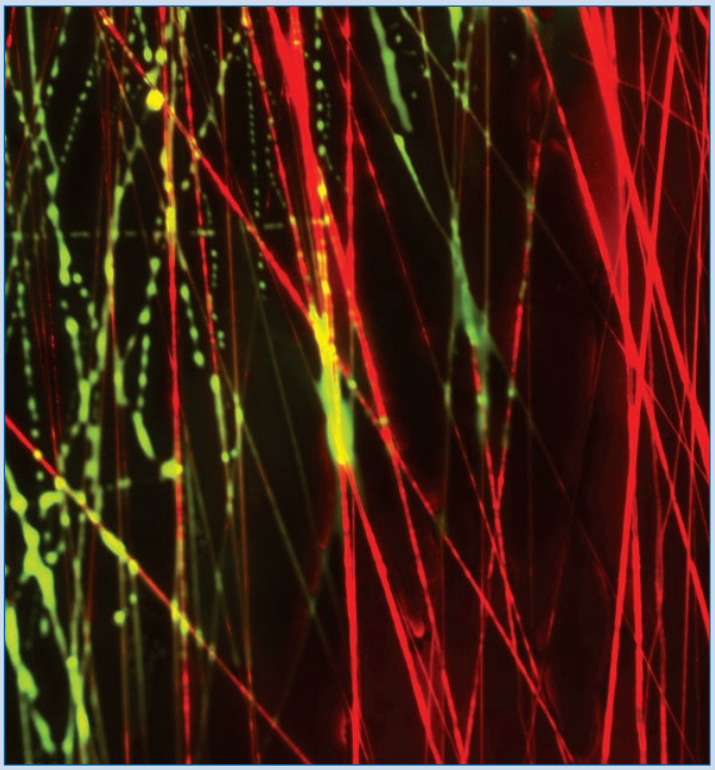
August 28, 2012 | vol. 109 | no. 35 | 13879–14280

In This Issue

PNAS
Proceedings of the National Academy of Sciences of the United States of America
www.pnas.org

Partially dissolving nanofiber composite helps rebuild connective tissue

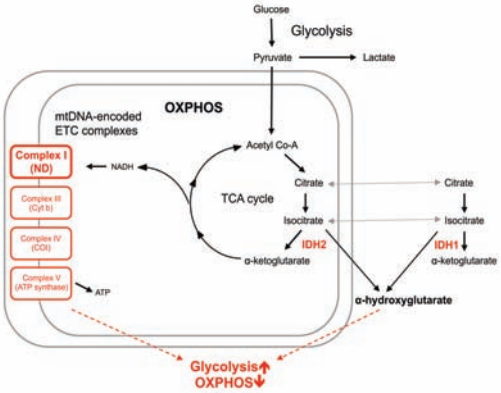
Polymer nanofibers can potentially be used to create scaffolds capable of organizing implanted cells into the 3D structures that support human fibrous musculoskeletal tissues. However, aligning these tiny fibers during fabrication packs them more tightly, and the resulting small pore sizes restrict tissue formation to the surface of the scaffold. Brendon Baker et al. (pp. 14176–14181) devised and validated a technology to produce customizable, composite nanofiber scaffolds with a so-called "sacrificial" component that enhances and expedites cell infiltration over time. The composite, according to the authors, uses a slowly degrading, water-soluble component to enhance the porosity of the matrix. Despite removing more than 50% of the initial fiber content, the authors found that the remaining scaffolding is sufficient to align cells and produce a highly organized extracellular matrix, both in vitro and in rat trials. Furthermore, the tensile strength of the engineered constructs nearly matches that of native tissue. According to the authors, the findings help advance the much sought after research goal of engineering load-bearing fibrous tissues, and can potentially be applied more broadly to other pursuits in regenerative medicine. — T.J.



Fibrous biomaterial with structural (red) and water-soluble, sacrificial (green) electrospun polymeric nanofibers.

Mitochondrial DNA mutations in human cancers

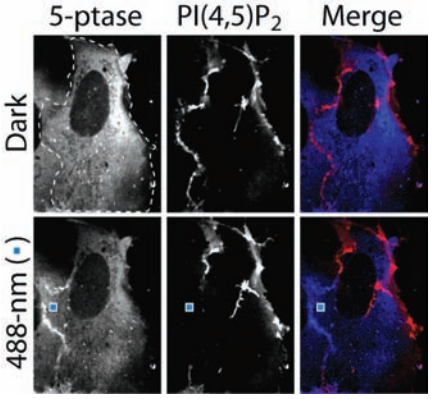
Mutations in mitochondrial DNA are increasingly found in human tumors, but the spectrum of such mutations and their role in cancer development remains unclear. Using whole genome sequence data generated by The Cancer Genome Atlas consortium as part of an ongoing effort to identify the genomic changes underlying various cancers, Tatianna Larman et al. (pp. 14087–14091) analyzed the inherited and somatic mitochondrial DNA mutations in 226 individuals with five different types of cancer, including glioblastoma and acute myeloid leukemia, as well as colon, rectal, and ovarian cancers. The authors discovered deleterious somatic mitochondrial DNA mutations in all five tumor types, but observed the greatest frequency of mutations in colon and rectal tumors. Furthermore, somatic mutations were more likely than inherited mitochondrial variants to alter protein amino acid sequence and the functions of encoded proteins, which include components of the electron transport chain. The frequency of damaging somatic mutations in early and late stage colon and rectal tumors remained relatively unchanged, suggesting to the authors that the mutations arose early during tumorigenesis. The findings suggest that some mitochondrial somatic mutations may confer a selective advantage to tumorigenic cells by contributing to metabolic deregulation, and that altered metabolism may be a key feature of many cancers, according to the authors. — N.Z.



