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Spotlight

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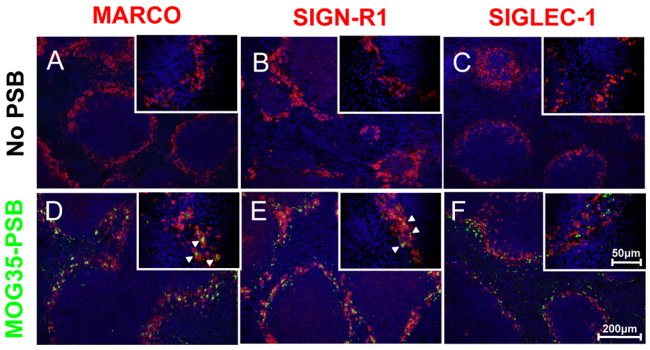
TOLERATING AUTOIMMUNE DISORDERS

Autoimmune diseases such as multiple sclerosis and type I diabetes affect approximately 8% of the population worldwide, ranking behind only cancer and heart disease in prevalence. In many autoimmune diseases, T-cells, which normally destroy foreign infectious invaders, instead launch an attack on normal, healthy tissue. A promising strategy to treat autoimmune disorders is to induce immune tolerance, or teach the immune system not to attack the antigen expressed by the normal tissue. Indeed, some success in prevention and treatment of a mouse model of multiple sclerosis has been found by cross-linking a specific peptide antigen to a leukocyte that has died by a mechanism called apoptosis, a process that does not result in immune activation. However, translating this approach to the clinic is hampered by the feasibility of producing the cross-linked white blood cells on a sufficient scale. To circumvent this challenge, Getts *et al.* (*Nat. Biotechnol.* 2012, advance online publication November 18, 2012; DOI: 10.1038/nbt.2434) now report that synthetic microparticles can be used as a surrogate for the dead white blood cells.



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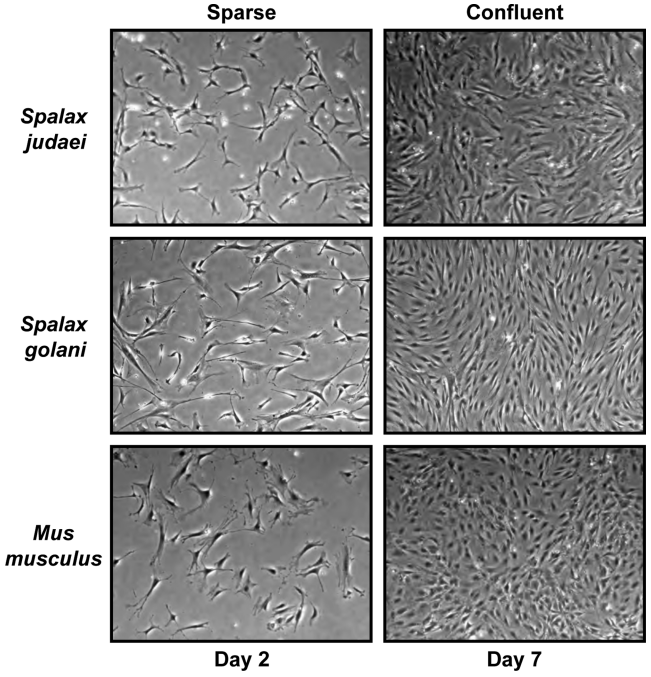
To effectively mimic the surface of a cell, a peptide epitope relevant in the multiple sclerosis model was covalently attached to polystyrene beads 500 nm in diameter, and the beads were injected into mice. Remarkably, when the beads were injected either prior to initiation or at the first signs of symptoms of the disease, the mice were protected from development of the disease. It was found that the microparticles were engulfed by macrophages expressing the scavenger receptor MARCO and that specific immune tolerance processes, including regulatory T cell activity; abortive T-cell activation, in which T cells rapidly proliferate and then rapidly die off; and T-cell anergy, where the cell is inactivated following an encounter with antigen, were involved. Similar results were achieved when antigen was coupled to poly(lactide-*co*-glycolide) biodegradable beads, pointing to the versatility of this exciting approach for prevention and treatment of autoimmune disorders. **Eva J. Gordon, Ph.D.**

BLIND TO CANCER

Blind mole rats, underground rodents native to the Middle East, have a surprisingly long life-span of up to 21 years and are remarkably resistant to developing cancer. This is in striking contrast to many other types of mice and rats who live about 4 years and frequently succumb to cancer. In an effort to understand this astonishing phenomenon, Gorbunova *et al.* (*Proc. Natl. Acad. Sci. U.S.A.* 2012, *109*, 19392−19396) investigate the behavior of blind mole rat cells in culture.



Gorbunova, V., *et al., Proc. Natl. Acad. Sci. U.S.A., 109*, 19392−19396. Copyright 2012 National Academy of Sciences, U.S.A.

