A rationally-designed fluorogenic protease reporter visualizes spatiotemporal dynamics of apoptosis *in vivo*

Awardee: Xiaokun Shu
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Awardee Institution: University of California, San Francisco

Fluorescence resonance energy transfer-based reporters have been widely used in imaging cell signaling. However, their *in vivo* application has been difficult due to poor signal. While fluorogenic reporters overcome this problem, no such reporter of proteases has been demonstrated for *in vivo* imaging. Now we have designed a fluorogenic reporter that becomes fluorescent upon protease activation and requires no exogenous cofactor. To demonstrate biological applications, we have designed a fluorogenic executioner caspase reporter (iCasper) to image apoptosis in vivo, which plays fundamental roles in animal development and disease. iCasper visualizes spatiotemporal dynamics of apoptosis during embryonic development of *Drosophila*, which suggests spatiotemporal coordination between apoptosis and morphogenesis. iCasper also reveals dynamics of apoptosis during tumorigenesis of the larval brain, which may suggest overproliferation induced apoptosis followed by evasion of apoptosis. iCasper will thus be an important tool in understanding biological function and molecular regulation of apoptosis during development and may shed light on molecular mechanisms of tumorigenesis that require evasion of apoptosis. The designed scaffold can be used to engineer genetically encoded fluorogenic reporters of other proteases, which play important roles in a diverse range of biological processes and disease. Our work opens a new door in designing bio-reporters by harnessing unique protein-chromophore interaction.