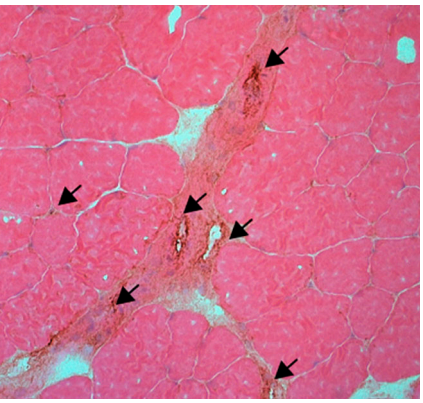


Androgen treatment repaired (arrows) damaged vessels in castrated mice.

Gender-biased vessel growth

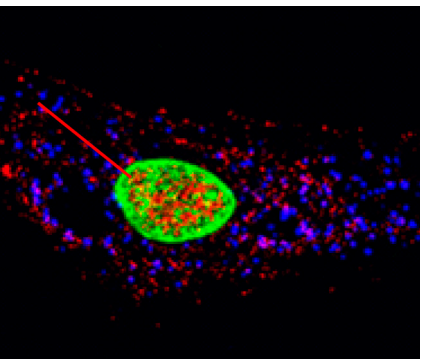
A man's male hormones may ward off heart damage by helping vessels around the heart regenerate, suggest Sieveking and colleagues.

Although studies have shown that estrogen helps regenerate blood vessels, both in the uterus after menstruation and around the heart after wear and tear, little is known about whether or not men make up for a lack of the female hormone. Some researchers have theorized that this disparity accounts for why men tend to suffer worse heart attacks more often and earlier in life than women. However, Sieveking and colleagues find that this trend may be due to a drop in androgens, a collective term for male hormones, as men age.

Angiogenic activities like cell migration ensued after the authors treated human cells derived from the umbilical cord of a male fetus with the androgen DHT. Meanwhile, female cells failed to respond to the androgen, unless they were supplied with extra androgen receptors. In this case, angiogenic activities increased slightly, indicating that hormone sensitivity accounts for some of the gender difference.

Castrated mice produced fewer androgens and fared poorly after the researchers inflicted vessel damage intended to resemble injuries that occur during a heart attack or a stroke. And treating the castrated mice with DHT hastened their recovery. Therefore, the authors suggest that androgen replacement therapy might one day be used to treat men at risk for heart disease. The therapy currently receives attention for possibly inducing other rejuvenating benefits, such as increased energy and muscle mass. However, it's been approached with caution as androgens have been shown to assist in tumor growth in prostate cancer—perhaps by stimulating cancer-promoting angiogenesis.

Androgen treatments correlated with spikes in the growth factor VEGF, and blocking VEGF interrupted androgen-induced angiogenesis. However, androgens may also modulate angiogenesis by mobilizing progenitor cells known to be critical for vessel repair; the authors found that castrated mice had fewer progenitor cells in circulation after injury than those with their organs intact.



CSB (red) moved into mitochondria (blue) after oxidative stress.

Accelerated aging

Mutations underlying a rare disorder in which children rapidly age disrupt mitochondrial DNA repair, show Kamenisch and colleagues. Faulty repair leads to an accumulation of mutations in mitochondrial DNA, a molecular hallmark of growing old.

Recent studies have connected the excess of mitochondrial gene mutations to signs of aging, including hair loss, bone loss, and the loss of subcutaneous fat. The early aging disorder, Cockayne syndrome (CS), is also marked by fat loss, along with sensitivity to UV radiation, which reflects faulty DNA repair. CS patients bear defects in the nucleotide excision repair (NER) pathway, which until now was only known to act on nuclear DNA. Here, Kamenisch and colleagues discover that NER proteins rush into the mitochondria during times of oxidative stress.

