RETROSPECTIVE

Martin Rodbell (1925–1998)

Lutz Birnbaumer

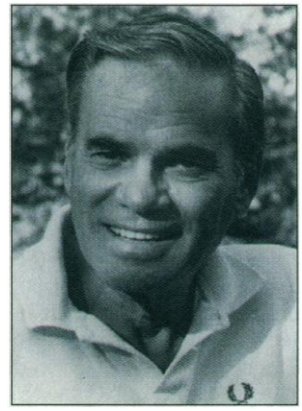
Marty Rodbell, founder of the field of signal transduction and a Nobel laureate, left this world on 7 December 1998. He was 73.

Signal transduction is now a household word in cell biology, but conceptually it did not exist in 1967 when I began working as a postdoctoral fellow for Marty at the National Institutes of Health (NIH). Borrowing from molecular linguistics and electrical engineering, Marty was the first to use the word "transducer" to describe how the binding of a hormone to its receptor is translated (transduced) into enhanced adenylyl cyclase activity. He postulated that hormone activity at the plasma membrane involved a vectorial transfer of information in which the hormone bound to a discriminator (receptor) that in turn interacted with a transducer responsible for modulating the activity of the amplifier—the enzyme adenylyl cyclase, which catalyzes the conversion of ATP to cyclic AMP. In Marty's model one binding event became "transduced" into many molecules of cyclic AMP.

Marty, who lived by the motto "models are meant to be disproven", initially thought that membrane lipids were responsible for signal transduction. This notion was based on his earlier finding that treatment of fat cells with phospholipase mimicked the action of insulin: stimulating glucose and amino acid uptake, and lipid synthesis, and counteracting lipolysis induced by agents that elevated cyclic AMP. Marty proposed that insulin exerted its antilipolytic and cyclic AMP inhibitory action by blocking adenylyl cyclase.

A close second to his passion for science was Marty's addiction to travel. Four months after I arrived in his laboratory, he left for a sabbatical in Geneva at the Institute de Biochemie Clinique. During Marty's sojourn, I had his 300 square foot-laboratory to myself and tested the effects of insulin on adenylyl cyclase. I, of course, failed to demonstrate an in vitro inhibition of adipose cell adenylyl cyclase, because insulin stimulates cyclic AMP degradation, rather than inhibiting its production. I wrote long reports about my experiments and Marty replied in kind with thoughts and suggestions. My letters were handwritten, Marty's were neatly typed. In World War II he had been in radio communications, typing out Morse code relayed to him through earphones. Little did he know then the importance that signal transduction would play in his life!

When Marty returned in September 1968, his laboratory expanded, first with the arrival of Stephen Pohl and then Michiel Krans. We published papers demonstrating that receptors and adenylyl cyclase were separate molecules, and that hormones regulated the fat cell adenylyl cyclase system by reducing the concentration of magnesium ions required to drive the activation process. With Steve, we studied the properties of the glucagon-sensitive adenylyl cyclase in liver membranes. Michiel and Marty began to iodinate glucagon and developed a receptor binding assay in which ^{125}I-labeled glucagon specifically bound to liver membranes with a high affinity for a finite number of (receptor) sites. Steve and I continued studying the properties of the cyclase system. Marty was in and out of the laboratory but was very much in town when the effect of GTP on glucagon binding showed up. GTP (a contaminant of ATP) was accidentally added to the adenylyl cyclase assay and increased the on- and off ligand binding rates resulting in a decreased affinity of the receptor for glucagon. When we cleaned up our reagents and used synthetic GTP-free AMP-P(NH)P as substrate instead of "dirty" ATP, we discovered that the hormone could not act unless we also added GTP.



The transducer became the wheel between discriminator and amplifier, impulsed by GTP. But how were lipids and magnesium involved, and why GTP? Marty came up with new models on a daily basis. We felt relieved when he left town: it gave us time to test the models. On one occasion, upon his return from a lavish meeting in Capri, he asked rhetorically whether we did not mind his traveling so much. We, of course, did not mind at all, because it allowed us to do bench work and to generate data that would be the basis for the next slew of models.

For all of us, these were golden years. Encumbered only by our lack of understanding of the GTP effect, we were spurred on by Marty's restless imagination. It became clear that what we saw with the glucagon-sensitive cyclase also occurred with other cyclases stimulated by different hormones. Then, Marty conceptually turned the system around. He realized that the hormone did not require GTP to activate adenylyl cyclase but rather that GTP required the hormone (or, more precisely, its receptor) to activate adenylyl cyclase.

With this, the groundwork was laid for the description of the G protein signal transduction machinery. In another seminal paper, he described the persistent superstimulation of adenylyl cyclase by the non-hydrolyzable GTP analog, GMP-P(NH)P. Ever intuitive, he postulated that GTP was a less effective stimulator of adenylyl cyclase because the cyclase system itself was hydrolyzing its activator, a prediction that was proven true shortly thereafter. Receptors were now viewed as nucleotide exchange factors. He proposed the existence of multiple nucleotide regulatory components, which he called N (now G) proteins, that independently mediated stimulation and inhibition.

In 1984, Marty became Director for Intramural Research at the NIH, a post that he held until 1989. Although now an administrator, his heart remained with models and hypotheses. His seminal contributions to the field of signal transduction earned him many prizes including the Nobel Prize for Physiology or Medicine in 1994.

From 1980 until his death, Marty concentrated on elucidating the molecular architecture of signal-transducing complexes. His interest was piqued when analysis of the target size of a resting hormone-responsive adenylyl cyclase system turned out to be far greater than expected. He thus began to investigate the importance of the cytoskeletal scaffold in cells earlier than most. Just as the role of GTP in hormonal stimulation was initially received with skepticism, the idea of supramolecular cellular architecture as an important, if not essential element in signal transduction was also received with caution, if not disbelief.

Martin Rodbell will be remembered for the *mensch* he was, for his seminal contributions and for his models. Without him the concept of signal transduction would have been born many years later.

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