sible for the accumulation of dendritic cells in the lymph nodes of type II — but not type I — ALPS patients[2]. Wang *et al.* showed that killing of dendritic cells by CD4-positive T cells is mediated mainly by the tumour-necrosis factor-related apoptosis-inducing ligand (TRAIL), through its receptor DR5, instead of by the Fas–FasL interaction. But dendritic cells from patients with type II ALPS are resistant to such TRAIL-mediated apoptosis. Using retroviral transduction, the authors further showed that mutant caspase-10 could interfere with TRAIL-mediated apoptosis in normal dendritic cells.

Wang *et al.* have documented, for the first time, caspase mutations in a human disease. Although their study clearly shows that people with type II ALPS carry mutant forms of caspase-10 that can interfere with apoptotic pathways of many death receptors, it raises other issues. First, it has yet to be established conclusively that mutation in caspase-10 is solely responsible for the ALPS in these patients. Are the expression levels of FADD and caspase-8 normal? And, despite the evidence that mutations in caspase-10 are responsible for the defective apoptosis in dendritic cells, the normal expression and function of TRAIL receptors in the patients should be measured.

Second, the dominant effect of the heterozygous caspase-10 mutant remains intriguing. Although the most likely possibility is that this mutant interferes with complex formation by directly binding to caspase-8 and FADD, such a picture does not explain why patients carrying the heterozygous allele have few clinical manifestations. This difference has also been noticed among type I ALPS patients with heterozygous mutations in Fas, and it probably reflects the presence of other genetic modifying elements. In the *lpr* mouse model, for example, the animals show varied symptoms with different genetic backgrounds[11].

Finally, the defective apoptosis of dendritic cells in patients with type II ALPS is a significant finding. The sustained lifespan of mature dendritic cells presenting self antigens could lead to enhanced autoreactivity of lymphocytes[12]. So, the involvement of TRAIL — and, as revealed here, possibly caspase-10 — in mediating dendritic cell death might provide new avenues for studying the regulation of dendritic cell lifespan, and its possible role in causing autoimmunity[13].

Five years after caspase-1 was shown to be the mammalian homologue of the nematode death protein ced-3, more than a dozen caspases have been identified[3]. Knockout studies have produced surprises about the involvement of caspases in mammalian development[14]. This latest finding by Wang and colleagues underscores the fact that caspases are indispensable in mammalian apoptosis, and further establishes these proteases as potential therapeutic targets for clinical applications. □

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Science policy

The business of research

Henk F. Moed and Marc Luwel

On page 433 of this issue, Plerou *et al.*[1] provide a quantitative study of the academic research system. Such studies are essential in examining claims as to the success (or otherwise) of the system in general, and forms of funding in particular. Whether the claims come from university scientists or policy makers, anecdote is no substitute for data.

The authors find that the growth dynamics of universities in the United States resemble those of business companies. In the same way that market forces operate in business, the peer review system appears to keep competition among scientists sufficiently strong. This intriguing result may mean that there is no need to make academic research at universities more business-like than it is already.

Plerou *et al.* include five different measures of research activity in their analysis. The largest database consists of 17 years of annual research and development (R&D) expenditure in science and engineering for 719 US universities. The authors find that the growth in research activity does not depend on the size of R&D expenditure (that is, the size of the university), in the same way that businesses (whether large or small) are subject to universal growth mechanisms. They find the same pattern in their analysis of the number of papers and patents published by more than 100 US universities over a similar time period. Moreover, they see the same behaviour in growth rates for research funding in English and Canadian universities, suggesting that the broad result holds for different academic systems.

Some historical context may help here. The classical von Humboldt model of universities — carrying out pure research without any consideration of practical application — was characterized by learning through science, and the unity of research and teaching[2]; conducting pure research was assumed to be the most appropriate training for a job in society. After the Second World War, this system underwent gradual transformation. The concept of pure research was increasingly replaced by one of fundamental research; intended to advance our knowledge of nature, but often motivated by and funded for specific technological objectives.

Besides their traditional mission of providing academic training and carrying out fundamental research, universities today are expected to help solve society's problems and strengthen economic development. In consequence, a new mode of knowledge production[3] has arisen, involving interdisciplinary research with the aim of applying knowledge in more rapid and flexible ways. These trends raise the question as to whether universities can continue to contribute to long-term basic research and maintain a balance between training and knowledge production and application[4].

Plerou and colleagues are rather cautious in drawing general conclusions from their findings. They note that some may see the business sector as a model for academic research. In these terms, the academic research system may be considered effective, and one could conclude that the funding structure of research in the United States, particularly the relatively high proportion of short-term research grants, should be a model for other countries. On the other hand, the authors suggest that the similarity in the growth dynamics of research and business output may show that the 'economization' of fundamental research has been pushed too far in some Western countries. A key factor here is that the 'time horizon' (the number of years that management looks ahead) in the business sector is now typically five years or less, whereas in fundamental research it is often believed to be much longer[5]. In this context, the findings of Plerou *et al.*[1] reflect a convergence of the time horizons of business and universities. To make fundamental contributions to science, the research programmes of high-quality groups have to continue for more than five years — longer than the average research grant.