The investigators isolated fibroblasts from two different species of blind mole rats and grew them in the laboratory. The cells grew well in culture for a while, but after 7−20 population doublings, they all abruptly stopped growing and died, a process designated "concerted cell death". The cells died through a combination of predominantly necrotic though some apoptotic mechanisms, and the tumor suppressor proteins p53 and Rb were found to be involved. This is interesting to note and consistent with the fact that the blind mole rat has a p53 variant that is defective in initiating apoptosis. In addition, it was determined that the cell death process is triggered by the cytokine interferon-β. Thus, blind mole rats appear to skillfully evade cancer by invoking a potent necrotic death response to cells that are growing too rapidly. These findings elucidate some of the mechanisms underlying this envious characteristic of the subterranean animal and could lead to new strategies for preventing and treating cancer in humans. **Eva J. Gordon, Ph.D.**

INDUCING CARTILAGE REPAIR

Articular cartilage, the smooth, collagen-rich tissue that covers the surfaces of joints, unfortunately does not have much capacity to heal itself after damage. Stem cell technology is an attractive approach for the generation of methods to replace

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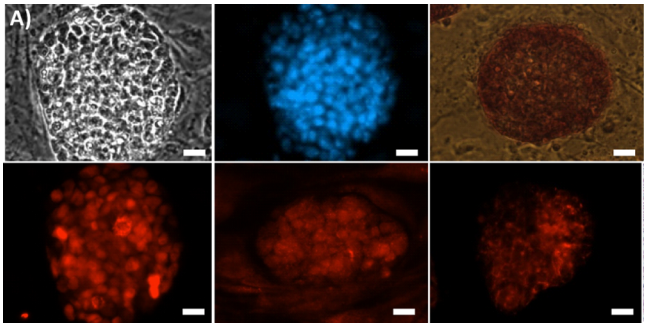
cartilage. Of the various stem cell technologies in development, induced pluripotent stem cells (iPSCs) are particularly enticing because they allow the generation of large numbers of patient-matched cells for therapeutic as well as biological discovery applications. iPSCs are adult somatic cells that have been genetically reprogrammed to have the potential to differentiate into nearly all cell types. Toward the development of iPSCs for cartilage repair, Diekman *et al.* (*Proc. Natl. Acad. Sci. U.S.A.* 2012, *109*, 19172−19177) now report the genetic engineering of iPSCs and demonstrate their value as tools for further exploration of stem cell-based alternatives for cartilage repair.



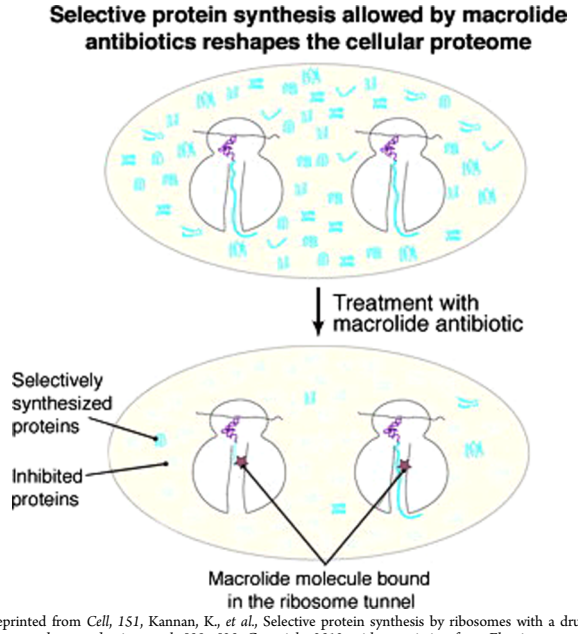
Diekman, L., *et al., Proc. Natl. Acad. Sci. U.S.A., 109*, 19172−19177. Copyright 2012 National Academy of Sciences, U.S.A.

To create the engineered iPSCs, tail fibroblasts from mice were first reprogrammed into iPSCs using standard methods and were then engineered to express green fluorescent protein (GFP) only when in the process of differentiating into cartilage cells, or chondrocytes. This strategy provided a mechanism for isolating the chondrocytes using flow cytometry, and thus access to a homogeneous cell population. Thorough characterization of the cells using immunohistochemistry, quantitative RT-PCR, pellet culture analysis, and atomic force microscopy offered compelling evidence of their chondrocyte-like behavior. In addition, the authors developed an in vitro cartilage defect model using these cells, where they demonstrated the ability of the cells embedded in agarose to produce cartilaginous matrix proteins and integrate with damaged cartilage. These findings demonstrate the promise of iPSCs for cartilage repair and highlight the value of genetically engineered iPSCs in developing tissue models of cartilage. **Eva J. Gordon, Ph.D.**

■ RESHAPING PROTEIN SYNTHESIS

Macrolide antibiotics such as erythromycin interfere with protein synthesis in bacteria, either by preventing peptide synthesis or producing truncated peptides. They can gum up protein synthesis by plugging up the passage through which synthesized peptides leave the ribosome, the nascent polypeptide exit tunnel (NPET). Now Kannan *et al.* have shown that macrolide inhibition is protein-specific and have demonstrated how some newly formed peptides can squeeze through the partially blocked exit tunnel (*Cell* 2012, *151*, 508−520).

