

Notable advances 2012

From the microbiome to the microenvironment, certain areas of biomedicine saw fast-paced discovery this year. Here's a rundown of the papers that helped these fields advance quickly in 2012.

■ Neuroscience

Netting new autism genes

The etiology of autism spectrum disorders has proved difficult to decipher, despite a wealth of evidence for genetic and environmental causes. But in April, four studies yielded a raft of new candidate genes for these neurological disorders, offering new avenues for autism research (*Nature* **485**, 237–241; 242–245; 246–250, 2012; *Neuron* **74**, 285–299, 2012).



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The four teams—headed up by researchers from Massachusetts General Hospital and Harvard Medical School in Boston, Yale University in New Haven, Connecticut, the University of Washington in Seattle and the Cold Spring Harbor Laboratory in Long Island, New York—sequenced the coding regions of the genomes from almost 1,000 individuals with 'sporadic' autism as well as unaffected members of their families. This process identified more than 100 spontaneously occurring mutations that might contribute to autism risk, although few genes were found that were mutated in more than one individual with the disease. These results suggest the genetics of autism are very heterogeneous and support models where many genes contribute to risk.

Intriguingly, two of the studies indicated that the *de novo* mutations contributing to autism were more likely to be inherited

from the father of the affected child and were positively correlated with paternal age. The importance of paternal age in autism was further hinted at by a paper published in August by researchers from deCODE Genetics in Iceland, which revealed that older fathers transmit more *de novo* mutations to their offspring than younger fathers (*Nature* **488**, 471–475, 2012). The next—and formidable—challenge will be to dissect the functional consequences of these newly identified genetic variants in autism. —MS

■ Cancer

Environmental issues

The importance of the tumor microenvironment, as well as the means by which cancer cells manipulate their adoptive niches, came into the foreground this year. Several groups, for example, provided key insights into how tumor cells subvert the natural inhibitory mechanisms that try to prevent their infiltration and growth in secondary sites. Evidence for how tumors use exosome secretion to make secondary organs more receptive to metastasis came from researchers at New York's Weill Cornell Medical College (*Nat. Med.* **18**, 883–891, 2012). Once cancer cells have reached pliant niches, they also actively counteract tissue-derived growth-restricting inputs through novel signaling components such as the BMP inhibitor Coco, which was identified by investigators from New York's Memorial Sloan-Kettering Cancer Center (*Cell* **150**, 764–779, 2012).

Metastatic cancer cells can also influence the immune and vascular cell components of their surroundings using paracrine signals, as reported by another Sloan-Kettering team (*Cell* **150**, 165–178, 2012). To boot, the study demonstrated that this cross-talk can protect tumor cells from the onslaught of antitumor therapy.

Even surrounding normal tissue might influence treatment response. A survey carried out at the Broad Institute in Cambridge, Massachusetts, revealed that stroma-mediated therapy resistance is a common phenomenon and that proteins secreted into the local microenvironment can make tumors insensitive to targeted

therapies (*Nature* **487**, 500–504, 2012). In a parallel study, a group from the Fred Hutchinson Cancer Research Center in Seattle uncovered how the damage to normal tissue by chemotherapy can prompt healthy cells to secrete proteins that promote the regrowth of tumor cells (*Nat. Med.* **18**, 1359–1368, 2012). These reports and others underscore the need to put cancer therapies in context. —VA

■ Aging

Calorie-cutting challenge

Modifying the diet of laboratory animals by sharply reducing their caloric intake has beneficial effects in many types of aging-related disease models and increases lifespan. A report published in 2009 from the Wisconsin National Primate Research Center in Madison found that caloric restriction increased the lifespan of rhesus monkeys (*Science* **325**, 201–204). But in a new study carried out at the US National Institute on Aging in Dickerson, Maryland, rhesus monkeys put on a calorie-restricted diet at either young or old ages did not live longer than their control counterparts (*Nature* **489**, 318–321, 2012). Although the case is not yet closed, the new work suggests that the



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health benefits of caloric restriction may not translate into a lengthened lifespan in humans.

