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research highlights

OPTOGENETICS

Lighting up gene regulation

PNAS **115**, E6722–E6730 (2018)

While CRISPR is the tool of choice for genome editing, it also has off-label applications. In recent years, biologists modified the targetable nuclease to regulate endogenous and exogenous gene expression by coupling it to transcriptional activators, with the complex controlled by illumination. By requiring irradiation, scientists can control spatial and temporal regulation. Most prior studies employed blue light actuation, but this approach suffers from phototoxicity issues. Authors in a current report put a twist on this by engineering a far-red light stimulated CRISPR-dCas9 effector (FACE) system. Using the longer wavelength technique, investigators showed *in vivo* upregulation of target genes in mouse muscle that significantly exceeded that of blue light activation, with no deleterious effects. As a further demonstration of its utility, FACE allowed illumination-dependent conversion of murine iPSCs to neurons via stimulation of a neuronal transcription factor. CN

<https://doi.org/10.1038/s41684-018-0138-0>

CANCER THERAPY

Improved cancer treatment through diet

Nature **559**, 632–636 (2018)

Methotrexate is an effective cancer therapy that blocks synthesis of tetrahydrofolate (THF), restricting nucleotide synthesis and proving lethal for cancer cells; however, practitioners often limit its use because of off-target toxicity. In a new study, investigators screened methotrexate-responsive cell lines for genes that impacted efficacy and identified the rate-limiting enzyme in histidine catabolism, formimidoyltransferase cyclodeaminase, which consumes THF during catalysis. When considering these and other data, authors speculated that the double whammy of increased histidine degradation and methotrexate would prove useful. Using mice injected with human leukemia cell lines, investigators compared control animals, animals fed supplemental histidine, animals dosed with moderate methotrexate, and animals that received a combination of histidine and methotrexate treatments. Mice receiving the dual intervention showed a significant decrease in tumor size compared to the other groups, paving the way for combination therapies involving diet. CN

<https://doi.org/10.1038/s41684-018-0139-z>

GENE DELIVERY

Change the ORF, please

Nat. Commun. <https://doi.org/10.1038/s41467-018-05425-9> (2018)

Genome engineering in arthropods with the CRISPR-Cas9 system is tedious, requiring microinjection of the nuclease and target sequence into individual embryos with expensive equipment. Additionally, it does not work with many species. Authors of a recent study circumvent this process by taking advantage of vitellogenesis, a nutrient delivery system driven by receptor-mediated endocytosis of yolk precursor proteins (YPP). To accomplish this, investigators conjugated the ribonucleoprotein complex to a truncated YPP and then injected the construct into female mosquitoes in order to transform eggs en masse, a process called receptor-mediated ovary transduction of cargo (ReMOT Control). After optimizing experimental conditions, including an endosomal release reagent, authors observed ReMOT Control transformation efficiencies similar to embryo injection. As YPP mediated uptake is conserved across oviparous taxa, the technique holds much promise for egg-laying species recalcitrant to other techniques. CN

<https://doi.org/10.1038/s41684-018-0140-6>

AGEING

Novel systemic factor mitigates aging

PLoS Biol. **16**, e2005796 (2018)

A hallmark of aging is discoordination of cellular processes across multiple organ systems. However, the degree to which tissues interact, be it beneficial or harmful, remains unclear. A contemporary article sheds light on this phenomenon by using genetics in *Drosophila melanogaster* to characterize a cytokine secreted from muscle and adipose tissues that impacts the gastrointestinal tract. The protein, Diedel, is an anti-apoptosis factor that enhanced proliferative homeostasis of gut tissues, improving lifespan and healthspan of flies, when expressed at appropriate levels. And despite no homologs in vertebrates, it inhibited apoptosis in murine cell lines. Interestingly, a Diedel homolog exists in Lepidopteran DNA viruses. Authors speculate it functions as a virokin, facilitating virus replication by blocking programmed cell death. CN

<https://doi.org/10.1038/s41684-018-0141-5>