Optogenetic activation of receptor tyrosine kinases

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Receptor tyrosine kinases (RTKs) are a large family of membrane receptors that sense growth factors and regulate a variety of cell behaviors in health and disease. We engineered RTKs that can be selectively activated by low-intensity blue light. We selected light-oxygen-voltage (LOV)-sensing domains for their ability to activate RTKs by light-activated dimerization. Incorporation of LOV domains resulted in robust activation of relevant RTKs and the induction of cellular signaling in human cells with high spatio-temporal precision. Furthermore, light faithfully mimicked complex mitogenic and morphogenic cell behavior induced by growth factors. Next, we used light-activated RTKs to create an optogenetics-assisted drug screening platform. Our *all optical* approach obviates the addition of chemical activators or reporters, and reduces the number of operational steps. Using this platform, we screened a small library of kinase inhibitors, and we found that *tivozanib* specifically blocks the ROS1 orphan receptor, which is critically involved in lung cancer. Finally, we applied our light-activated RTKs to optically manipulate cell signaling *in vivo*. We generated a light-based fly model to trigger proliferative behavior during development, and to rescue cellular degeneration in a Parkinson's disease fly model. These results suggest that engineered light-activated receptors promise a fast and precise approach to control signaling in cells and living animals.