What drawbacks and limitations are there to Plerou and colleagues' analysis? Their approach aims to characterize the system as a whole. As a result, deviations from the general pattern are not discussed, although such differences may help show

how the findings should be interpreted. Take, for instance, studies in which one or both of us participated[6,7]. In one[6] a mechanism known as the Matthew effect was found to influence the growth rates of research departments in the natural sciences and medicine at Flemish universities. From a management point of view, these departments are academic business units. Both in terms of attracting external funding and publication output, large departments became larger and small departments remained small, contrary to the findings of Plerou and colleagues. Moreover, an overemphasis on short-term objectives led to a decrease in the publication output per full-time equivalent spent on research .

In the other[7], which involved an analysis of universities in the Netherlands during 1980–96, changes in the distribution of students among universities and the outcomes of research evaluation studies seem to have been responsible for a trend towards a uniformity of publication output in the natural and life sciences. Smaller universities had a higher growth rate of publication output than larger ones. This highlights the importance of basic public funding of universities, based on student enrolments, in the Dutch academic research system. In the United States, such basic funding is considerably less important than in several Western European countries, as most research activities are funded through grants[8]. So differences between academic systems in different countries need to be taken into account.

Finally, Plerou and colleagues' analysis[1] can be taken further in two respects. First, more sophisticated indicators of research performance are available[9], and could be used. Second, in their study all scientific disciplines are aggregated; yet there are big differences between disciplines in the amount and origin of funding, partly due to the increasing importance of targeted research programmes in priority areas. The effects of the increasing mobility of scientists, of informal networks and of the growing links between universities and other parts of the R&D system should also be considered. Nonetheless, the observed similarities between universities and business firms will stimulate further debate and research on the effectiveness of national academic research systems. □

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Bioenergetics

Two phases of proton translocation

Denis L. Rousseau

The 'central dogma' of bioenergetics is the chemiosmotic theory, which states that energy stored as a proton gradient across biological membranes (the proton-motive force) is converted to useful chemical energy in the form of ATP. In eukaryotes, the proton-motive force is generated across the inner membrane of the mitochondria by harnessing the energy released from serial electron-transfer events in membrane-bound proteins. This chain culminates in the four-electron reduction of oxygen to water by an enzyme called cytochrome *c* oxidase. Associated with this oxygen chemistry, four protons are pumped across the membrane in opposition to a proton gradient[1].

The molecular mechanism by which oxygen reduction is coupled to proton translocation — the redox linkage — remains a central question. Guided by spectroscopic[2,3], crystallographic[4,5] and mutagenesis[6] results, several models for redox linkage have been proposed, but each has its flaws. One feature that has been lacking is a quantitative temporal relationship between the chemical steps and the translocation of protons[7]. On page 480 of this issue, Mårten Wikström and co-workers[8] propose a surprising time frame for this relationship.

To study the reaction of cytochrome *c* oxidase, all four of its redox centres (Fig. 1) are reduced, and the enzyme is exposed to oxygen. Complete turnover of the enzyme requires two phases. During the oxidative phase, four electrons are transferred to the oxygen molecule, the O–O bond is cleaved, and the enzyme becomes fully oxidized. This is followed by the reductive phase, in which the enzyme is re-reduced. Looking at the reaction as a whole, four protons (the chemical protons) are taken up from the matrix side of the inner mitochondrial membrane and four electrons from cytochrome *c* are used in the formation of water at the catalytic site. Four more protons (the pumped protons) are translocated from the matrix to the cytosolic side of the membrane. In sum, then, eight charges are translocated across the dielectric barrier in the protein.

It was thought that, to efficiently capture the energy released by the oxygen chemistry for proton translocation, the proton-pumping steps occur during the oxidative phase. Indeed, ten years ago, Wikström postulated[9], from equilibrium measurements, that the translocation of all four pumped protons was coupled to two specific reactions within the oxidative phase. This model, which has been the foundation for our thinking about proton translocation ever since, was called into question last year by Hartmut Michel[10], who proposed that one proton is pumped during the initial reduction of the enzyme, before the reaction with oxygen, and that the other three protons are pumped during the oxidative phase. But Michel's model was not substantiated by experiment.

By making two types of measurement, Wikström and co-workers[8] have now determined the amount of charge that is translocated during each phase of the enzymatic cycle. In the first set of experiments, the authors measured the pH change of liposomes with cytochrome *c* oxidase embedded in their membranes during the two halves of the catalytic cycle. In the second set, the time-resolved potential across a membrane containing cytochrome *c* oxidase was followed during turnover. It came as a complete surprise to find that the translocation of charge is incomplete at the end of the oxidative phase.

So what happens to the remaining charge? This, it turns out, is translocated only when the reductive phase immediately follows the oxidative phase. About half of the charge is translocated during each of the phases, indicating that part of the energy generated in the oxidative phase is conserved in the protein and indirectly coupled to proton translocation during the reductive phase. This remarkable result requires a shift in how we must think about proton pumping in cytochrome *c* oxidase, because it invalidates the hypothesis that proton translocation is directly coupled to the oxygen chemistry during the oxidative phase. But where is the energy stored at the end of the oxidative phase? And how is it converted to proton translocation in the subsequent reductive phase?

At the end of the oxidative phase, the four metal centres of the enzyme are fully oxidized. This state, termed O~, is a metastable intermediate that lasts for several seconds under the conditions used by Wikström and colleagues. The structure of O~ must be very different from that of the resting oxidized enzyme — the 'O' state — because reduction of O does not induce proton translocation[8]. The energy for driving the delayed charge translocation could be stored locally in a few highly strained chemical bonds near or at the catalytic site. On reduction of the metal