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Journal club

A NEW PROTEIN KINASE CASCADE

In 1978, when I was just setting up my own laboratory, a short paper from David Gibson's group at the Indiana University School of Medicine, Indianapolis, USA, (Ingebritsen *et al.*) suggested that a protein kinase that inactivated the cholesterol biosynthetic enzyme hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase was itself activated by phosphorylation and was therefore part of a kinase cascade. The concept of a kinase cascade is now familiar, but in 1978 only one of these, the protein kinase A (PKA)–phosphorylase kinase cascade, which was discovered by Ed Krebs, was known. More remarkable still, fewer than ten protein kinases (including the kinase for HMG-CoA reductase ('reductase kinase') and an apparently unrelated kinase for acetyl-CoA carboxylase) had been defined and only then in terms of their enzyme activity (the first kinase domain sequence, which was of PKA, was not determined until 1981).

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HMG-CoA reductase was an endoplasmic reticulum (ER) membrane protein, the enzymatic activity of which could only be assessed by a difficult assay that involved thin-layer chromatography. Furthermore, the only way to assay reductase kinase was by its ability to inactivate HMG-CoA reductase in crude membrane preparations. It was therefore remarkable that Gibson's graduate student Tom Ingebritsen was able to work out that 'reductase kinase' could be inactivated by a partially purified protein phosphatase and that the resulting inactive kinase could be reactivated by incubation with Mg·ATP; they correctly surmised that this was due to phosphorylation of the kinase itself. It took my own laboratory another 9 years (Carling *et al.*) to realize that reductase kinase was the same as the kinase for acetyl-CoA carboxylase (now known as AMPK). It took 25 years for ourselves and others (Hawley *et al.*; Woods *et al.*; *Shaw et al.*) to show that the upstream kinase of reductase kinase that was first observed by Ingebritsen was the tumour suppressor liver kinase B1 (LKB1; also known as STK11). Since 1990, the original paper from the Gibson laboratory has been cited only 21 times (including 12 times by myself), but it was certainly very influential in my own career.

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