A cell-penetrating artificial metalloenzyme regulates a gene switch in a designer mammalian cell

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Complementing enzymes in their native environment with either homogeneous or heterogeneous catalysts is challenging due to the sea of functionalities present within a cell. To supplement these efforts, artificial metalloenzymes are drawing attention as they combine attractive features of both homogeneous catalysts and enzymes. Herein we show that such hybrid catalysts consisting of a metal cofactor, a cell-penetrating module, and a protein scaffold are taken up into HEK-293T cells where they catalyze the uncaging of a hormone. This bioorthogonal reaction causes the upregulation of a gene circuit, which in turn leads to the expression of a nanoluc-luciferase. Relying on the biotin-streptavidin technology, variation of the biotinylated ruthenium complex: the biotinylated cell-penetrating poly(disulfide) ratio can be combined with point mutations on streptavidin to optimize the catalytic uncaging of an allyl-carbamate-protected thyroid hormone triiodothyronine. These results demonstrate that artificial metalloenzymes offer highly modular tools to perform bioorthogonal catalysis in live HEK cells.
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