Previously researchers had shown that ribosomes only produce very short peptides in the presence of these antibiotics. Crystallography studies of the ribosome with bound macrolides had suggested that some peptide chains could slip through the tunnel. Using radioactive methionine, Kannan *et al.* carried out pulse labeling experiments and saw that some full-size proteins were synthesized in the presence of the antibiotics. Unexpectedly, cells treated with the more potent ketolide antibiotics such as telithromycin produce many more proteins.



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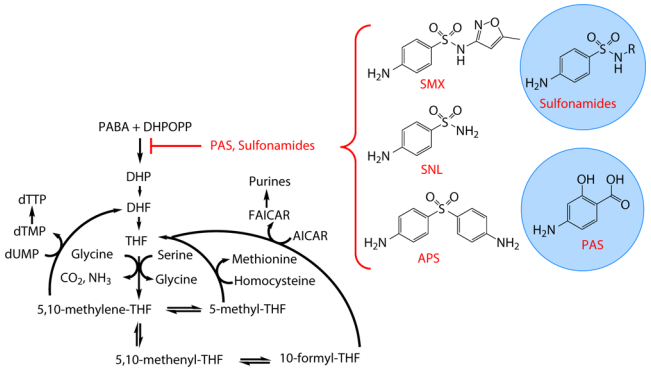
The researchers then chose to study a small cytoplasmic protein, H-NS, and determined that the 18-residue N-terminal region of this protein allows it to scoot beyond the antibiotic blockage in the NPET, even when they appended those initial residues to a different protein sequence. Although some full-size proteins are made in cells treated with macrolides, the blockage can also truncate peptide synthesis after this N-terminal region, producing shortened polypeptides that are harmful to the cell. Certain amino acid sequences in a protein sequence can halt synthesis, and the stalling occurs at different efficiencies depending on the structure of the macrolide. By modifying the structure of the antibiotic bound in the NPET, researchers can influence the spectrum of proteins produced antibiotic-exposed cells.

The results suggest that macrolides do not simply block production of new proteins but modulate protein synthesis in more nuanced ways. Furthermore, pathogens may be more sensitive to partial rather than complete blockage of protein synthesis. These findings could allow researchers to develop more powerful and more targeted antibiotics. **Sarah A. Webb, Ph.D.**

■ PAS ON METABOLOMICS

Sulfonamides were among the first antibiotics, arriving on the commercial market in the 1930s. This generation of drugs established the folate biosynthesis pathway as a legitimate drug target and inspired some of the first attempts at rational design of enzyme inhibitors. *p*-Aminosalicylic acid, or PAS, was an early designed drug made to mimic a folate precursor. PAS was and continues to be an effective treatment for tuberculosis, but like many prescription drugs, its mechanism of action was poorly understood. Since its invention, PAS was assumed to be a competitive inhibitor of the enzyme dihydropteroate synthase, DHPS, a folate pathway enzyme that naturally uses a structurally similar substrate, para-aminobenzoate, or PABA. Now, 50 years after PAS entered the fight against infections, a surprising new picture emerges as to how this drug poisons *Mycobacterium tuberculosis*.

Using a filter culture system coupled with sensitive mass spectrometry methods, Chakraborty *et al.* (*Science* 2012,



From Chakraborty, S., *et al.*, *Science*, November. 1, 2012; DOI: 10.1126/science.1228980. Reprinted with permission from AAAS.

advance online publication November 1, 2012; DOI: 10.1126/science.1228980) profiled the metabolites generated by *M. tuberculosis* under different growth and drug conditions. This approach allowed parallel quantification of many enzymatic substrates and products as they accumulated in the culture. Since the DHPS enzyme uses PABA as a natural substrate, monitoring residual PABA levels in the culture indicated the degree of enzyme inhibition in response to various drug treatments. The result indicated how the conventional view of PAS was incorrect. Instead of inhibiting DHPS like the sulfonamides, PAS actually acts as a substrate for this enzyme to produce a product that enters downstream cascades and poisons these reactions. The metabolomic data demonstrated that folate-dependent pathways such as amino acid and purine synthesis are inhibited by PAS in a manner that is inconsistent with simple DHPS inhibition alone. This study indicates how an old drug can be better understood using modern techniques, but more importantly, it shows that when designing a therapeutic, exploiting a bacterial enzyme's activity can be just as effective as inhibiting it. **Jason G. Underwood, Ph.D.**

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