Also this year, new research showed how the plant-derived compound resveratrol might mimic the benefits of caloric restriction through the activation of Sirt1, a protein deacetylase. A team led by scientists at the US National Heart, Lung and Blood Institute in Bethesda, Maryland, uncovered a new class of direct targets for resveratrol—phosphodiesterase enzymes—and mapped out a pathway by which phosphodiesterase inhibition leads indirectly to Sirt1 activation (*Cell* **148**, 421–433, 2012). As the icing on the cake, the researchers showed that a widely known inhibitor of the phosphodiesterase PDE4, rolipram, could mimic the metabolic benefits of resveratrol in mice. —MB

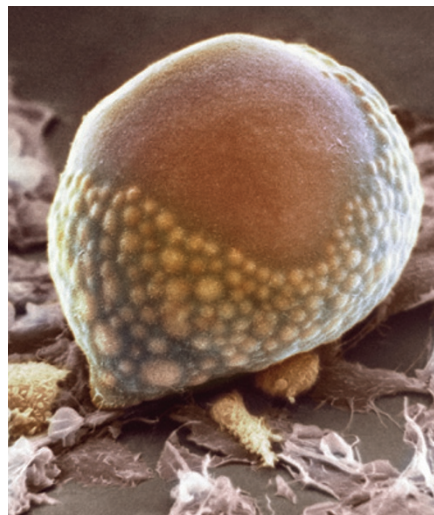
■ Metabolism

Beige is the rage

So-called ‘beige fat’—white fat that is induced to express high levels of uncoupling protein 1 (UCP1) and other functional markers of brown adipose tissue—burns energy instead of storing it. Scientists at the Dana-Farber Cancer Institute in Boston published a potential landmark paper in which they identified the novel hormone irisin, which can turn white fat cells ‘beige’ (*Nature* **481**, 463–468, 2012). They also detailed that exercise induction of peroxisome proliferator-activated receptor- γ (PPAR- γ) co-activator-1 (PGC-1 α) in muscle results in increased production of the surface protein fibronectin type III domain containing 5 (FNDC5), which is cleaved to release irisin. By modestly overexpressing FNDC5 in mice, they saw an elevation of serum irisin levels, accompanied by a decrease in body weight; additionally this caused an increase in the ‘beiging’ of the white fat, as well as glucose tolerance and insulin sensitivity.

This study adds irisin as a potential new therapeutic target to increase energy expenditure and, thus, combat obesity and its comorbidities. But other factors were also identified this year. Researchers from the Sanford-Burnham Medical Research Institute in Orlando, Florida, demonstrated that cardiac natriuretic peptides, which are released upon cold exposure, also induce beiging of white fat (*J. Clin. Invest.* **122**, 1022–1036, 2012). Likewise, a team from Columbia University in New York showed that sirtuin 1 deacetylates the liganded form of PPAR- γ to promote beiging of white fat (*Cell* **150**, 620–632, 2012).

As thiazolidinediones are potent PPAR- γ activators, these results potentially breathe new life into their therapeutic use. Further, a group at the University of Cambridge, UK, found that bone morphogenetic protein 8b acts both locally and centrally to increase peripheral thermogenesis (*Cell* **149**, 871–885, 2012). Finally, the scientists who identified irisin published a follow-up report showing that genetic or pharmacological inhibition of transient receptor potential cation channel, subfamily V, member 4 promotes PGC-1 α expression in white adipocytes and thus their beiging (*Cell* **151**, 96–110, 2012). —RL



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■ Immunotherapy

Co-receptor clampdown

A pair of papers made the inhibitory co-receptor PD-1 (programmed cell death protein 1) one of the darlings of the cancer immunotherapy field this year. PD-1 is found on T cells; when it binds the ligands PD-L1 and PD-L2, the subsequent signaling pathway dampens the function of effector T cells and promotes regulatory T cell activity.

