Intramural papers of the month
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- NTP researchers find potential treatment for damaged salivary glands is safe and effective
- Human obesity increases colon cancer risk
- New computational approach identifies essential stem cell genes
- p53 and NF-kappaB work together to promote inflammation
- More evidence for smoking-related changes in DNA methylation

NTP researchers find potential treatment for damaged salivary glands is safe and effective

Researchers from NTP and the National Institute of Dental and Craniofacial Research have demonstrated that an adeno-associated virus (AAV) that contains the human aquaporin-1 gene (hAQP1) may be used to treat salivary gland dysfunction. The hAQP1-encoded protein is a molecular water channel that promotes the rapid movement of water in or out of a cell. Since patients with head and neck cancers often experience irreversible salivary gland damage as a result of radiation therapy, the new strategy may offer a way to prevent the conditions that arise in these patients, such as dry mouth, oral infections, and difficulty swallowing.

In a previous small-scale clinical trial, involving 11 patients with damaged salivary glands, researchers delivered adenoviral vector encoding hAQP1, which resulted in increased salivary flow in 5 patients. However, the gains were short-lived. The research team then evaluated a serotype 2 recombinant AAV encoding AQP1 (rAAV2hAQP1).

The scientists delivered increasing concentrations of rAAV2hAQP1 directly to impaired parotid glands in mice. The procedure caused mild local inflammation, but the vector remained localized to the ducts. Proper salivary gland function was restored and no significant adverse effects were noted in clinical chemistry or histopathology evaluations, indicating the treatment is clinically safe. Submission for a clinical trial is underway. (GK)


Human obesity increases colon cancer risk

A research team, led by NIEHS scientists, determined that obesity, rather than diet, causes changes in the colon that may lead to colorectal cancer. The work provides support to the belief that calorie control and frequent exercise are keys to lowering risk.

The researchers used two groups of mice. The first contained a human version of the gene NAG-1, which protects against colon cancer, and the second lacked this gene. Both groups were fed a high-fat diet. The scientists determined that the NAG-1 group did not gain weight, while the second group grew plump. After studying histone acetylation patterns in isolated colon cells, team members found that the acetylation patterns in the obese group resembled patterns from mice that had colorectal cancer. The additional weight carried by this group also activated genes that helped promote the rapid progression of cancer.

The findings suggest that preexisting colon lesions in obese individuals are more likely to rapidly evolve into malignant tumors. The group is working to identify signaling pathways, which may help scientists find ways to treat colorectal cancer in obese patients. (SB)


New computational approach identifies essential stem cell genes

NIEHS researchers have developed a computational approach to systematically integrate published gene expression data to identify genes that define a cell’s identity. The approach, which was validated in an article that appeared in the journal PNAS, identified genes with essential roles in embryonic stem cell (ESC) maintenance and cell fate decisions in cancer.
Although genetic screens have implicated more than 400 genes in ESC maintenance, these screens have limited overlap, and secondary validation remains a costly and time-consuming alternative. To preselect and prioritize candidate genes, the authors developed a bioinformatics framework to rank-order genes based on gene expression data from 68 experiments profiling undifferentiated ESCs and various differentiated cell types. The effectiveness of the approach was evident from the enrichment of well-characterized ESC regulators, including Oct4, Nanog, and Sox2. Furthermore, the authors uncovered many novel ESC maintenance genes, including Nucleolin, which they report, for the first time, as a key upstream regulator of Nanog.

The authors believe that the utility of their computational approach to identifying ESC gene regulators reaches beyond understanding basic ESC biology. Many parallels exist between ESC self-renewal and tumorigenesis. Identifying and understanding the gene networks that are associated with traits found in both ESCs and cancer will likely enhance scientists’ understanding of tumor initiation. (SW)


p53 and NF-kappaB work together to promote inflammation

Scientists at NIEHS and the University of North Carolina at Chapel Hill reported that the tumor suppressor p53, and the transcriptional regulator nuclear factor-kappaB (NF-kappaB), work together in human macrophages to induce inflammation. The study, which was published in the journal Cancer Research, suggests that pharmaceutical compounds designed to block this interaction could help treat the inflammation many cancer patients experience during chemotherapy.

The study compared expression levels of cytokines and chemokines in macrophages from healthy humans and tumor-conditioned macrophages. The authors observed increased expression of proinflammatory genes, interleukin 6 (IL-6), and chemokine (C-X-C motif) ligand 1 (CXCL1), in the macrophages, when p53 was activated by chemotherapeutic drugs. They noted that NF-kappaB coactivation is essential for upregulation of these genes.

The authors also showed a role for p53 in tumor-associated macrophages (TAMs). In the tumor microenvironment, macrophages are programmed to produce proinflammatory proteins, such as IL-6, which promote tumorigenesis. They found that p53 is activated in TAM-like cells, facilitating the production of IL-6. This discovery reveals that p53 may have significant functions in carcinogenesis outside of its well-described function as a tumor suppressor, which could have important implications in tumor progression and tumor responses to chemotherapy. (RG)


More evidence for smoking-related changes in DNA methylation

In a paper published in April, NIEHS scientists reported altered DNA methylation in relation to cigarette smoking in adult women. The work both validated 10 CpG sites that had been previously identified and discovered smoking associations at 2 new CpG sites. These discoveries may help identify the epigenetic pathways by which smoking leads to a variety of adverse health outcomes.

The scientists utilized data from the Sister Study, a prospective cohort study of women designed to identify the environmental and genetic causes of breast cancer. Team members examined the relationship between smoking and methylation using two epigenetic datasets: one that had methylation array data on 27,578 CpG sites for each of 908 women, and one that had methylation array data on 473,844 CpG sites for each of 200 women. In addition, they validated their primary findings using pyrosequencing. Notably, one of the new sites they identified was in a gene responsible for heme synthesis, the molecule that carries oxygen in blood. This work helps to extend the findings that cigarette smoking and other environmental exposures are associated with persistent epigenetic modifications to DNA. (AW)


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