Illuminating the Single-Cell Biology of Chemical Signals in Bacterial and Immune Cells

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Abstract
The current decade has seen several unexpected discoveries of nucleotide-based signals that control the autonomous behavior of bacterial and immune cells. The newfound signaling pathways may provide new ways to combat antibiotic-resistant pathogens and to enhance the effectiveness of cancer immunotherapy treatments. However, critical questions remain about the biochemistry of the signaling enzymes and cell biology of the signals themselves. Tackling these questions requires tracking nucleotide-based signaling molecules in the complex environment of the cell, which poses a difficult molecular recognition challenge. My lab has taken a structure-based design coupled to high-throughput screening approach and was among the first to develop RNA-based fluorescent biosensors, or RBF biosensors, for live cell imaging. Our biosensors exhibit remarkable specificity and affinity for nucleotide-based signals, are the brightest to date in live cell imaging studies, and can be rationally reprogrammed to sense new ligands. In this seminar, I will present the design principles that enable effective allosteric coupling of ligand binding to fluorescence activation of a small molecule chromophore. We have demonstrated performing, in essence, in vivo biochemistry experiments to track dynamic effects of endogenous chemical cues and inhibitor compounds on enzyme activity in live bacteria. This approach has revealed a new strategy to combat antibiotic resistance. We also have applied these biosensors to make several biological discoveries, including a signaling pathway that regulates how some bacteria interact with redox reactive surfaces. Finally, I will describe another broad application for these biosensors, as novel high-throughput screening assays for promising enzyme targets in cancers and autoimmune diseases.