Illuminating biology at the nanoscale with super-resolution fluorescence microscopy

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Dissecting the inner workings of a cell requires imaging methods with molecular specificity, molecular-scale resolution, and dynamic imaging capability such that molecular interactions inside the cell can be directly visualized. Fluorescence microscopy is a powerful imaging modality for investigating cells largely owning to its molecular specificity and dynamic imaging capability. However, the spatial resolution of light microscopy, classically limited by diffraction to a few hundred nanometers, is substantially larger than molecular length scales in cells, making many sub-cellular structures difficult to resolve by light microscopy. We developed a super-resolution fluorescence microscopy method, stochastic optical reconstruction microscopy (STORM), which breaks the diffraction limit by using photo-switchable fluorescent probes to temporally separate the spatially overlapping images of individual molecules. This approach has allowed multicolor and three-dimensional imaging of living cells with nanometer-scale resolution and enabled discoveries of novel sub-cellular structures. In this talk, I will discuss the recent technological advances and biological applications of STORM. I will also describe a new single-cell transcriptome imaging method that we recently developed. System-wide analyses of the abundance and spatial organization of RNAs in single cells promise to transform our understanding in many areas of cell and developmental biology, such as the mechanisms of gene regulation, the heterogeneous behavior of cells, and the development and maintenance of cell fate. Single-molecule imaging approaches are powerful tools for counting and mapping RNA; however, the number of RNA species that can be simultaneously imaged in individual cells has been limited, making it challenging to perform transcriptomic analysis of single cells in a spatially resolved manner. To overcome this challenge, we developed a transcriptome imaging approach, multiplexed error-robust fluorescent in situ hybridization (MERFISH), which allows thousands of RNA species to be localized and quantified in single cells in situ. In this talk, I will also discuss the technology development and application of MERFISH. hhjhg