dramatically. In addition, the authors noted two other unexpected results. First, PPARγ simultaneously bound two molecules of the C18 fatty acid ligands, and second, oxo fatty acids were covalently attached through the thiol group of Cys285. An increase in both thermal stability and transcriptional activation capacity supported the potential biological relevance of these covalent ligands, while mutation of Cys285 abrogated the oxo fatty acid–dependent response. Collectively, these data suggest that a pool of natural ligands may coordinately activate PPARγ and that covalent coupling of particular ligands may alter the duration of the PPARγ response. (*Nat. Struct. Mol. Biol.*, published online 17 August 2008, doi:10.1038/nsmb.1474) *AD*

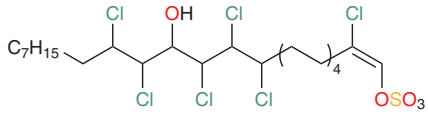
Vanquishing virulence



Discovering new broad-spectrum antibiotics is a persistent challenge that requires the identification of potential microbial drug targets while avoiding pathways that may induce bacterial resistance. Recent antibacterial approaches have eschewed compounds that kill or limit bacterial growth in favor of agents that target other important microbial pathways, such as virulence. Virulence gene expression can be triggered by bacterial autoinducers or adrenergic compounds from the host organism, which are sensed by certain membrane-bound histidine kinase receptors. To identify compounds that would inhibit the sensing properties of one of these receptors, QseC, Rasko *et al.* screened a library of 150,000 compounds for their ability to inhibit virulence gene activation in enterohemorrhagic *Escherichia coli* (EHEC). Subsequent toxicity and structure-activity studies yielded a compound called LED209 that was a picomolar antagonist of norepinephrine activation of QseC. LED209 blocked the expression of EHEC virulence genes in infected endothelial cells but produced only a small reduction of EHEC virulence in a rabbit model system. In contrast, administration of a single dose of LED209 dramatically reduced the virulence of *Salmonella typhimurium* and *Francisella tularensis* infections and increased survival times in inoculated animal models. LED209 did not affect normal β-adrenergic signaling in human cells, which indicates that QseC receptors may be an attractive target for antibacterial development. (*Science* **321**, 1078–1080, 2008) *TLS*

Written by Amy Donner, Catherine Goodman, Joanne Kotz & Terry L. Sheppard

The state of the chlorination



Chlorine is a relatively infrequent but important element in natural products such as malhamensilipin A (shown) and other chlorosulfolipids found in mussels and algae. Total synthesis of these compounds is necessary to decipher both the absolute structure of these interesting natural products and the biological role of the chlorine substituents. However, inserting these multiple chlorines can be complicated owing to the presence of neighboring functional groups and the importance of controlling stereochemistry during the reaction. Shibuya *et al.* reasoned that allylic alcohols could serve as a starting point for the construction of dichlorinated products. The authors first investigated the efficiency and stereoselectivity of two procedures, one using tetraethylammonium trichloride as a reagent and the other using an unknown reagent generated from a chemical mix of a tetraalkylammonium permanganate and trimethylsilyl chloride (TMSCl). After optimization of the reaction, the authors were able to reliably access dichlorinated products with >4.6:1 diastereomeric ratios and in reasonable (> 65%) yields, with the vicinal hydroxyl also serving in some cases as a convenient handle for stereochemical determination via cyclization. The authors then used this methodology to create a trichlorinated product that bears four stereogenic centers in common with a known chlorosulfolipid. Further application and elaboration of this strategy should allow new insights into the purpose of these unusual lipid modifications. (*J. Am. Chem. Soc.*, published online 22 August 2008, doi:10.1021/ja804167v) *CG*

Cotargeting cochaperones

Heat shock protein 90 (HSP90) is a molecular chaperone that has emerged as a promising cancer drug target because it ensures the proper folding of many oncogenic proteins in cancerous cells. Small-molecule inhibition of HSP90, for instance with the geldanamycin derivative 17-AAG, induces degradation of these oncogenic HSP90 'client' proteins through the ubiquitin-proteasome pathway, which leads to apoptosis. HSP70 proteins, of which HSC70 and HSP72 are the major isoforms, are cochaperones that bind and transfer client proteins to HSP90, and increased expression of HSP70 proteins has been implicated as a 17-AAG resistance mechanism. Powers *et al.* examined the roles of HSP70 proteins by selectively silencing either HSC70 or HSP72, but they observed no effect on cell viability. However, HSP72 silencing increased the proapoptotic effects of 17-AAG. This synergism was not due to increased HSP90 inhibition, which suggests that alternative antiapoptotic functions of HSP72 are involved. In contrast, HSC70 silencing had no impact on 17-AAG activity, likely because silencing HSC70 induced HSP72 expression. Based on these results the authors simultaneously silenced HSC70 and HSP72. Strikingly, combined depletion of these two HSP70 proteins was equivalent to 17-AAG in promoting proteasome-mediated degradation of HSP90 client proteins. Further, cancer cells, but not noncancerous cells, underwent much higher levels of apoptosis with combined HSP70 silencing than with pharmacological inhibition of HSP90. These results suggest combinatorial targeting of HSC70 and HSP72 as a new anticancer strategy. (*Cancer Cell* **14**, 250–262, 2008) *JK*