CC/NUMBER 32
AUGUST 12, 1985

This Week's Citation Classic®

Novikoff A B & Goldfischer S. Nucleosidediphosphatase activity in the Golgi apparatus and its usefulness for cytological studies.
Proc. Nat. Acad. Sci. US 47:802-10, 1961.
[Department of Pathology, Albert Einstein College of Medicine, Bronx, NY]

The Golgi apparatus was visualized in animal and plant cells by an enzyme cytochemical procedure free of the artifacts associated with the metallic methods of Camillo Golgi. This was the first cytochemical demonstration of the Golgi apparatus, an organelle that has received much attention from cell biologists. (The *SCI*® indicates that this paper has been cited in over 695 publications since 1961.)

Alex B. Novikoff
Department of Pathology
Albert Einstein College of Medicine
Yeshiva University
Bronx, NY 10461

July 23, 1985

My first papers in histochemistry were published while I was at the University of Vermont where I was doing research in biochemistry. Three publications demonstrated that the staining of nuclei and salivary chromosome bands (after the Gomori-Takamatsu procedure) was an artifact.[1-3]

I studied the effects of different fixatives and metallic ions upon cytoplasmic particles isolated from rat liver homogenates and in tissue sections, publishing the results in 1953.[4] Most biochemists at the time were of the opinion that enzymes could not be demonstrated cytochemically. But in fact, as we and others showed, the activities could be shown *in situ*, in tissues.

In 1955, when I came to the Albert Einstein College of Medicine, I vigorously pursued this histochemical and cytochemical work. I was encouraged to do so by Alfred A. Angrist, the first chairman of the Department of Pathology. The enthusiasm and abilities of my assistants, Phyllis Iaciofano and Barbro Runling, were invaluable to my research.

In 1958, Sidney Goldfischer joined me as a research assistant. To localize "nucleoside diphosphatase" in the cerebellum (the organ used by Golgi with his classic metallic method[5]), we incubated sections for 3-18 hours, as opposed to the 60-90 minutes that we were using for liver and kidney. We saw that a reaction product was deposited in a pattern suggesting the "Golgi apparatus." I was not sure whether the stained structures were extracellular or intracellular, and I telephoned Sanford Palay, at Harvard, for advice. He said he knew of nothing outside the cell resembling what I described. I thought to myself, "If it is within the cell, it must be the Golgi apparatus!" In a wide variety of tissues, the enzyme cytochemical results were identical to those revealed by the capricious metal impregnation procedures. The ensuing paper was communicated to the *Proceedings of the National Academy of Sciences* by Severo Ochoa.

Our tests using other diphosphatase substrates in tissues with characteristic Golgi apparatus made it clear that there was a specific diphosphatase (hydrolyzing UDP, IDP, GDP, and TPP) in the Golgi apparatus. These observations helped establish the very existence of the Golgi apparatus; its reality was the subject of prolonged, often sharp controversy.[6-8] Not only was the enzyme cytochemical method reproducible, it also provided the first information about the enzymatic properties of this ubiquitous and complex organelle. Combined staining for lysosomal acid phosphatase (β-glycerophosphate or cytidine monophosphate as substrate) and Golgi nucleoside diphosphatase demonstrated a topographical and, presumably, a functional association between the Golgi apparatus and lysosomes.

Subsequent studies revealed that lysosomes probably originated from a region of smooth endoplasmic reticulum situated at the *trans* aspect of the Golgi apparatus. This region I termed GERL.[9] The role of GERL in processing lysosomal enzymes is currently under investigation in my laboratory.

We utilized nucleoside diphosphatase to distinguish the *trans* aspect of the Golgi apparatus (Daniel Friend made me aware of this distinction[10]) and the endoplasmic reticulum in some cells; NADH-tetrazolium reductase to visualize the mitochondria; catalase to localize the peroxisomes and microperoxisomes; and acid phosphatase to reveal the lysosomes and GERL.[11,12] We are currently using immunocytochemistry to visualize other enzymes in the Golgi apparatus and in lysosomes.

The development of the GERL concept evolved slowly from the earlier studies on the Golgi apparatus. We view this organelle as part of a unique cellular processing system.

1. **Pearson B, Novikoff A B & Morrione T G.** The histochemical localization of alkaline phosphatase during carcinogenesis in rats fed *p*-dimethylaminoazobenzene. *Cancer Res.* 10:557-64, 1950.
2. **Novikoff A B.** Histochemical demonstration of nuclear enzymes. *Exp. Cell Res.* (Suppl. 2):123-43, 1952.
3. **Novikoff A B, Korson L & Spater H W.** Alkaline phosphatase activity in the Golgi substance of intestinal mucosa. *Exp. Cell Res.* 3:617-18, 1952.
4. **Novikoff A B, Podber E, Ryan J & Noe E.** Biochemical heterogeneity of the cytoplasmic particles isolated from rat liver homogenate. *J. Histochem. Cytochem.* 1:27-46, 1953. (Cited 165 times since 1955.)
5. **Golgi C.** Sur la structure des cellules nerveuses. *Arch. Ital. Biol.* 30:60-71, 1898. (Cited 60 times since 1955.)
6. **Gatenby J B, Moussa T A A & Dosekun F.** The cytoplasmic inclusions of the fixed spinal cord cells of the kitten with the Zernicke microscope and Sudan dyes. *Cellule* 53:13-32, 1949.
7. **Baker J R.** New developments in the Golgi controversy. *J. Roy. Microsc. Soc.* 82:145-57, 1963.
8. **Palade G E & Claude A.** The nature of the Golgi apparatus. I. Parallelism between intercellular myelin figures and Golgi apparatus in somatic cells. *J. Morphology* 85:35-112, 1949.
9. **Novikoff A B.** GERL, its form and function in neurons of rat spinal ganglia. *Biol. Bull.* 127:358, 1964. (Cited 125 times.)
10. **Cheetham R D, Morré D J, Pannek C & Friend D S.** Isolation of a Golgi apparatus-rich fraction from rat liver. IV. Thiamine pyrophosphatase *J. Cell Biol.* 49:899-905, 1971. (Cited 60 times.)
11. **Novikoff A B.** The endoplasmic reticulum: a cytochemist's view (a review). *Proc. Nat. Acad. Sci. US* 73:2781-7, 1976. (Cited 315 times.)
12. **Novikoff A B & Novikoff P M.** Cytochemical contributions to differentiating GERL from the Golgi apparatus. *Histochemical J.* 9:525-51, 1977. (Cited 175 times.)