Spectacular cancer mechanism doubted

Cornell retracts reports of kinase cascade

Boston

The authenticity of one of the year's most exciting biochemical announcements has been cast in doubt. The remarkable biochemical pathway presented at the 20–24 May Cold Spring Harbor Tumor Virus meeting, the "kinase cascade", has slipped back into the ranks of the unconfirmed. This provocative scheme, described to the meeting by Mr Mark Spector, offered a mechanism whereby the products of RNA tumour virus transforming genes initiated a sequence of reactions that helped explain how a normal cell is converted into a tumour cell.

Professor Efraim Racker, of Cornell University, in whose laboratory the work was done, has now sent a carefully worded retraction to *Science* and *Cell* withdrawing his confidence in some of the data from his laboratory's latest work and its recent publication in the pages of those two journals. In his retraction, Professor Racker says that although he believes the major concepts and components of the protein kinase cascade are correct, he doubts the authenticity of some of the data. Professor Racker also hopes to substitute a new paper for one he submitted to the Cold Spring Harbor Symposium, thus preventing further unreliable data from reaching publication.

The retraction Professor Racker is sending to *Science* and *Cell* is problematic because although his group has had difficulty reproducing results pointing to a cascade, such a pathway may turn out to be correct.

The presentation of the "kinase cascade" was the high point of the Cold Spring Harbor meeting (see *Nature* **292**, 15; 1981) and has been the centre of discussion in the biochemical community since then. The result was so exciting that it was even placed on the front cover of the Cold Spring Harbor abstract book. But some members of the audience were sceptical of the work from the start. Sceptics believed that the results looked too clean and were shocked at the speed with which it had been completed. Professor Racker was confronted with these suspicions soon after the meeting and further questions arose when other laboratories nationwide were unable to reproduce the results.

Professor Racker says that he went into the laboratory himself six weeks ago to try to reproduce the work. He quickly confirmed that the final step of the cascade (the phosphorylation of a tyrosine residue on the B-subunit of a membrane ATPase), was correct as first reported (*J. biol. Chem.* **255**, 5504; 1980).

He later confirmed another interesting result: the identification of a 6,000-dalton polypeptide which activates some kinases and phenotypically transforms cell lines. He has since sent this tumour growth factor to outside laboratories for verification.

But except for these two pieces of good news for those rooting for the cascade, all attempts at reproducing previously reported results have failed. Professor Racker and his collaborator Dr Volker Vogt (also of Cornell University) who is a co-author of the *Cell* paper, both believe that all experiments reported involving antisera are suspect.

Professor Racker's retraction comes less than a month after the publication of his latest article. Other than the two confirmed results, the substantiation of all other data will take months to complete. Until then the biochemical community must wait.

David Dickson adds (from Washington): Mr Mark Spector is a graduate student at the Department of Biochemistry and Molecular and Cell Biology at Cornell University, where he has a reputation for working eighteen hours a day. Professor Racker said that the paper read at the Cold Spring Harbor symposium had now been withdrawn.

He also said that while some parts of the scheme worked out by Spector had been confirmed, including the role of the 6,000-dalton polypeptide isolated by Spector, "we are finding more and more things that we suspect".

Michael D. Stein

Biochemical cascades and carcinogenesis

The biochemical pathway described in a series of papers published in the past year by Mark Spector and Professor Efraim Racker, with or without others from Cornell University, centres on four new enzymes. The enzymes were said to be linked in a cascade of reactions such that the activation of any one of them had the end result of reducing the efficiency of the cell membrane enzyme that is responsible for pumping sodium out of cells. Only in tumour cells did the cascade appear to be activated and the sodium pump to be inefficient.

The link of this observation with cancer was tenuous but enticing. Otto Warburg, in the 1920s, first showed that tumour cells exhibit an excessive fermentation of glucose to lactic acid, a biochemical pathway that consumes ADP and inorganic phosphate. These are the two products of the hydrolysis of ATP which accompanies the pumping of sodium from the cell and which provides the energy to drive the pump.

An inefficient pump, as described by Spector and Racker for tumour cells, would hydrolyse more ATP than a normal cell in keeping the cellular sodium at acceptable levels. Since that would result in the production of abnormally large amounts of ADP and inorganic phosphate, the observed increase in tumour cells of glucose fermentation was explained.

There was an additional link between cancer and the cascade, forged particularly in the July issue of *Cell*. The infection of many cells by tumour viruses is known to be followed by the appearance of new phosphorylating enzymes in the cell. But exactly what they phosphorylate and with what consequence has remained an enigma. The cascade provided a solution.

In their *Cell* paper, Spector *et al.* presented evidence that the enzyme produced when one particular tumour virus infected cells was very similar to one of the cascade enzymes. The virus might activate the cascade by the production of increased amounts of one of its members. In other cases it was thought more likely that activation followed phosphorylation of one of the members of the cascade by a virally produced phosphorylating enzyme.

Despite the attraction of this scheme, it came in for sceptical comment from September 1980, with the publication of the evidence that the sodium pump from tumour cells was phosphorylated and rendered inefficient. Doubts centred on the identity of the pumping enzyme and the likelihood of the result, given the artifical — if elegant — system used.

Data published by Spector *et al.* in the 10 May issue of the *Journal of Biological Chemistry*, and in *Cell* (and reviewed in 17 July *Science*) attempted to establish the identity and activity of the cascade enzymes. Doubts about this work centred largely on the speed of progress.

At the Cold Spring Harbor meeting in May, Spector was allowed to give the longest talk of any contributor — his talk was rescheduled to be the last of an evening session so that he could present as much of his data as possible. Even so, much of it had to be passed over at too great a speed for appraisal and it was widely felt that Spector's response to some of the questions was vague. It was also clear that Spector was being cold-shouldered by the majority of senior participants at the meeting. In private, Spector admitted to being hurt by the scepticism but readily agreed that many of his conclusions were tentative and needed substantiation. When it was put to him that even if only 50 per cent was substantiated, the work would still be of great importance, as basic biochemistry even if not related to cancer, Spector said he would be pleased if 20 per cent were confirmed.

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