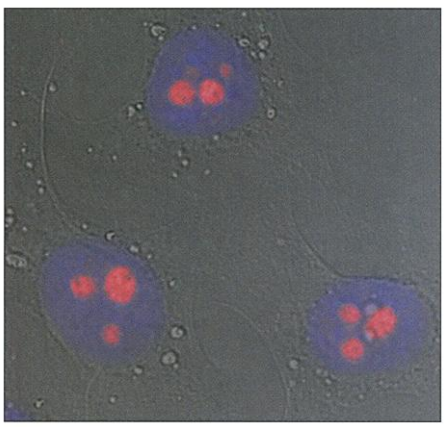
CELL BIOLOGY

Stripping the Nucleolus Down to Its Proteins

The human genome may be the mother of biological blueprints, but it's spawning plenty of offshoots: more modest lists of molecules powering often crucial bits of cells. The latest such roster—271 proteins identified in a compartment of the cell nucleus called the nucleolus—is a first step toward fully deciphering this organelle, a critical element in the construction of ribosomes, which go on to make proteins. With scientists now debating the nucleolus's role in additional functions, including cell cycle regulation and gene silencing, this starter list of proteins—30% of which are uncharacterized—offers plenty to chew on.

To assemble the protein map, the largest ever reported for a single organelle, cell biologists Angus Lamond of Scotland's University of Dundee, Matthias Mann of the University of Southern Denmark in Odense, and their colleagues at both institutions melded a decades-old method with cutting-edge technology and the latest human genome data. Applying an updated version of a 1960s technique, they treated human nuclei with sugar and sound waves and, using a centrifuge, separated the relatively dense nucleolus from its gelatinous home in the nucleus. Mass spectrometry combined with searches of human gene databases enabled the biologists to identify and characterize what they found.



Revealed. The nucleolus (red) has 271 proteins and counting.

"It's like being in a candy store: They've got all these wonderful proteins," says Joseph Gall, a cell biologist and staff member of the Carnegie Institution of Washington's branch in Baltimore, Maryland. Still, he and others caution that painstaking research lies ahead. "It is a framework for future work," says Tom Misteli, a cell biologist at the National Cancer Institute in Bethesda, Maryland. "But it doesn't really answer any single question."

As Lamond and his colleagues report in the 8 January issue of *Current Biology*, 191 of the proteins have been characterized, and over half of them share links to the nucleolus, adding a layer of certainty to past research. This set includes various ribosome builders, as well as other proteins that process and transcribe ribosomal RNA, a necessary step before the ribosomes can be assembled and pushed out of the nucleolus.

The remaining 90 or so characterized proteins participate in a hodgepodge of functions. They include molecular chaperones, which prevent other proteins from sticking together; translation machinery, which coaxes messenger RNAs and ribosomes to form proteins; and so-called DEAD-box proteins, which control the structure of RNA. "The actual overall complexity of the nucleolus was somewhat surprising," says Lamond, who suspects that it's far more than a ribosome factory.

That's likely to be the case, cell biologists agree. But the British and Danish team's list may also include non-nucleolar, contaminant proteins, say Gall, Misteli, and the researchers themselves. Without a membrane, the nucleolus is notoriously difficult to separate from the nucleus, and even the purest sample could contain molecules that accidentally stuck to it during the split. In addition to those that may have erroneously made the cut, several dozen known ribosomal proteins are absent from the roster; Lamond agrees that more nucleolus proteins remain to be found.

Nevertheless, biologists believe that only by paring down the nucleolus to its biochemistry can they read its part of the script. Surprises are expected. –JENNIFER COUZIN

MILITARY RESEARCH

Army Ordered to Hunt Down New Technology

Congress has ordered the U.S. Army to be all that it can be to promising high-tech start-up companies. Lawmakers have given the Army $25 million to establish an independent venture capital fund that will take an ownership stake in companies with promising military technologies. The unusual approach is drawing good reviews from some analysts. But some of the Army's own science advisers doubt that it can succeed, much less ever turn a profit.

The new venture fund is included in a $317 billion defense spending bill signed last week by President George W. Bush. It's aimed at shaking up a $1.2 billion Army R&D program that critics say has been too slow to deliver battlefield advances, from lighter weapons to better communications systems. The Army is also accused of relying on a few well-established defense contractors and overlooking smaller companies with better ideas but less political clout. "There is a bit of the hardening of the arteries over there," says Greg Dahlberg, acting Secretary of the Army under President Bill Clinton and now a top Democratic staffer on the House Appropriations subcommittee that oversees the Pentagon.

New venture. Congress hopes a new R&D investment fund will bolster the Army's arsenal.

To help unclog the Army's technology pipeline, Dahlberg and other fund supporters have borrowed an idea from the Central Intelligence Agency (CIA). In 1998, the CIA set up In-Q-Tel, an independent venture capital fund that has since funneled nearly $50 million into several dozen youthful information technology companies. The fund looks for firms that can both produce promising new intelligence tools and turn a healthy profit selling products to other consumers, and it sometimes takes a stake in the company. Eventually, the federal investment is supposed to generate enough income to make the fund self-sustaining.

Although In-Q-Tel is still far from breaking even, last year an outside review panel praised its contribution to modernizing the CIA and told Congress to continue funding it. The $25 million in start-up cash for the new fund will come from an across-the-board tax on the Army's basic and applied research budgets, although legislators fenced off several dozen projects deemed essential.

Army officials have already begun to assemble a wish list of technologies to guide fund managers—to be recruited from government and the private sector—in their search for "those nimble young companies that don't usually deal with the Army but have a lot to offer," says Army chief scientist A. Michael Andrews II. One potential pool of candidates, he notes, will be the several hundred researchers who have won recent grants from the Army's small business development program.

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