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A tribute to Dr. Setsuro Ebashi

The area of calcium in muscle contraction has had an unusual historical development. That calcium was essential for heart muscle contraction was serendipitously discovered by S. Ringer at the end of the 19th century. Surprisingly, that momentous discovery, which showed that calcium had a role that was totally distinct from its long-known structural function in the bones, remained essentially ignored for decades. It was only in the 1940s that a handful of scattered observations confirmed the unexpected signaling role of calcium. Setsuro Ebashi came into the scene in the 1950s, and in a few years changed it. When he started working in the area, the sliding filament model of muscle contraction had already been proposed by J. Hanson and H. Huxley, but the triggering of the sliding process was unknown. Although there were hints of a possible role of calcium, the first one of course being the observation by Ringer, no credible results had been produced, owing to the routine contamination of reagents with low levels of calcium. It was Ebashi who showed that, in the presence of ATP, the addition of minute amounts of calcium to an actin–myosin system from which he had painstakingly eliminated all traces of calcium elicited contraction. The observation was simultaneous with the finding by A. Weber that the hydrolysis of ATP by actomyosin required calcium, and complemented it beautifully. Naturally, because contraction is followed by relaxation, the role of calcium had to be reversible; i.e., calcium had to be somehow eliminated from the system to induce relaxation. In the 1950s, a fraction from muscle homogenates—Marsh's relaxing factor—had been shown to induce the relaxation of actin–myosin systems. In collaboration with F. Lipman, Ebashi showed that the relaxing factor was constituted by vesicles of the newly discovered sarcoplasmic reticulum. The vesicles accumulated calcium in the presence of ATP, removing it from the system. This fundamental observation, together with similar observa-

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tions made independently at about the same time by W. Hasselbach and M. Makinose, established that a calcium-activated ATPase—today we would say a calcium pump—was at work as the main actor in the muscle relaxation process.

At this point in time, the role of calcium in the muscle contraction–relaxation process had thus become well established. What was still mysterious was the molecular mechanism by which calcium induced the contraction of the actomyosin filaments. Another landmark contribution by Ebashi clarified it in the 1960s: he had noticed that the regulatory action of calcium on the ATPase activity of actomyosin required a protein factor. A mixture of tropomyosin and a novel protein, which he proceeded to isolate and characterize, constituted this factor. He named the new protein troponin and showed that it was the calcium receptor in the myofibril. The discovery of troponin and of its calcium binding and modulating properties, as well as the discovery of the active uptake of calcium by sarcoplasmic reticulum, in effect initiated the phenomenal development of the calcium signaling area, to which Ebashi contributed very significantly up to the last days.

We now know that calcium controls not only the relaxation/contraction cycle of muscle but also scores of other essential cell functions, from fertilization, to gene expression, to secretion, including that of neurotransmitters, to the phosphorylation and dephosphorylation of proteins. All of us working in the calcium field, *particularly as related to muscle*, unanimously recognize Ebashi as the pioneer who has shaped it into the present all encompassing area.

This Memorial Issue collects contributions by colleagues who had known Ebashi since the old days and/or had been pupils. It also contains contributions from numerous colleagues active in Ebashi's areas of work, who felt this to be an appropriate way to honor his memory. Finally, it reprints three old original contributions of Ebashi: they are perhaps his most important. The Editors of the Issue wish to express their thanks to Prof. Iwao Ohtsuki for his invaluable help.

Ernesto Carafoli *
Claude B. Klee
Universitá degli Studi di Padova,
Dipartimento di Chimica Biologica,
Viale Giuseppe Colombo, 3 I-35121 Padova, Italy
E-mail address: ernesto.carafoli@unipd.it
(E. Carafoli)

* Corresponding author. Fax: +39 049 827 6125.