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Gender matters

How infertility-causing mutations are inherited is a tough puzzle. A dominant mutation with sex-specific phenotypes provides a clue (*PLoS*, doi:10.1371/journal.pbio.0050105).

In screening mice for infertility, Laura Bannister *et al.* isolated a male sterile allele of the DNA repair gene *DMC1*, $DMC1^{Mei11}$, which caused sex-specific phenotypes during meiosis. In males heterozygous for $DMC1^{Mei11}$, double strand breaks were not repaired during meiosis, causing spermatogenesis to fail during the first meiotic division.

Despite similar defects in double strand break repair during oogenesis, female $DMC1^{Mei11}$ heterozygotes were fertile, though their oocyte pool declined more rapidly.

While other mutations can have sexually dimorphic effects on gametogenesis, DMC^{Mei11} is the first to allow for viable oocytes. These oocytes may carry this dominant allele, which is how an allele causing infertility could be maintained in a population. —*KS*

Universally available?

A new enzymatic approach efficiently converts type A, B and AB red blood cells into universally accepted O-type blood (*Nat. Biotech.*, doi:10.1038/nbt1298).

On their surface, red blood cells can have carbohydrate structures called the A or B antigens, which limit blood transfusions to those who share a blood type. O-type blood has neither antigen and, if the supply were large enough, could safely be used for all transfusions.

Qiyong Liu, Gerlind Sulzenbacher *et al.* screened an enzyme library to isolate glycosidases that could remove the A and B antigens with high efficiency. The authors isolated an α-*N*-acetylgalactosaminidase and an α-galactosidase, which worked individually or in concert to remove the A and B antigens, respectively, functionally creating O-type blood.

Previous studies have shown that enzyme-converted O-type blood can be safely transfused, but these studies generated this blood with inefficient enzymes that required extreme reaction conditions. The glycosidases identified by Liu *et al.* have more promise for industrial use.—*KS*

Demethylase goes mental

X-linked mental retardation (XLMR) has been mapped to the *SMCX* locus. Two reports in *Cell* reveal the endogenous function of SMCX and indicate how *SMCX* mutations lead to XLMR.

Kristian Helin and colleagues (**128**, 1063–1076) and Shigeki Iwase, Fei Lan *et al.* (**128**, 1077–1088) report that *SMCX* encodes a histone H3 lysine 4 (H3K4) demethylase.

Iwase *et al.* also reduced expression of *SMCX* in zebrafish embryos and discovered alterations in brain patterning and reduced neuronal survival. Knocking down expression of *SMCX* in rat cerebellar neurons in culture reduced dendrite length.

Methylation of H3K4 activates transcription, so the findings suggest that H3K4 demethylation by SMCX downregulates gene expression during brain development. Additional experiments must determine which gene expression changes induced by mutant *SMCX* disrupt brain development—and lead to XLMR. —*EC*

Innate autoimmunity

The innate immune receptor NALP1 is a 'risk gene' for the skin autoimmune condition vitiligo and the group of autoimmune diseases that associate with it, including Grave's thyroid disease, lupus, rheumatoid arthritis and autoimmune diabetes (*New Eng. J. Med.* 356, 1216-1225).

With a sample of 656 patients from 114 extended families, Ying Jin *et al.* identified two variants in *NALP1* that conferred high susceptibility to these autoimmune diseases.

Like the Toll receptor, NALP1, NACHT leucine-rich-repeat protein 1, is a pattern-recognition receptor, which recognizes invading pathogens without the need for immunological memory. These proteins can also detect self-antigens such as exposed DNA from dead cells, thereby promoting self-directed immune responses. An overzealous innate immune system, triggered by Toll receptors, has been associated with the development of lupus.

Although Jin *et al.* did not define the functional effect of *NALP1* risk mutations, the work offers tantalizing new treatment strategies within the innate immune system for autoimmune disorders.—*KJ*

Platelet clocks

Platelet life-span is determined by how long the cell can stave off apoptosis (*Cell* **128**, 1173–1186).

Platelet counts are maintained through constant cycles of generation and death, where each platelet circulates for only about ten days. How this life-span is timed was unknown.

In a screen for genetic causes of low platelet counts in mice, Kylie Mason *et al.* isolated mutations in the anti-apoptotic gene *Bcl-x_L*. In *Bcl-x_L* mutant mice, the authors found a dose-dependent reduction of platelet half-life with decreased *Bcl-x_L* activity.

Older cells died prematurely in the *Bcl-x_L*–deficient mice, suggesting Bcl-x_L extends platelet lifespan.

Bcl-x_L prevents cell death by inhibiting the pro-apoptotic protein Bak, which is also highly expressed in platelets. *Bcl-x_L* expression levels decrease over the lifetime of the platelet and when they are too low, Bak can initiate apoptosis. Mason *et al.* propose that Bak/Bcl-x_L antagonism establishes a molecular clock for platelet life-span.

These findings suggest the Bcl-x_L/Bak antagonism may be a therapeutic target to maintain healthy platelet counts. —*KS*

Fighting the resistance

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E. coli bacterial culture

Certain drug combinations can select against drug-resistant bacteria (*Nature* **446**, 668–671).

In combination, drugs sometimes suppress each other's efficacy. Suppressive interactions can render the drugs ineffective on bacteria, but Remy Chait *et al.* propose that suppressive drug combinations might have different effects on wild-type and drug-resistant bacteria. By this hypothesis, drug 'A'-resistant bacteria neutralize drug 'A'. High doses of drug 'B' can treat drug 'A'-resistant bacteria, but select for drug 'B' resistance. When both drugs are at low concentrations, however, the resistant bacteria neutralize drug 'A', relieving the suppressive effects on drug 'B', and are more susceptible to drug 'B' treatment than wild-type bacteria to the same cocktail.

The authors tested this hypothesis by measuring growth rates of doxycycline-resistant and -sensitive bacteria. They found that, in doxycycline-inoculated media, resistant bacteria grew faster than sensitive bacteria. When doxycycline was paired with the suppressive drug ciprofloxacin, however, sensitive bacteria grew better than resistant bacteria.

These studies show that such selection may be a new approach for antibiotic treatment. Against drug-resistant bacteria, it may be more effective to fight with strategy than force.—*KS*

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