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Hilz H & Stone P. Poly(ADP-ribose) and ADP-ribosylation of proteins.
Rev. Physiol. Biochem. Pharmacol. 76:1-58, 1976.
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This paper evaluates data on the structure, metabolism, and quantitation of nuclear poly(ADP-ribosyl) proteins, and it reviews the nonnuclear ADP-ribosylation reactions as catalyzed by bacterial toxins, phages, and cellular enzymes. Also, possible functions of this pluripotent protein modification are analyzed. [The *SCI*® indicates that this paper has been cited in over 285 publications.]

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November 2, 1987

At the beginning of my research career in the 1950s, I was confronted with Fritz Lipmann's concept[1] of energy-rich bonds and group transfer reactions. My thesis work, under the supervision of Feodor Lynen, dealt with the activation of acetic acid to form acetyl coenzyme A, the first compound with an energy-rich bond not involving phosphate groups.[2] Good contacts had developed between the Munich laboratory and Lipmann's group, then located at the Massachusetts General Hospital in Boston. When I finished my dissertation, Lipmann offered me a postdoctoral position. It was a unique invitation in those days, when the war and the cruelties of the Nazi regime were still in vivid memory: a young German was asked by a Jewish emigrant to join his group in the US.

My work in the stimulating atmosphere of the Boston laboratory was, of course, devoted to group activation, and it resulted in the description of active sulfate as an acid anhydride formed by replacement of the pyrophosphate residue in ATP.[3] Thus primed with the omnipresence and general importance of activated groups in biochemical processes, it seemed only natural that my interest turned to nicotinamide adenine dinucleotide (NAD) as a form of activated ADP-ribose.

Use of this pyridine nucleotide as a substrate of ADP-ribosyl transferases represents a fascinating example of nature's variation on a theme: the basic reaction can be used to attach monomeric and polymeric ADP-ribosyl residues to various proteins in different cellular compartments, leading to the modulation of such divergent processes as DNA repair and adenylate cyclase activation. The nuclear system in particular, with its dependence on DNA fragmentation and a milieu of other factors, gave rise to many seemingly unrelated and often contradictory reports.

When approached by Helmut Holzer and Lynen to write a critical review in this controversial area, Peter Stone, a postdoctoral fellow from England, and I used the opportunity to clear our own minds and to offer newcomers to the field guidance through the labyrinths of experimental details and individual interpretations.

The persisting popularity of our paper certainly flatters me, and I relate this to a clear presentation of the basic findings, critical evaluation of the experimental data, and the expression of a strong opinion as to the impact of published data. However, the continuous accumulation of citations might well indicate that references are often cited a considerable number of times just by "tradition." Our paper was published when interest in ADP-ribosylation entered a phase of rapid expansion, and involvement of this reaction in various basic chromatin functions appeared to be likely.

Today, the detection of novel ADP-ribosylation reactions in eukaryotic and prokaryotic organisms continues,[4] which demonstrates the universal significance of the modification for processes ranging from carcinogenesis to differentiation and from transmembrane signaling to bacterial nitrogen fixation. Thus, a better understanding of ADP-ribosylation certainly will improve our knowledge of chromatin functions, metabolic regulations, and transmission of external signals.

Although engaged for years with this type of covalent modification of proteins, the early imprint of group activation as a basic biochemical phenomenon kept me open to other ways in which pyridine nucleotides could serve as group transferring coenzymes. This awareness led us recently to establish phospho-adenylylation as a novel type of NADP-derived protein modification.[5]

1. **Lipmann F.** Metabolic generation and utilization of phosphate bond energy. *Advan. Enzymol.* 1:99-162, 1941. (Cited 290 times since 1955.)
2. **Lynen F & Reichert E.** Zur chemischen Struktur der "aktivierten Essigsäure" (The chemical structure of "activated acetic acid"). *Z. Angew. Chemie* 63:47-8, 1951. (Cited 60 times since 1955.)
3. **Hilz H & Lipmann F.** The enzymatic activation of sulfate. *Proc. Nat. Acad. Sci. USA* 41:880-90, 1955. (Cited 100 times.)
4. **Althaus F, Hilz H & Shall S.** *ADP-ribosylation of proteins.* Berlin: Springer-Verlag, 1985. 585 p.
5. **Hilz H, Fanick W & Klapproth K.** 2'-phosphoadenylylation of eukaryotic proteins: a type of covalent modification. *Proc. Nat. Acad. Sci. USA* 83:6267-71, 1986.

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