When the defective NER proteins that characterize CS—CSA and CSB—entered mitochondria after irradiation, errors accumulated rapidly during mitochondrial DNA replication in cultured cells from CS patients. CSA and CSB interacted with mitochondrial proteins in the base excision DNA repair pathway, which normally removes oxidative damage. The authors speculate that interactions between NER proteins and base excision proteins form a reparative complex; however, the details of that proposed network remain elusive. How CSA and CSB enter the mitochondria in times of stress remains to be investigated as well.

A buildup of mitochondrial gene mutations could be responsible for the subcutaneous fat loss characteristic of CS, suggest the authors. Indeed, the subcutaneous fat of adult, irradiated mice lacking CSA and CSB was teeming with mitochondrial DNA mutations. And fat cells with many mutations often died, reducing the overall number of fat cells in the mice.

Antibodies attack IL-17

Two new studies suggest why patients with the autoimmune disorder APS-I are susceptible to chronic yeast infections. According to Puel et al. and Kisand et al., APS-I patients produce autoantibodies against microbe-fighting cytokines—making this disorder one of a small handful of diseases enhanced by antibodies that target cytokines.

The yeast infection, known as chronic mucocutaneous candidiasis, usually develops before other symptoms of APS-I. The infection is perplexing given that many autoimmune disorders are characterized by exaggerated Th17 cell responses, which produce cytokines like interleukin (IL)-17A,

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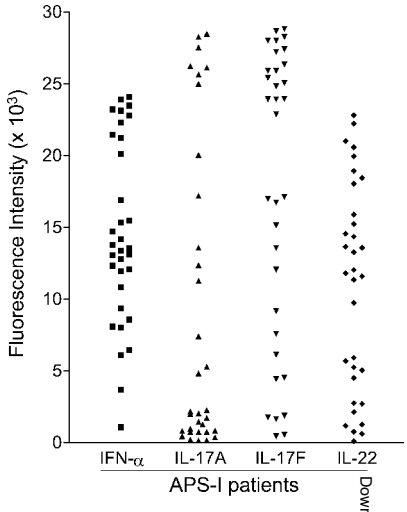
IL-17F, and IL-22 that fight microbial pathogens at mucosal surfaces. On the contrary, here the teams suggest that APS-I patients have diminished Th17 activity due to autoantibodies against these signature cytokines. Kisand et al. found that cultured progenitor cells from APS-I patients produced less IL-17F and IL-22 in response to yeast antigens or polyclonal stimuli. And although some cells made less IL-17A as well, cytokine levels varied overall, likely reflecting variation in genetic, environmental, or clinical backgrounds.

The paucity of cytokines correlated with the presence of autoantibodies against IL-17A, IL-17F, and IL-22. These autoantibodies blocked or neutralized the cytokines but, according to Kisand et al., did not obstruct Th17 cell differentiation. Other inflammatory cytokines were unaffected, with the exception of interferon (IFN)-α, which is known to be blocked by autoantibodies in APS-I patients. However, APS-I patients do not appear prone to recurrent viral infections despite neutralization of this antiviral cytokine—perhaps because other IFNs compensate.

How these autoantibodies arise remains a mystery. Infection was not the trigger, because APS-I patients without candidiasis produced them as well. The authors suggest that their origin may be due to mutations in the gene underlying APS-I, which disrupt the autoimmune regulator AIRE. AIRE normally prevents autoreactive T cells from leaving the thymus, but a direct connection between the AIRE disruption and anti-cytokine antibodies remains to be seen.



APS-I patients harbored autoantibodies against IFN-α, IL-17A, IL-17F, and IL-22.

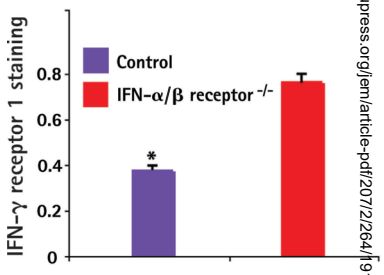
Interferon crossfire

Interferons (IFNs) establish a pecking order in a study by Rayamajhi and colleagues. When type I IFNs muffled type II during bacterial invasion, the bacteria won.

