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Official Publication of the Federation of American Societies for Experimental Biology
February 1996, Volume 10, Number 2
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Serial Reviews

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Carotenoids 3. In vivo functions of carotenoids in higher plants. B.
Demmig-Adams, A. M. Gilmore, and W. W. Adams III

State-of-the-art Reviews

G. C. Zeng, B. P. Doctor, K. Pardhasaradi, and P. P. McCann
Regulation of gene expression by alternative promoters. T. A. Y. Aoyubu
and W. J. M. Van de Ven
Masking of mRNA by Y-box proteins. J. Sommerville and M. Ladomery
Nicotinamide nucleotide transhydrogenase: a model for utilization of
substrate binding energy for proton translocation. Y. Hatetfi and M.
Yamaguchi

The Leloir pathway: a mechanistic imperative for three enzymes to change
the stereochemical configuration of a single carbon in galactose. P. A. Frey

COVER: A working model for the induction of the microsomal enzyme cytochrome
P450IA1. The mechanism involves increased expression of the cognate
CYP1A1 gene. Two novel regulatory proteins the aromatic hydrocarbon
receptor (AhR) and the Ahf nuclear
translocator (Arnt) mediate the response. Enzyme induction represents an interesting
mechanism by which cells adapt to
xenobiotics, such as the environmental
contaminant 2,3,7,8-tetrachlorodibenzo-
p-dioxin (TCDD). (From an upcoming review
in this series, Whickett et al., FASEB J., June 1996.

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chaser-provided relationships," to establish "market principles" in the way our public expenditure works. Often this seems to have meant or has been represented as having meant simplistic arrangements where scientists, hospitals, schools, and railways set out their stall as in a food market. The public or the government then chooses what to buy and what not to buy. Those resisting this philosophy have usually made the mistake of arguing about the extent to which the detailed mechanisms of competition and choice can be read across from the food market to particular public services. For science, this misses the main point, which is simply that, regardless of mechanisms, scientists are sellers not buyers and if we are to take public money, this principle is here to stay. To remain in business as our nations and indeed humankind need us to, we must sell projects, visions, and organizations for the delivery of good things from our science. To brandish instead shopping lists of projects and facilities that we need for the sake of science, is to cast ourselves in the opposite role of buyers rather than sellers. This won't work, because we have no currency with which to buy, and any credit we have is too precious for impulse purchases. If the stance of buyer has ever worked in the past, it will never work again. This is the lesson that European science is currently learning, and learning fast. Is this a trendsetter for the United States, or not?

Dai Rees
Sir Dai Rees, F. R. S., is the chief executive of the Medical Research Council, 20 Park Crescent, London W1N 4AL, U.K., and president of the European Science Foundation, 1 quai Lezay-Marnésia, 67080 Strasbourg Cedex, France.

COMMUNICATIONS CAPSULES

The following are summaries of original research articles that appear in this issue.

NEGATIVE EFFECT OF PROTEOGLYCANS ON EMBRYONIC CELL MOVEMENT

Large molecular weight chondroitin/keratan sulfate-bearing proteoglycans may act negatively on cell adhesion and cell movement. Evidence is presented by Perris et al. (pages 293-301) that, in their purified form, members of the aggrecan and PG-M/versican subfamilies of proteoglycans interfere with embryonic cell movement, with aggrecans being significantly more efficient inhibitors than PG-M/versicans. The molecular mechanism underlying the inhibitory action of these proteoglycans involves both the core protein and the side chains, in particular the keratan sulfate chains, and is domain-specific. Hyaluronan and lectin-like components are the cell surface mediators of the neural crest cell-proteoglycan interactions.

LEAKY CALCIUM STORES

Agonist-sensitive internal Ca stores possess an inherent leak to Ca that requires continuous compensation by Ca pumps in order to maintain stores in the filled state. By measuring free intraluminal [Ca] in organelles with low affinity fluorescent Ca indicator, Hofer et al. (pages 302-308) found that the leak pathway in the internal store membrane was inactivated when cytosolic [ATP] was decreased. Such regulation may be a physiologically important mechanism for controlling the efficiency of Ca sequestration following global or local reductions in cellular [ATP].