Building on preclinical work and early clinical data, this year a team led by scientists from the Johns Hopkins School of Medicine in Baltimore reported the findings of a study of a PD-1-specific antibody; of 236 evaluable patients with non-small-cell lung cancer, melanoma or renal cancer, response rates ranged from 18% to 28%, depending on cancer type. In 42 of the patients, more than half of the individuals had tumors that tested positive for PD-L1, and, of these individuals, nine (36%) had an objective response to the treatment. In contrast, none of the patients with PD-L1-negative tumors had an objective response (*N. Engl. J. Med.*

366, 2443–2454, 2012).

In a companion study, the researchers reported that of 207 patients with advanced cancer who received an anti-PDL1 antibody, 6–17% of evaluable patients experienced an objective response (either complete or partial) (*N. Engl. J. Med.* **366**, 2455–2465, 2012). Interestingly, the anti-PD-1 antibody did not appear to produce a response in colorectal or prostate cancer, and the anti-PD-L1 antibody did not produce a response in patients with colorectal or pancreatic cancer. But even though the reason why only certain tumors and patients responded to the antibodies remains unknown, these trials further validate immune modulation of T cell activity as a therapeutic approach to cancer treatment. —AF

■ Virology

Pushing the envelope

Despite many million of dollars poured toward the development of a reliable HIV vaccine, there remains a distance to go before reaching this goal. In 2009, the results of the RV144 vaccine trial showed modest yet encouraging evidence for efficacy, preventing the acquisition of HIV infection in roughly a third of those who received the shots. Why did the vaccine work in this subset of patients and not in others? Identifying the immune correlates of protection is crucial to develop more efficient vaccines, and a study published this year provided a tantalizing answer to this key question.



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A team of researchers from the US and Thailand found that IgG antibodies against the variable V1 and V2 regions of the HIV envelope (Env) protein correlated with reduced risk of HIV infection in vaccinated subjects (*N. Engl. J. Med.* **366**, 1275–1286, 2012). This region of Env is important for HIV binding to the CD4 T cell receptor and chemokine receptors, and earlier studies had identified it as the binding site of neutralizing antibodies against the virus. Unexpectedly, the levels of Env-specific IgA antibodies showed the opposite correlation, raising the possibility that they may have mitigated the protective effect of the IgG antibodies.

A subsequent study added granularity to the analysis by examining the genomes of viruses isolated from patients who participated in the RV144 trial. This exercise led to the identification of two specific amino acids in the V2 region that were associated with protective vaccine-induced immune responses (*Nature* **490**, 417–420, 2012). According to the authors of the paper, the next generation of HIV vaccines must incorporate these findings into their design. —JCL

■ Gastroenterology

Friends, not foes

The commensal relationship between mammals and the microbes they harbor in the gut came to the fore this year, with several papers showing how disruption of the microbial composition of the gut might increase susceptibility to colitis. Researchers at the University of Chicago found that, in

mice, a diet high in saturated fat can alter host bile acids and promote growth of the Gram-negative bacterium *Bilophila wadsworthia* in the intestine, leading to colitis in susceptible mice (*Nature* **487**, 104–108, 2012).

Malnutrition can also trigger this condition, which is known as dysbiosis. Mice engineered to have a deficiency in angiotensin-converting enzyme 2 have disrupted intestinal uptake of the amino acid tryptophan and increased susceptibility to colitis and intestinal inflammation (*Nature* **487**, 477–481, 2012). Colitis is also seen in mice fed a protein-free diet, confirming the link between dietary influences and microbial composition. These microbial alterations induced by intestinal inflammation and colitis are linked to colorectal cancer in mice, owing in part to expansion of the commensal bacteria *Escherichia coli* NC101 (*Science* **338**, 120–123, 2012).

Researchers at Cedars-Sinai Medical Center in Los Angeles have also found that it's important to keep fungi in check, as mice deficient in the innate immune receptor dectin-1, which detects fungi, are susceptible to gut disease (*Science* **336**, 1314–1317, 2012).

