MEDBULLETIN

EPIGENETICS

INSIGHT INTO EPIGENETICS

HUMNA AMJAD

In 2010, Dr. Isabelle Mansuy and colleagues at the University of Zurich provided evidence that stress-related impact can be associated with epigenetic changes, such as the regulation of gene expression in mice.[1,2]

In contrast to direct alteration of DNA base pairs, epigenetics involve cellular mechanisms that modify chromatin to modulate gene expression without affecting the DNA sequence itself. These primarily include DNA methylation, histone posttranslational modifications, and small noncoding RNAs.[1] When these changes occur in germ cells, they can be passed on to the next generation. It was found that early-life stress induced depressive-like behaviours and changes in the behavioural responses in mice.[2] These behavioural changes were also observed in the offspring of males that were subjected to early-life stress in the form of maternal separation. Moreover, DNA methylation was observed not only in the sperm of the fathers, but also in the brain and germline of the offspring as well. Hence, epigenetic processes in germ cells may contribute to disease heritability.[2]

In the recent issue of *Biological Psychiatry*, Dr. Mansuy and colleagues conducted a review of trans-generational transmission in the regulation of gene expression and stated that "[al]though it has been consistently observed as early as in the 18th century, the time has now come that sufficiently strong and convincing evidence has accumulated to firmly accept it." With many diseases such as cancer, diabetes and neurological disorders having strong heritable components, epigenetics has garnered increasing attention and interest within the scientific community at large.

NEURONS

A "COOL" ADVANCE IN NEUROSCIENCE

JOHNNY WEI BAI

The skin is the largest organ in the human body and detects environmental stimuli such as temperature and pain through sensory neurons.[1] While most of these neurons are polymodal (i.e., one neuron can detect multiple sensations), scientists have recently discovered neurons that solely sense cold temperature.[2]

Dr. McKemy and colleagues from the University of Southern California discovered the gene for TRPM8, showing that it is chiefly responsible for sensation of cold temperature as well as menthol, the "chilling" ingredient in mints.[2] In a more recent study, they investigated how specific neurons could 'turn off' cold sensation in mice by selectively ablating these neurons using chemical injections.[3] The mice were placed on a multi-temperature surface ranging from 0-50 °C. Mice with intact TRPM8-expressing neurons avoided extreme surface temperatures, but the ablated mice spent more time on the colder side, showing that only their cold sense was affected. Although the mice could no longer detect temperature- and cold-related pain, they were still able to sense heat, touch, mechanical pain, and display normal grip strength. This finding implies that it may be possible to shut off a single sensation within the nervous system.[3]

Dr. McKemy's research may lead to more pain-prevention therapies. Current pain drugs and anaesthetics are usually not specific to pain sensation, leaving the patient undesirably numb to other senses as well. Through his research, Dr. McKemy wants to "pave the way for medications that address the pain directly in a way that does not leave patients completely numb".[2]

ANTIBIOTICS

HUMAN FECES: NO WASTE FOR MEDICINE

MOHSIN ALI

Clostridium difficile (C. difficile) is an antibiotic-resistant bacterium that causes diarrhoeal disease, and is a common cause of nosocomial infections. While failure rates for traditional antibiotic chemotherapy rise, recent research points toward another approach to treat *C. difficile*–associated diarrhoeal illness: an ecologic approach whereby other bacteria compete with *C. difficile* for the niche of the gut. Such a turf war to evict *C. difficile* can be induced through probiotics (to introduce 'good' bacteria),[1] or as emphasized in a recent *New England Journal of Medicine* clinical trial, fecal transplantation from a healthy host.[2]

The trial randomized patients with recurrent *C. difficile* infections to one of three treatment groups: standard antibiotic therapy (a two-week course of vancomycin); standard antibiotic therapy with bowel lavage; or an initial four-day vancomycin regimen, followed by bowel lavage and infusion of donor feces. The success of patients in the infusion group prompted an early closure to the trial: 13 of 16 (81%) patients had resolution of their *C. difficile*–associated diarrhoea after the first infusion. Of the three remaining patients, the diarrhoea resolved for two patients following another infusion with feces from a different donor. In contrast, of the 13 patients in each antibiotic therapy group–with or without bowel lavage–only three (23%) and four (31%) patients, respectively, achieved resolution of their diarrhoea after the first infusion.