DIFFERENT PROTEASE-ACTIVATED RECEPTORS IN T CELLS

Mari et al. (pages 309-316) report that besides the thrombin receptor, leukemia T cells express a functional trypsin-activated receptor, possibly the human counterpart of the murine protease-activated receptor (PAR2). Also, thrombin and trypsin increase calcium mobilization in these cell lines essentially by activating their own receptors. The physiological ligand and precise function of this newly characterized trypsin-activated receptor in T cells remain to be identified. Circulating serine proteinases involved in the processes of blood coagulation and complement cascade represent good candidates for activating such a receptor.

S-100a0 REGULATES DESMIN ASSEMBLY-DISASSEMBLY

S-100a0, a Ca2+-binding protein of the EF-hand type abundant in skeletal muscle cells, inhibits the assembly of desmin, the type III intermediate filament (IF) subunit specific to mature muscle cells, and stimulates desmin IF disassembly in the presence of Ca2+ (Garbuglia et al., pages 317-324). Other S-100 isoforms also affect desmin assembly, but with reduced potency, the extent of effects depending on the fraction of 8 subunit (the most potent) or 3 subunit (the least potent) present in the isoform tested. The S-100-like proteins, calcylin and p11, are not effective. The results suggest that S-100a0 might play a role in remodeling the IF cytoskeleton in muscle cells following elevation of the free Ca2+ concentration.

MECHANISMS OF RESISTANCE TO APOPTOSIS

Tumor cell survival in vivo may be promoted by mutations of epigenetic changes that confer resistance to apoptosis, the cell death pathway activated by host defenses and many chemotherapeutic drugs. Wright et al. (pages 325-332) examined the biochemical basis for resistance to tumor necrosis factor of UV light-induced apoptosis in a variant of the human histiocytic lymphoma, U937. They demonstrated that resistance was due to a block in upstream signaling events that activate sphingomyelinase, an enzyme that transmits signals to stimulate the 24 kD apoptotic protease in normal U937.

(continued on p. 201)
MEETING

The annual Women in Science and Engineering program (WISE) will be held in early April 1996 at the National Academy of Sciences. This year's theme explores the same one discussed at the Once and Future Action Network formed at the 1995 United Nations Conference on Women—how scientific research crosses national borders and how international linkages improve the quality of science. The program honors women who embody creativity and excellence in science and stand as models for upcoming generations of scientists and engineers. Expected speakers are Lynn Goldman, Assistant Administrator for Prevention, Pesticides, and Toxic Substances, Environmental Protection Agency, and Joan Lubchenco, President, American Association for the Advancement of Science. For updated information, contact Gaelyn Davidson (Gdavidso@NAS.edu) or Sheila David (202-334-3422).

AT FASEB

Michael Sela (ASBMB-H, AAI-H, Protein), a member of the editorial board of The FASEB Journal, was awarded UNESCO's Albert Einstein Medal. Sela, a renowned Israeli immunologist and cancer researcher, received the medal in recognition of his outstanding research in the field of immunology and longstanding efforts to promote scientific cooperation worldwide. UNESCO created the medal in 1979 to mark the 100th anniversary of the birth of the physicist who promoted peace and scientific cooperation during his lifetime.

"Reshaping the Graduate Education of Scientists and Engineers," a report delineating a new model of PhD education that speaks to the changing job market, is available free in a short version (Report Brief) from FASEB (Office of Publications, 9650 Rockville Pike, Bethesda, MD 20814-3998; 301-530-7100).

The full report comes from COSEPUP, a joint committee of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. It is available in its entirety for $29.00 each from National Academy Press, 2101 Constitution Ave., NW, Box 285, Washington, DC 20055 or by calling 1-800-624-6242 or 202-334-3313 (Washington metropolitan area). For shipping and handling, please include $4.00 for the first copy ordered and $.50 for each additional copy. Applicable sales tax or GST if CA, MO, TX, VA, or Canada resident. The report may also be ordered from the NAS home page on the World Wide Web at <http://www.nas.edu>, on gopher <gopher.nas.edu>, or through FTP <ftp.nas.edu>.

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topological, evolutionary, and mechanistic relationships between the molecules and illustrations of known 3-dimensional structures. Also, the University of Houston has recently provided a series of servers for Drosophila, Arababopsis, and nematode gene identification. [http://adeneine.bchs.uh.edu] One can do splice site prediction, find exons, and model genes. This site also provides a multiple sequence alignment service on the Internet. Further, the Worm Community System network of databases for C. elegans was recently enhanced so that the user can conduct a rather sophisticated search. Suppose you're interested in genes involved in the worm's sense of touch. You begin by entering "sensory," and the system finds every piece of literature that contains that word, displaying a one-line summary of each. Next, you perform a "group follow" to get all the genes mentioned in that literature. Each gene—or any set of genes—can then serve as the starting point for a new search. A user might, for example, ask for a display of a genetic map indicating the locations of all these genes. Or the user can choose one gene and get its sequence, its location on a physical map, or a list of genes that have related functions.

