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Detecting membrane contacts and associated Ca2+ signals by reversible chemogenetic reporters

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Membrane contact sites (MCSs) enable different intracellular organelles to coordinate their activities, yet the small size and the dynamic nature of these regions hinder their study by current imaging techniques. By designing a series of reversible chemogenetic reporters based on improved, low-affinity variants of splitFAST, we analysed the dynamics of different MCSs at high spatiotemporal resolution, both in vitro and in vivo. We demonstrated that these versatile reporters suit different experimental setups well and identified a hitherto unknown pathway, in which calcium (Ca2+) signalling regulates the juxtaposition between endoplasmic reticulum and mitochondria. Finally, the integration of Ca2+-sensing domains into the splitFAST technology allowed us to introduce PRINCESS (PRobe for INterorganelle Ca2+-Exchange Sites based on SplitFAST), an unprecedented class of reporters to simultaneously visualize MCSs and the associated Ca2+ dynamics by a single biosensor.

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