The relation between the central black hole and the surrounding starburst is a crucial puzzle. Did the black hole arise from the condensation of small, stellar-mass black holes produced in earlier starbursts within the galaxy? Determining the answer requires observations of primordial starburst galaxies and primordial quasars. Several speakers pointed out that galaxies are now winning the redshift race because the most distant objects currently known in the universe are starburst galaxies rather than quasars.

Malcolm Longair (University of Cambridge) summarized the new and intriguing evidence that we may not yet have seen the real contestants in this race because they are obscured by dust. New observations from the SCUBA (Submillimeter Common-User Bolometer Array) submillimeter camera imply a large population of very dusty objects at high redshifts (*3*). They supplement similar hints from deep infrared images with the European Space Agency's Infrared Space Observatory (*4*). These mysterious sources are evidence that the bulk of luminosity in the distant universe, whether from young stars or AGN, is so obscured by dust as to be invisible in the optical and ultraviolet light observable by Hubble Space Telescope or large ground-based optical telescopes. Such evidence reinforces the motivation for NASA's Space Infrared Telescope Facility (SIRTF), scheduled for 2001, and makes more compelling the plan by the U.S. National Radio Astronomy Observatory to lead development of a millimeter array interferometer project.

Astronomers in attendance at the Byurakan symposium were gratified that 30 years' accumulation of observational data on active galaxies, at wavelengths from gamma ray to radio, has yielded unified explanations for a once-bewildering assortment of galaxies. Fundamentally similar phenomena can now be described and traced over three-fourths of the history of the universe.

References and Notes

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PERSPECTIVES: IMMUNOLOGY

Developmental Options

Ken Shortman and Eugene Maraskovsky

Dendritic cells (DCs)—sparsely distributed migratory immune cells that can ingest and display antigens on their surfaces—link the innate and the adaptive immune systems. "Immature" DCs in peripheral tissues prone to invasion by infectious agents form a network of sentinels that sample the antigenic environment. Infection or tissue damage initiates migration of antigen-bearing DCs out of the tissue, through the endothelium into lymphatic ducts and thence to lymph nodes. In the lymph nodes, the now "mature" DCs initiate immune responses by efficiently presenting the processed antigen to T lymphocytes (*1*). On page 480 in this issue, Randolph *et al.* (*2*) investigate the migration of DCs and their precursors through a layer of vascular endothelial cells in vitro. The results revealed much more than the mechanics of transendothelial movement; in fact this migration process turns out to be central to the developmental choice between macrophages and DCs.

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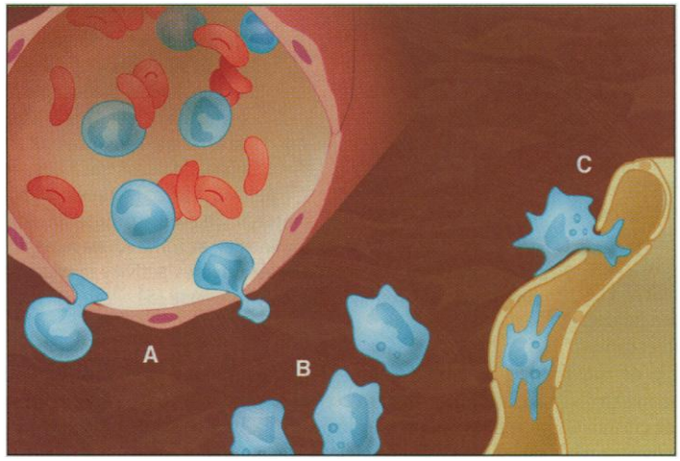
The capacity for antigen uptake and general morphology of the DCs suggest that they are related to blood monocytes and tissue macrophages. Whether DCs are a distinct cell lineage or merely a form of macrophage was vigorously debated 5 to 10 years ago. The conclusion: They are related but clearly distinct, not just in morphology and surface marker expression, but in antigen processing and T cell activation functions (*1, 3, 4*). This notion is now complicated by evidence that DCs are heterogeneous in lineage origin (*5*). The Langerhans cells of the skin epidermis are the immature form of one DC lineage that, despite a common myeloid precursor origin, seems separate from most macrophage-related DCs in intermediate precursors, in tissue localization, and in several antigenic markers (*6, 7*); these DC lineages are nevertheless closely related, because certain cytokines induce markers for Langerhans cells in monocyte-derived DCs (*8*). More distinct is a subgroup of lymphoid-related DCs found in mouse spleen and thymus; these DCs express several markers characteristic of lymphoid cells, and they derive from a precursor closer to the lymphoid than to the myeloid lineage (*9–11*). The DC type with the closest relation to macrophages appears to be the interstitial DCs of tissues such as heart or skin dermis. The study of Randolph *et al.* applies particularly to this DC type, although similar issues probably arise with all migratory DCs.



Dendritic cell origins. Migration and differentiation of dendritic cells and their precursors in intact tissues.