Although the protective type II cytokine, IFN-γ, was expressed after bacteria invaded, infected cells weren't listening. *Listeria*-infected macrophages up-regulated the type I IFNs, IFN-α and -β, which down-regulated IFN-γ receptors on the cell surface and thus stifled IFN-γ signals. Without IFN-α/β receptors, mice resisted *Listeria*. They expressed IFN-γ–dependent genes, indicating that IFN-γ had made contact with its receptors.

In demonstrating that IFN-α/β mutes IFN-γ, this team presents a new solution for a long-standing conundrum. Namely, why mice deficient in virus-fighting type I IFNs are protected from pathogenic bacteria like *Listeria monocytogenes* and *Mycobacterium tuberculosis*. Earlier studies postulated that IFN-α/β hinder bacterial clearance by triggering the immune-suppressing cytokine IL-10. If this were true, one might predict an increase in IFN-γ in the absence of IFN-α/β signals because IL-10 stifles IFN-γ. However, the authors found that with or without IFN-α/β receptors, mice produced IFN-γ after infection. The problem was instead that IFN-γ messages failed to send with IFN-α/β receptors intact.

Interferon cross talk may explain why IFN-β treatments work for many multiple sclerosis patients. Perhaps, speculate the authors, IFN-β intercepts inflammatory signals from IFN-γ by dampening expression of its receptors.



IFN-α/β down-regulated IFN-γ receptors on the surface of infected macrophages.

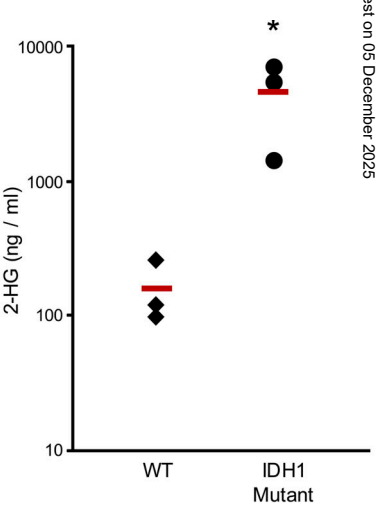
Cancers converge at 2-HG

Several mutations associated with acute myelogenous leukemia (AML) lead to the same metabolic change, report Gross and colleagues.

Mutations in the enzyme isocitrate dehydrogenase 1 (IDH1) occur in about 80% of secondary brain cancer tumors, and in nearly a tenth of AML tumors. Normally, IDH1 catalyzes a critical step in glucose metabolism in the cytoplasm—the conversion of isocitrate into α-ketoglutarate. However, when the amino acid arginine at position 132 of IDH1 mutates, the enzyme acquires new powers. It reduces α-ketoglutarate into R(-)-2-hydroxyglutarate (2-HG), an "onco-metabolite" recently linked to the development of brain cancer and here, to AML.

The authors find that AML patients with IDH1 mutations at position 132 harbor high serum levels of 2-HG. However, the mutations from AML patients often differed from those of brain cancer patients by an amino acid; instead of primarily switching to histidine, arginine had frequently changed to cysteine. And the cysteine variant showed a higher affinity for α-ketoglutarate, which led to more 2-HG. The team uncovered an additional mutation in IDH2, IDH1's counterpart that acts in the peroxisome. Likewise, this mutant IDH2 enzyme converted α-ketoglutarate into 2-HG.

Although the effect of 2-HG on tumor growth is unknown, the authors speculate that it may promote tumor progression by elevating reactive oxidative species or by altering cell metabolism by inhibiting key enzymes. In any case, because these ID1H mutations appear to be unique to cancer, they provide promising targets for drugs and biomarkers of the disease.



AML patients with the IDH1 R132 mutation harbored high serum levels of 2-HG.