Betwixt muscle and blood vessel

A ready source of muscle progenitor cells might be useful for treating diseases that involve muscle atrophy. Huard, Péault and colleagues have isolated and characterized a novel progenitor cell in human adult skeletal muscle that is more potent in regenerating muscle than previously identified muscle progenitor cells, or ‘satellite cells’. The new progenitors, called myoendothelial cells, express cell-surface markers of both satellite cells (CD56) and endothelial cells (CD34 and CD144). They are easily isolated by fluorescence-activated cell sorting and can be differentiated in vitro into muscle, bone and cartilage lineages. Myoendothelial cells are considerably more efficient at forming muscle fibers in vivo compared with both satellite and endothelial cells: 1,000 myoendothelial cells transplanted in the injured skeletal muscle of immunodeficient mice produce on average 89 myofibers, whereas the same number of endothelial or satellite cells generate only 9 and 5 myofibers, respectively. In vitro and in vivo assays show that cultured myoendothelial cells have no propensity to form tumors. [Articles, p. 1025]

SCHEMA for thermostable enzymes

Technologies to isolate thermostable proteins with new enzymatic activities are important for industrial biotech. Arnold and colleagues show that structure-guided SCHEMA recombination can be used to isolate a large number of novel thermostable cytochrome P450s that are catalytically active. Previously, using the heme domains of cytochrome P450 BM3 from Bacillus megaterium and two homologs, the authors had shown that recombination guided by SCHEMA—an algorithm that enables identification of fragments of proteins that can be recombined without disrupting the integrity of a protein’s three-dimensional structure—can create chimeric P450 sequences comprising eight different fragments. Here, the authors show that linear regression of experimental sequence stability data on 204 P450 chimeras can be used to accurately predict the most thermostable variants for all 6,561 chimeras in the library. Although not as accurate as the linear regression model, consensus analysis of multiple sequence alignments on a subset of folded chimeras also enables prediction of thermostable chimeras. The authors show that the 44 most thermostable variants constructed in this study retain catalytic activity, and that some of these chimeras are more active than the most active parent enzyme. In addition, two chimeras have new enzymatic activities, converting two clinically approved drugs into products that are known metabolites of human cytochrome P450s. [Letters, p. 1051]

Mice from engineered bi-maternal embryos

DNA methylation at CpG dinucleotides in mammalian germ cells results in long-term transcriptional silencing. These genomic methylation imprints are erased in primordial germ cells and reestablished in a sex-specific manner during spermatogenesis and oogenesis. Bi-maternal embryos constructed by combining the haploid genome of an imprint-free, nongrowing oocyte and the haploid genome of a fully grown, maternally imprinted oocyte are embryonic lethal because the former genome lacks proper paternal imprinting. Kono and colleagues overcome this problem by combining wild-type, fully grown oocytes and nongrowing oocytes in which two paternally methylated imprinting-control regions are deleted. Of the three paternally methylated imprinting-control regions that have been identified to date, the authors deleted the H19 differentially methylated region on chromosome 7 and the Dlk1-Dio3 intergenic germline–derived differentially methylated region on chromosome 13. The resultant bi-maternal embryos are capable of developing into viable mice at a frequency equivalent to that of in vitro fertilization of normal embryos. These mice are phenotypically equivalent to wild-type mice, with the exception of slightly reduced body weight after birth. Insight derived from this bi-maternal reconstruction scheme could potentially contribute to the development of more efficacious therapeutic cloning techniques. [Letters, p. 1045]

Genome of a beneficial bacterium

Borriss and colleagues report the complete genome sequence of Bacillus amyloliquefaciens strain FZB42, a naturally occurring isolate of a plant root–colonizing Gram-positive bacterium that stimulates crop growth and suppresses soil-borne phytopathogens. Comparison with the genomes of other members of the genus Bacillus reveals genes likely to account for the beneficial features of B. amyloliquefaciens FZB42 and the molecular basis of its plant-associated lifestyle in the rhizosphere. They estimate that >8.5% of the B. amyloliquefaciens FZB42 genome is devoted to synthesis of secondary metabolites that counteract bacterial or fungal competitors by their antibiotic activities or abilities to sequester nutrients such as iron. These insights open the way for enhancing the agricultural potential of this biocontrol agent, represented here by machinery used to coat potato tubers with a suspension containing B. amyloliquefaciens FZB42 spores. [Articles, p. 1007]
Quantitative kinobead assays

Identifying the full complement of proteins bound by small-molecule drugs is key to enhancing their efficacy and counteracting undesirable side-effects. However, attempts to optimize the therapeutic potential of kinase inhibitors have been frustrated by the inability to directly quantify binding of these drugs to their targets in cells or cell lysates. Bantscheff et al. use kinobeads—an affinity matrix modified with multiple copies of seven different kinase inhibitors—to trap hundreds of kinases and other purine-binding proteins from samples pretreated with varying concentrations of an inhibitor of interest. Not only does quantitative mass spectrometry, involving the iTRAQ labeling reagent, report the relative abundances of all kinobead-bound proteins captured in a single experiment, but comparison of the binding profiles for a single protein using a range of inhibitor concentrations enables direct calculation of affinity binding constants. This approach reveals novel kinase and nonkinase targets of the leukemia drugs imatinib, dasatinib and bosutinib. [Articles, p. 1035; News and Views, p. 994] PH

ES cells mend the heart

Human embryonic stem (hES) cells will readily differentiate into cardiomyocytes that beat synchronously in a dish. When such cardiomyocytes are transplanted into animal hearts, they are able to survive for months and integrate functionally with the host myocardium. But transplantation into the forbidding environment created by a heart attack is another matter entirely—in this setting, most of the donor cells do not survive. In an effort to overcome this problem, Murry and colleagues investigate several strategies known to inhibit cell death caused by ischemia, anoikis and inflammation. These studies allow them to formulate a cocktail of factors that substantially improves the engraftment of hES cell–derived cardiomyocytes in the hearts of rats subjected to experimental heart attacks. The authors also develop an in vitro differentiation system based on activin A and BMP4 that permits more efficient generation of cardiomyocytes. The increased engraftment of donor cardiomyocytes in infarcted hearts translates into improved cardiac function, with treated animals showing reduced ventricular dilation and higher contractile function at 4 weeks after transplantation compared with control animals that received noncardiac cells. [Articles, p. 1015; News and Views, p. 993] KA

Patent roundup

The potential for gene patents to have a negative effect on clinical, diagnostic molecular genetic testing is common knowledge. However, according to Roger Klein, patent law precedents suggest that the legal threats preventing pathologists and other laboratory professionals from performing such tests lack substance. [Patent Article, p. 989] MF

Recent patent applications in stem cell culture. [New Patents, p. 991] MF

Next month in nature biotechnology

- Nanoparticle vaccines for dendritic cells
- In vivo delivery of lipophilic siRNAs
- Controlling expression during directed evolution
- Pluripotency revealed by morphology
- Renal clearance of nanoparticles
- Improving antibody affinity in silico

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