Cell cultures treated with cytokines clearly demonstrate that blood monocytes have a capacity to differentiate, with little or no cell division, either into macrophages or into these macrophage-related DCs (*3–5, 12*). Exposure to macrophage colony-stimulating factor (M-CSF) induces only macrophage formation, whereas granulocyte-macrophage colony-stimulating factor (GM-CSF) also induces DC formation. Although the initial transformation into a DC form is reversible, exposure to proinflammatory cytokines such as tumor necrosis factor–α (TNFα) induces an apparently irreversible maturation to DCs. GM-CSF, TNFα, and interleukin-4 are widely used to induce DC development from blood mono-

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cytes, and this is currently the favored procedure for generating DCs for immunotherapy. Despite this central role for GM-CSF in culture systems, mice deficient in either GM-CSF or its receptor still produce DCs (*13*). In addition, enhancing GM-CSF levels in mice produces only modest increases in DC numbers, in contrast to another cytokine, Flt-3 ligand (*13, 14*). In part, this reflects the existence of other DC lineages, less dependent on GM-CSF (*15*), although it may also indicate that other stimuli can induce differentiation of even the macrophage-related DCs.

The culture system of Randolph *et al.* does not require exogenous cytokines. Rather, two different nonhormonal stimuli that can drive monocytes to develop into DCs were delineated, phagocytosis and transendothelial transport. In the model of Randolph *et al.*, monocytes first cross a layer of endothelial cells and lodge in a collagen matrix, mimicking entry of monocytes into tissues from the bloodstream (see figure at left). A proportion of these monocyte-derived cells then "reverse transmigrate," mimicking migration of DCs out of the tissues into lymph. Those that remain in the "tissue" become macrophages. Those that reverse transmigrate become DCs. The extent of this differentiation and transmigration is greatly enhanced if the cells are undergoing active phagocytosis of foreign particulate material in the collagen matrix. This fits with evidence that phagocytosis of bacteria provides a strong stimulus for DC maturation (*16*). The new and intriguing possibility is that reverse transmigration across an endothelial barrier provides additional signals that induce or enhance differentiation into DCs.

The factors that control movement across the endothelial barrier include chemokines, adhesion molecules, and, surprisingly, the p-glycoprotein (MDR-1) on the DC surface (*17, 18*). But does any part of the transmigration process itself promote DC development, or does the endothelium simply act as a filter, allowing egress of DC-committed cells but retaining in the tissue macrophage-committed cells? And if transmigration induces DC differentiation, are the signals fundamentally different from those revealed by the earlier cytokine-driven cultures? The endothelial cells themselves may be the source of GM-CSF and proinflammatory cytokines, a more efficient presentation by this route accounting for the rapid generation of DCs.

Finally, is a single type of uncommitted blood monocyte driven by environmental factors to become either a macrophage or a DC? The alternative is that blood monocytes are a mixture of cells of predetermined developmental disposition, the endothelial culture system selectively maturing the DC committed precursors, rather than determining DC or macrophage commitment. There is evidence that early myeloid progenitor blasts can produce distinct precursor cells, some with a capacity to form DCs when appropriately stimulated, but others committed exclusively to macrophage production (*19*). It may be possible to answer this question by recycling partially differentiated cells through an endothelial culture system a second time.

DCs have a complex life history. By modeling just one part of DC physiology in culture, Randolph *et al.* have provided unexpected insights into an important developmental decision point. If some of the basic questions still remain, we now have available a new and very useful culture model to help answer them.

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PERSPECTIVES: CHROMOSOME STRUCTURE

How to Compact DNA

Andrew W. Murray

During cell division (mitosis), the chromosomes must be condensed into discrete, compact bodies. For each chromosome, this means packing about 4 cm of DNA into a rod 10 μm long and 1 μm in diameter. In this form, the chromosomes can be separated into two separate sets without entangling or breaking them. For the rest of the cell division cycle (interphase), the chromosomes are much more diffuse structures, long strands that allow access to the DNA by enzymes that replicate DNA and transcribe it into messenger RNA. A report in this issue on page 487 reveals an important insight into how progress through the cell cycle regulates the packing of DNA into chromosomes (*1*).

Which proteins drive these enormous changes in chromosome architecture that occur as cells enter mitosis? How are they regulated by the biochemical oscillator that drives the cell division cycle? Early attempts to study this problem focused on the histone proteins, around which the chromosomal DNA is wrapped and which are the most abundant of the chromosomal proteins. There are major changes in the phosphorylation of histones as cells enter mitosis (*2*), and one protein kinase that performs this phosphorylation (the complex of Cdc2 and cyclin B) is the principal biochemical activity that induce mitosis (*3*). Despite this correlation, however, the importance of histone phosphorylation in mitotic chromosome condensation is unclear.

Hirano and his colleagues have taken an alternative approach to understanding chromosome condensation that exploits the early cell cycles of fertilized frog eggs. Two aspects of these cell cycles make them attractive: First, there is little transcription, so differences between the proteins associated with interphase and mitotic chromosomes are likely to reflect the different structural organization of the two types of chromosomes rather than different transcriptional states; second, the entire cell cycle occurs in extracts made from eggs. In the first experiments, the authors added sperm nuclei to interphase or mitotic extracts, recovered the decondensed or condensed chromosomes, and examined the proteins that were associated with them (*4*). This approach identified two large proteins, XCAP-C and XCAP-E, that were specifically associated with mitotic chromosomes and that contained a long coiled-coil domain and a region with strong homology to other proteins that hydrolyze adenosine triphosphate (ATP). Depleting XCAP-C or -E from the egg extracts prevented mitotic chromosome condensation. An even more interesting result is that inactivating the proteins in extracts that were already in mitosis led to chromosome decondensation, suggesting that con-

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