

Symposium: Protein Phosphatase—Targets for Cellular Regulation

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INTRODUCTION

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Beginning interest in the phosphoproteins can be traced to about the time the Society for Experimental Biology and Medicine was founded. Shortly after the turn of the century, Levene and Alsberg reported that vitellin, a major protein in chicken egg yolk, contained about 10% phosphorous (1). Some 20 years later the Posternaks, based on analysis of tryptic digests, suggested that the phosphorous in both vitellin and the milk protein, casein, was associated with serine (2). In 1932, Lipmann and Levene firmly established the presence of phosphoserine residues in vitellin (3), which was subsequently renamed phosphovitin (4). The pioneer studies of Krebs and Fischer (5, 6) and Larner (7) in the late 1950s and early 1960s clearly established that the key regulatory enzymes involved in glycogen metabolism (phosphorylase, phosphorylase kinase, and glycogen synthase) could be interconverted between active and inactive forms, and that such interconversions reflected their state of phosphorylation. These findings spawned the concept that covalent modification involving phosphorylation and dephosphorylation of key metabolic enzymes is an important cellular regulatory mechanism. The identification of cAMP as the second messenger for epinephrine and glucagon by Sutherland and co-workers (8), and the subsequent discovery of cAMP-dependent protein kinase by Walsh *et al.* (9) led Kuo and Greengard (10) to suggest that the physiological effects of neurohumoral agents involving the formation of cAMP might be ascribable to phosphorylation of specific proteins. To date, the activity of more than 30 different enzymes is thought to be modulated by reversible phosphorylation-dephosphorylation (11-13). Such regulation encompasses a broad spectrum of biological mechanisms

including cellular transformation, fertilization, protein synthesis, muscular contraction, membrane-bound ion channels, release of hormones, and a variety of anabolic and catabolic processes.

Rapid, significant, and progressive advances have been realized in elucidating the structure, function, and regulation of a variety of protein kinases including (a) cyclic nucleotide-dependent forms, (b) Ca^{2+} -calmodulin-dependent enzymes such as phosphorylase kinase and myosin light-chain kinase, and (c) independent kinases whose activities are expressed in the absence of either cyclic nucleotides or Ca^{2+} (11, 12). Until recently, however, progress in unraveling fundamental properties of the protein phosphatases has been conspicuously slower.

It was generally believed that cellular regulation of both the extent and kind of proteins phosphorylated was governed largely through selective activation of specific kinases by appropriate second messengers (cAMP, Ca^{2+} , etc.) rather than modulation of protein phosphatase activity. Moreover, the occurrence of multiple forms of protein phosphatases, usually with overlapping substrate specificity, and often quantitatively different when utilizing different preparative schemes for the same tissue, created a very confusing data base (see (13-17) for reviews). In addition, the existence of inhibitory or modulatory proteins exerting differential and sometimes variable effects on enzymatic activity probably aggravated the confusion. More recently, however, it has become increasingly clear that inhibitory proteins may represent specific subunits of a particular protein phosphatase, and that a given phosphatase may exist in inactive and active interconvertible forms. It is also clear that regulation of phosphatase

activity may be mediated by both substrate-directed and enzyme-directed mechanisms. This symposium is aimed at reviewing and examining some recent and exciting findings regarding the nature and regulation of protein phosphatases.

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