There is even available a PCR primer database, a practical bank of information of fully tested and optimized primers for PCR reactions. [http://www.ebi.ac.uk/primers_home.html] The database contains all the items required to reproduce precisely the conditions of the submitting author. It also gives details on how to contact the author should you have questions.

As you can see, an explosion of significant developments on the Internet in the past year or so has us going far beyond e-mail and newsgroups.

Next: Where do we go from here?

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**COMMUNICATIONS CAPSULES** *(continued from p. 198)*

**GLUTATHIONE AND MITOCHONDRIAL DNA DAMAGE**

Aging causes oxidation of mitochondrial glutathione. de la Asuncion (pages 333-338) report that changes in the glutathione redox ratio (GSSG/GSH) in mitochondria are an order of magnitude higher than in the whole cell. Mitochondrial levels of 8-hydroxy-2’-deoxyguanosine (oxo8dG), an index of oxidative damage to DNA, also increase with age. The levels of oxo8dG are much higher in mice (a shorter-lived species) than in rats. Age-related changes in both glutathione and oxo8dG can be partially prevented by antioxidant administration. There is a linear relationship between oxidation of mitochondrial glutathione and damage to mitochondrial DNA.

**AIDS DEMENTIA: FYN DISRUPTED?**

A devastating complication of HIV infection in AIDS dementia complex (ADC). The pathologies contributing to ADC at the molecular level are unknown. In a murine model of AIDS, Sei et al. (pages 339-344) found that hippocampal neurons from mice with murine AIDS had defects in the protein tyrosine kinase fyn, an enzyme involved in learning and memory. Fyn kinase from hippocampi of mice with murine AIDS is highly phosphorylated, abnormally localized in the neurons and functionally unresponsive to glutamategic stimulation. These findings suggest that disruption of fyn-mediated signalling may be involved in the spatial learning deficits observed in these mice. Similar changes in fyn kinase may contribute to the neuropsychiatric manifestations of ADC in patients infected with HIV.

**P/O RATIOS RE-ASSESSED**

For over five decades, the yield of respiratory chain-linked oxidative phosphorylation—the P/O ratio—has been one of the most frequently performed measurements in biochemistry. A maximal P/O ratio of 3 for mitochondrial ATP synthesis has long been the generally accepted textbook value. Lower, non-integral values were interpreted in terms of energy-dissipating side reactions. Recently, however, a value of 2.5 as the maximal mechanistic P/O ratio has been proposed, and subsequently adopted by several textbooks. The present paper by Lee et al. (pages 345-350) is a re-appraisal of this issue. It is shown that under optimal conditions the mitochondrial P/O ratio can definitely exceed 2.5. A revision of the original value of 3 appears unwarranted.

**NEURO-IMMUNE INTERACTION**

The cytokine interleukin-1 (IL-1) plays an important role in inflammation-induced brain-mediated symptoms of sickness such as fever, depressed behavior, anorexia, increased sleep, and altered neuroendocrine activity. Van Dam et al. (pages 351-356) demonstrate in vitro and in vivo the presence of functional IL-1 type 1 receptors on brain endothelial cells of adult rats. They hypothesize that during sickness, circulating IL-1 may activate brain endothelial cells to produce brain accessible signals including interleukin-6 and prostaglandin E2. This mechanism may be crucial because IL-1 produced by peripheral immune cells does not have ready access to the brain and IL-1 receptors have so far not been detected in rat brain tissue.

**CYTOSKELETAL CONTROL OF K+ RECTIFICATION**

K+ rectifier channels are responsible for resting potential in cardiac cells. Mazzanti et al. (pages 357-361) report that native inwardly rectifying K+ channels have four subconductance states, both in inward and outward one-channel recording. Intracellular submicromolar [Ca2+] controls the expression of outward states by favoring low-conductance substrate opening. The ability of Ca2+ to promote rectification is abolished by cytochalasin, a microfilament disrupter, which also accelerates loss of rectification in divalent-cation-free solutions. Thus Ca2+-induced rectification needs functional cytoskeletal microfilaments to operate. This may be an important mechanism to control rectification in cardiac cells with beat-to-beat resolutions.