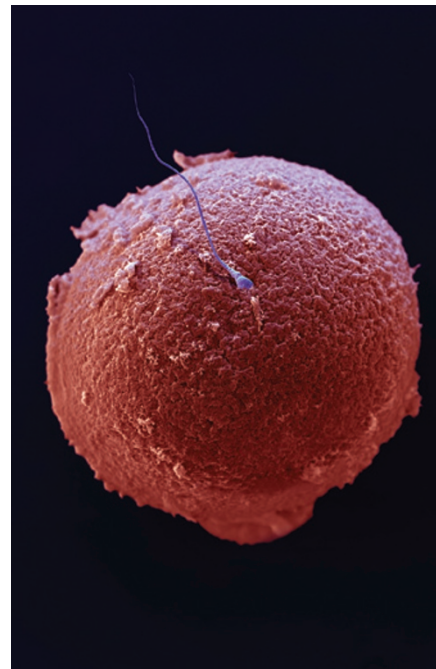
Dysbiosis can cause trouble beyond the intestines, worsening hepatic steatosis and obesity (*Nature* **482**, 179–185, 2012) and increasing adiposity (*Nature* **488**, 621–626, 2012). Moreover, exposure to antibiotics early in life impairs the development of immune cells, including natural killer T cells (*Science* **336**, 489–493, 2012) and basophils (*Nat. Med.* **18**, 538–546, 2012), promoting allergic airway inflammation. Ultimately, the significance of such findings will be known when researchers test specific therapeutic strategies aimed at targeting the microbiome to treat disease. —KDS

■ Reproduction

Germinating debate

Almost a decade ago, a group of scientists challenged the dogma that female mammals had a limited number of eggs—which were thought to be established at or before birth and not replenished—by providing evidence that germline stem cells can renew and sustain egg production in the juvenile and adult mouse ovary (*Nature* **428**, 145–150, 2004). Yet, skepticism remained in the research community. A study published early this year has now offered data that these female germline stem cells, called

oogonial stem cells (OSCs), are also found in young women. The discovery, by a team led by scientists at Massachusetts General Hospital in Boston, has important implications that could change the paradigm of female reproductive biology and fertilization strategies.

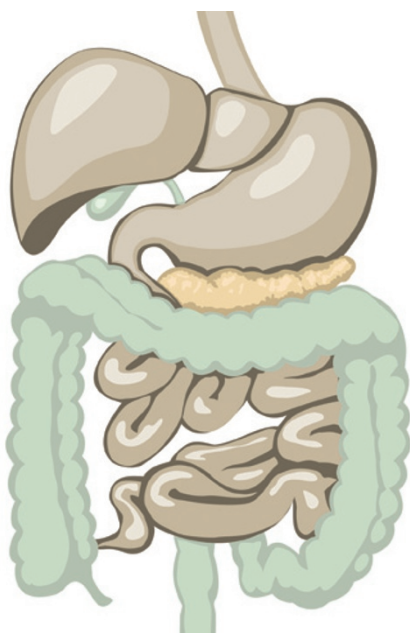


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This rare population of germline stem cells was isolated from human ovarian tissue using a FACS strategy that extracted only viable OSCs by targeting the N terminus of the membrane-bound form of an RNA helicase called DDX4, which is specific for germ cells. Scientists injected OSCs into human ovarian tissue and transplanted the tissue into mice. The oocytes derived from these OSCs were found in primordial follicles in the mouse ovary, indicating that the isolated human OSCs can form human primordial follicles (*Nat. Med.* **18**, 413–421, 2012). The excitement spurred by the findings was great, but it was tempered by a challenge to the methodology used by the authors to isolate OSCs (*Proc. Natl. Acad. Sci. USA* **109**, 12580–12585, 2012).

Future research into the existence of OSCs in humans will address whether such cells could have true potential to generate healthy offspring through *in vitro* techniques and whether they could be stimulated to produce eggs *in vivo*. —CP

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