GENE EDITING

Shining a light on conditional CRISPR gene editing

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Although the CRISPR/Cas9 toolbox offers researchers the ability to target genes for editing with high specificity, the approach could still benefit from some additional spatiotemporal control over when and where the molecular scissors set to work. New work from Molly Steven's lab at Imperial College London shines light—literally—on such conditional CRISPR editing.

Light, they explain, has the advantages of high spatial resolution and fast on/off response, while being relatively non-invasive and with a minimal molecular footprint. To use light to control CRISPR editing, they photocaged the guide RNAs; this renders the guides inactive until the chemical bonds of the cage are 'broken' with brief exposure to ultraviolet light. Within seconds, the released guide can then initiate the editing process at its target.

They tested their photo-switchable system in cell culture and in developing zebrafish. "By using zebrafish embryos,

we could test the effect of light-induced CRISPR editing throughout the early embryo development all the way up to the point where the embryos had become swimming larvae," commented the authors via email. They chose a guide RNA that targeted the *slc45a2* gene, which is involved in melanin production—mutations disrupt pigmentation and cause albino-like phenotypes.

After confirming that the embryos tolerated the intended UV dosage, the team microinjected the editing components into the fish at the 1-2 cell stage and then uncaged the guide RNA at different developmental stages to test for temporal control. No albinism was detected in controls, while irradiated fish had more extensive mutations the earlier they were exposed to UV light.

To test for spatial control, the team waited until the head and tail of the zebrafish were visible and then activated editing only in a developing eye. Streaks

of white appeared there, while tail pigmentation remained unaffected.

There are some limits—the current photocages must be injected and will degrade over time, and the resulting mutations are mosaic in nature, which may be a drawback in some applications. The tissues that can be targeted are also limited to those that can be adequately illuminated. But encouraged by the zebrafish results, the team would like to test the system in additional animal models. "We think that the most exciting and straightforward applications of our technology are in (mammalian) embryology, as well as studies of certain pathophysiological processes, such as macular degeneration, tissue regeneration (wound healing), and skin or GI cancer progression," they said.

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