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Chemical tools to probe protein ubiquitination

Ubiquitin (UB) is transferred through an E1-E2-E3 enzymatic cascade to the substrate proteins to regulate their stability and biological functions in the cell. The human genome encodes 2 E1s, 45 E2s, and more than 600 E3s. Together they assemble a complex network of UB transfer for the modification of cellular proteins. Currently, key questions are unsolved on how to identify ubiquitination targets of important E3s to map them on the cell signaling networks, and how UB chains of specific linkages are assembled to encode unique signals in the cell. We have developed a method that we refer to as “orthogonal UB transfer” (OUT) to untangle the complexity of protein ubiquitination networks. The key to OUT is to engineer a cascade of engineered E1, E2 and E3 enzymes (xE1, xE2, and xE3) that exclusively transfers an engineered UB (xUB) to the substrates of a xE3. We express xUB and the OUT cascade in the cell, purify xUB-conjugated proteins, and reveal their identities by proteomics. The proteins from the OUT screen are the potential substrates of the E3 in the OUT cascade. We have developed OUT cascades with HECT E3 E6AP and U-box E3s E4B and CHIP and identified new cellular circuits regulated by these E3s. To investigate the mechanism of E2-catalyzed UB chain synthesis, we have generated linkage-specific di-UB conjugates by unnatural amino acid incorporation and expressed protein ligation. The di-UB conjugates mimic the binding modes of donor and acceptor UBs at the E2 active site for UB chain synthesis. By characterizing the structure of E2-diUB conjugates, we are to reveal how E2 regulates the synthesis of UB chains of different linkages.

Biography

Jun Yin has completed his PhD from University of California, Berkeley and postdoctoral studies from Harvard Medical School. He is an Associate Professor at the Department of Chemistry of the Georgia State University. His research focus is ubiquitin-mediate cell signaling processes and the catalytic mechanisms of protein ubiquitination enzymes.

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