Somatic mitochondrial DNA mutations (red, *Left*) deregulate metabolism.

Blue-light dimerization dissects phosphoinositide activities

Lipids known as phosphoinositides (PIs), core signaling components of most cell membranes, regulate a range of important cellular functions. Researchers have manipulated PIs with a variety of techniques to better understand their function, but have met with limited success. Olof Idevall-Hagren et al. (pp. 13894–13895) draw on recent advances in the field of optogenetics—a methodology to noninvasively manipulate cell function with genetically encoded, light-sensitive probes—to devise a technique that uses blue light-induced dimerization between two plant proteins to rapidly, locally, and reversibly control plasma membrane PI levels. The light-dependent system avoids the potential off-target drug effects of chemically induced dimerizations, the authors report, and offers additional advantages such as the ability to spatially and reversibly control dimerization and regulate PI activity with high subcellular precision. In addition, the technique can be used to independently study multiple cell types in a single cohort and applied, in principle, to tissues of intact organisms, thereby overcoming problems related to systemic drug administration. The light-dependent probe represents a high-precision tool for revealing the cellular functions of various PIs and reversibly controlling downstream effectors of these signaling lipids, according to the authors. — T.J.



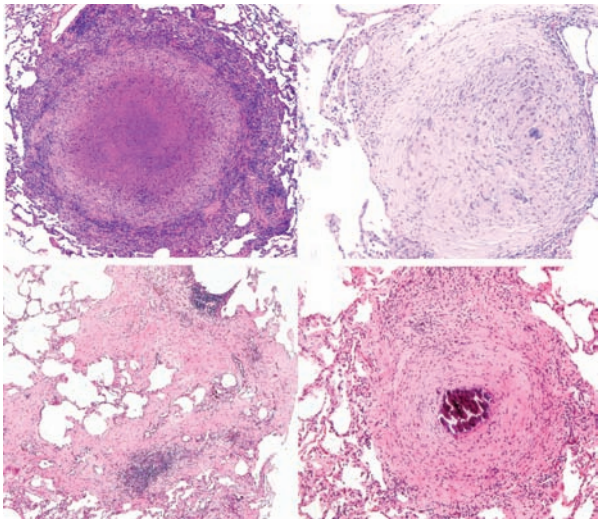
Local, blue light-induced $PI(4,5)P_2$ dephosphorylation.

Linking cellular phenotype to inflammatory disease

Genome-wide association studies (GWAS) compare common genetic variants in disparate groups to identify differences that promote human phenotypic diversity and increase disease susceptibility. The technique, however, reveals little about how specific variants contribute to pathogenesis. Dennis Ko et al. (pp. 13900–13901) combined the GWAS approach with a protocol that tests how variants alter cellular physiology to develop an in vitro association screen of human host response to microorganisms. The screen, named high-throughput human in vitro susceptibility testing (Hi-HOST), allowed the authors to pinpoint a common single nucleotide polymorphism associated with reduced expression of a methionine salvage pathway enzyme. In particular, the authors found that this genetic variant increased caspase-1–mediated cell death, a proinflammatory response to pathogens that has been linked to multiple human diseases including inflammatory bowel disease and gout. Examining cellular phenotypes, the authors argue, can disclose how human variation impacts the activation of inflammatory pathways that affect disease susceptibility. Furthermore, linking the methionine salvage pathway to the inflammatory response demonstrates that the Hi-HOST screening approach can potentially reveal unexpected insights into cell biology, according to the authors. — T.J.

Preventing the reactivation of latent tuberculosis

While *Mycobacterium tuberculosis* infection can lead to active tuberculosis (TB), about 2 billion people have an asymptomatic latent infection that carries a 10% lifetime risk of reactivation. Philana Ling Lin et al. (pp. 14188–14193) found that targeting *M. tuberculosis* in low-oxygen microenvironments could prevent reactivation of latent infections and possibly shorten the length of therapy regimens for active infection. Drugs routinely used to treat latent TB, including isoniazid (INH) and rifampicin (RIF), are inefficient at clearing organisms from the low-oxygen environments within the small nodules, or granulomas, that characterize TB infection in humans. The study revealed that metronidazole (MTZ), a drug that acts solely on anaerobic, nonreplicating bacteria, was as effective at preventing induced reactivation of latent TB as either 6 months of INH treatment or 2 months of a combined INH/RIF therapy. The authors further showed that the addition of MTZ to INH/RIF combination therapy effectively treated animals with active TB in 2 months by targeting bacteria in the low-oxygen microenvironments where INH and RIF are less useful. The findings suggest that drugs capable of targeting *M. tuberculosis* in low-oxygen environments could provide important tools in the fight against TB, the authors suggest. — S.R.



Tuberculosis granuloma.