Biochemical Activity Architecture in Living Cells

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The assembly/disassembly and enzymatic activities of protein nanomachines underlie all aspects of cellular functions. The quest of understanding the molecular logic behind cellular functions requires the biomedical field to go beyond our current focus on molecular constituents of the cellular machinery and to start establishing conceptual framework to understand cellular organization of molecular activities. We hypothesize that cellular biochemical activities are spatially organized into an "activity architecture", which together with structural and mechanical architecture of the cell, encodes all the necessary information that drives cellular functions. However, testing this hypothesis is beyond the reach of the current technology because in conventional light microscopy, the diffraction of light hampers direct observation of any minute activity domains at the molecular length scale. We address this challenge by introducing a new molecular ruler, which we term Fluorescent fLuctuation Increase by Nonlocal Contact (FLINC). Exploiting its nanometer sensitivity, we developed a new class of biosensors that enabled the visualization of biochemical activities in living cells at a resolution three fold better than the diffraction limit. This general approach is applied to protein-protein interactions and kinase activities. We further present compelling evidence that cAMP dependent protein kinase (PKA) activity is restricted to distinct domains on the plasma membrane of living cells. We anticipate that this new molecular ruler will lead the way in revealing the currently hidden live-cell biochemistry activity architecture.