■ NEURODEGENERATION

Arresting aggregation

Frontotemporal dementia and amyotrophic lateral sclerosis (ALS) are neurodegenerative diseases that have been linked to a repeat expansion of the hexanucleotide sequence GGGGCC in *C9ORF72*. RNA transcribed from this repeat forms aggregates in the nucleus of neurons that can sequester key RNA-binding proteins. Non-ATG translation from the hexanucleotide sequence also occurs, leading to the formation of potentially toxic peptide aggregates within neurons. Both of these mechanisms could contribute to disease pathogenesis. Zhaoming Su *et al.* now report their development of small molecules that bind to RNA transcribed from this sequence, which could protect vulnerable neuronal populations (*Neuron* **83**, 1043–1050, 2014).

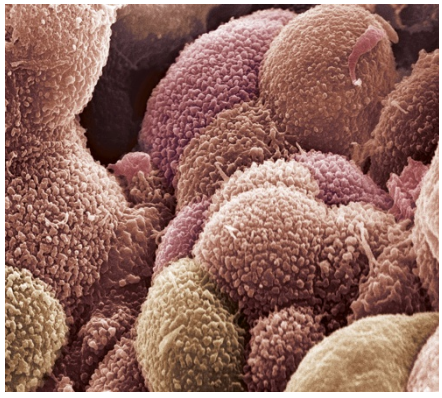
By studying the structure that the hexanucleotide RNA adopts, the researchers generated small molecules that bind the transcript. These compounds reduce formation of RNA aggregates and peptides in neurons derived from fibroblasts of human carriers of the repeat expansion. In addition, Su *et al.* developed an immunoassay that enabled detection of these peptides in the cerebrospinal fluid (CSF) of individuals with ALS carrying the repeat expansion. This suggests that peptide levels in the CSF could serve as a biomarker for therapeutic response to the compounds they identified. —*EC*

■ CANCER

Decoding the noncoding

In a recent study, Lin Zhang and his colleagues identify an oncogenic long noncoding RNA (lncRNA), *FAL1*, that may contribute to the progression of a number of different cancers (*Cancer Cell* **26**, 344–357, 2014).

The authors analyzed single nucleotide polymorphism arrays of 2,394 tumor specimens from 12 cancer types and, using the genomic locations of 13,780 lncRNAs, calculated the somatic copy number alteration frequency of each locus. lncRNAs were defined as oncogenic if they were found in at least 25% of specimens of any single tumor type, were located in a focal amplicon and could be detected in more than half of the 40 cell lines tested. Of the oncogenic lncRNAs identified, the group went on to verify that *FAL1* contributed to clonogenicity and proliferation of cell lines derived from multiple tumor types.



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In patient samples, *FAL1* copy number gain was more frequent in epithelial tumors, compared to hematopoietic and neural tumors. Furthermore, in ovarian cancer samples, *FAL1* RNA levels and genomic gain were associated with decreased survival. The authors found that *FAL1* associates with BMI1, inhibiting the proteasomal degradation of the protein and leading to altered expression of MBI1 target genes, including *CDKN1A* (encoding the cyclin-dependent kinase inhibitor p21). Intraperitoneal *FAL1* siRNA injection decreased tumor growth in the A2780 orthotopic ovarian cancer model, concomitant with an increase in p21.

This study suggests that targeting the lncRNA *FAL1* may be beneficial in cancer treatment, particularly for ovarian tumors. —*KS*

■ VACCINES

Bacteria improve vaccine responses

Influenza vaccines elicit antibodies that protect against infection. A new study by Oh *et al.* shows that gut bacteria are required for optimal antibody responses to a flu vaccine in mice (*Immunity* **41**, 478–492, 2014).

This group reported previously that Toll-like receptor 5 (TLR5) expression is increased in humans after vaccination with a trivalent inactivated influenza vaccine (TIV), and this induction correlates with antibody levels produced. Oh *et al.* now show that the influenza-specific antibody response to TIV is significantly reduced in Tlr5-deficient mice at 7 d and 84 d after vaccination, and again after a second vaccination, indicating an impaired memory response.

The authors hypothesized that flagellated bacteria are required to elicit optimal antibody responses to TIV, as flagellin is the ligand for TLR5. They showed that flu-specific antibody levels were reduced in germ-free mice after vaccination and restored by transfer of flagellated *Escherichia coli*. Antibiotic treatment also reduced antibody levels generated by the vaccine, which were restored by flagellated *E. coli*. Moreover, flagellin treatment increased the number of antibody-producing short-lived plasma cells and antibody levels produced by B cells in *vitro*. Mice with TLR5-deficient macrophages also had reduced antibody responses, suggesting that TLR5 signaling on multiple cell types is necessary for optimal humoral responses to TIV.

Understanding how high levels of antibodies are elicited by unadjuvanted vaccines such as TIV could help develop methods to improve vaccine efficacy. —*AF*

■ METABOLIC SYNDROME

Sweeteners and glucose intolerance

Consumption of noncaloric artificial sweeteners (NAS) such as saccharin, sucralose and aspartame has been tentatively linked to metabolic syndrome. Eran Elinav and his colleagues (*Nature* doi:10.1038/nature13793) now find a connection between NAS consumption, glucose intolerance and changes in the gut microbiota in mice and humans.

NAS consumption over several weeks induced glucose intolerance in both lean and obese mice. Antibiotic treatment prevented this, suggesting a role for the host microbiota. Fecal transplantation from a NAS-fed mouse to a germ-free host also induced glucose intolerance, in the absence of host NAS consumption. The effect of NAS on gut microbial content was direct, as transplant of fecal samples from naive mice that had been cultured with saccharin to germ-free mice led to host microbiota changes that were similar to those caused by dietary consumption.

The authors also found that in humans, self-reported levels of long-term NAS consumption are correlated with clinical measures of metabolic syndrome. A causative role for NAS in abnormal metabolic parameters was also established in a small short-term trial, in which NAS-naive individuals consumed saccharin for 1 week. This led to deterioration in glycemic responses in four out of the seven people studied that was mirrored by changes in the gut microbiota. These findings suggest dietary NAS consumption has a negative effect on metabolism in some individuals. —*FC*

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