CANCER

Modeling cachexia

Talbert, E. E. et al. *Cell Rep.* **28**, 1612–1622.e4 (2019)

No clinical therapies exist to treat cancer cachexia, a condition characterized by a loss of skeletal muscle mass that negatively affects the quality of life and survival of patients with cancer. Existing animal models fail to fully recapitulate human cancer cachexia, limiting our understanding of the condition and the development of new therapies.

A new study confirms that the two most commonly used xenograft mouse models of cachexia—the C-26 and LLC models—do not recapitulate the gene expression changes seen in muscles from patients with cachexia. The study also describes the development of a new genetically engineered mouse model of pancreatic ductal adenocarcinoma (PDA), the KPP mouse, which exhibits a cachectic phenotype and a transcriptional profile that more closely resemble those of patients with PDA. *ALB*

https://doi.org/10.1038/s41684-019-0412-9

GENE THERAPY

A new approach to treat muscular dystrophy

Kemaladewi, D. U. et al. *Nature* **572**, 125–130 (2019)

Congenital muscular dystrophy type 1A (MDC1A) is a neuromuscular disorder caused by mutations in the *LAMA2* gene. No cure is available but advances in gene-editing technologies might accelerate the development of new therapies.

Previous studies have established that transgenic overexpression of *Lama1*, which encodes laminin-α1, can compensate for the effects of *Lama2* mutations in a mouse model of MDC1A. However the large size of the *Lama1* cDNA, exceeding the capacity of AAV vectors, hampers the clinical translation of this approach. In a new study, investigators from the SickKids Research Institute in Toronto developed a CRISPR/Cas9 activation system to upregulate the expression of *Lama1* in MDC1A mice. This approach improved dystrophic features and disease progression and could be applied to modify the expression of a variety of disease-modifying genes. *ALB*

https://doi.org/10.1038/s41684-019-0414-7

GUT MICROBIOME

A gut microbiota–skeletal muscle axis

Lahiri, S. et al. *Sci. Transl. Med.* **11**, eaan5662 (2019)

Many studies have shown that the gut microbiome (GM) influences liver and intestinal metabolism, but few have investigated how GM regulates skeletal muscle metabolism and function. A new study comparing germ-free (GF) and pathogen-free mice (PF) reveals that GF mice lacking a GM show signs of muscle atrophy that can be rescued by transplanting GM from PF into GF mice. GF mice also display alterations in the amino acid metabolic pathway, the expression of serum choline—a precursor for the neurotransmitter acetylcholine—and the expression of genes involved in the formation and maintenance of neuromuscular junctions. Altogether these results demonstrate the role of GM in the regulation of skeletal muscle homeostasis and function. *ALB*

https://doi.org/10.1038/s41684-019-0413-8

GENE EXPRESSION

Di-siRNAs silence genes in the CNS

Alterman, J.F. et al. *Nat. Biotechnol.* **37**, 884–894 (2019)

Technologies to modulate gene expression in the central nervous system (CNS) include adeno-associated virus, antisense oligonucleotides, and siRNAs. A variety of chemical modification patterns have been explored to improve siRNA delivery into the brain, which remains challenging. In a new study, a team of investigators from the University of Massachusetts Medical School developed a divalent chemical scaffold of siRNA (di-siRNA) that allows widespread distribution of siRNA and sustained gene silencing in the CNS of mice and nonhuman primates after injection into the cerebrospinal fluid. In addition, in a mouse model of Huntington's disease, the delivery of di-siRNAs targeting *HTT* downregulated huntingtin expression throughout the brain. This siRNA design could be used in future siRNA-based strategies for the treatment of neurological disorders. *ALB*

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