Donor fecal transplantation therefore provides an efficacious treatment for recurrent *C. difficile* infection. Designing therapies based on an ecologic understanding of our gut may resolve diseases that antibiotics are incapable of resolving.

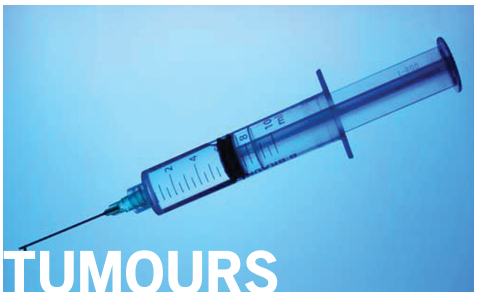
DNA TRANSFER

RNA-GUIDED GENOME EDITING

GRACE ZHANG

Genome engineering is the targeted modification of specific sequences contained within genetic information. Current eukaryotic gene editing has largely been accomplished using DNA nucleases, enzymes that target and cleave a specific DNA sequence. However, increasing the DNA nuclease's binding site specificity to fit a target sequence is often laborious and time-consuming.[1]

The Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) system, which targets and initiates the degradation of foreign nucleic acids in bacterial immune systems, has recently been investigated by researchers at Harvard University and Boston University as a potential new tool for genome engineering.[2] This system consists of CRISPR RNA (crRNA), Cas9 nuclease, and trans-acting crRNA. The crRNA guides the complex to the target (its complementary DNA sequence), while Cas9 performs the double-stranded cleaving when assisted by the trans-acting crRNA.[3] The researchers engineered a CRISPR system similar to that found in bacteria, and demonstrated that the system is able to successfully perform genome editing in human embryonic kidney cells. The CRISPR system produced measurable results in half the time when compared to TALENs (artificial enzymes currently used for targeted DNA cleaving).[2]
A notable advantage of the CAS system (such as Cas 9 nuclease) over other genomic manipulation techniques is its versatility. To target a new DNA sequence, only the crRNA must be changed to be complementary to this sequence; the Cas9 protein itself is universal. With further refinement, this RNA-guided genome manipulation system has the potential to greatly impact the future treatment of genetic disorders.



TUMOURS

CANCER PREVENTION: VACCINES?

KIMIA SOROURI

The purpose of cancer vaccines is to generate a long-term anti-tumour response in patients who are either at risk for cancer or diagnosed with cancer, in order to prevent its recurrence or spread.[1] These vaccines involve administration of proteins associated with tumours (called tumour-associated antigens, or TAAs), which subsequently prompt host recognition and immune response to the antigen. Specifically, the immune system produces proteins called antibodies that are specific to that TAA. Antibodies contribute to immune defense by neutralizing pathogens and preventing them from entering cells, stimulating immune cells to destroy antigen-presenting cells, and activating the complement pathway to induce cell lysis.[2]

However, complications may arise from this procedure. For instance, tumour cells are highly complex, both genetically and in their function. When selecting a TAA to target, it is important to select one that is conserved across all tumour cells (i.e., the cell cannot simply get rid of it as a mechanism of immune evasion).[1] Because tumour cells can evade and suppress the immune system, complementary or adjuvant systems may be necessary to counteract the immunosuppressive nature of tumour cells.[1] Despite all of these barriers, scientists are close to creating a vaccine against breast and prostate cancer that targets specific TAAs associated with both types of tumour cells.[1,3]

Another type of anti-cancer vaccine involves targeting the infectious agents responsible for particular cancers.[4] For instance, Gardasil targets the human papillomavirus (HPV), known to cause 70% of cases of cervical cancer.[5] It is clear that cancer vaccination is a very promising approach to cancer prevention and treatment.

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