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Review

Key events in the history of calcium regulation of striated muscle

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I am happy to be a participant in this celebration of Setsuro Ebashi's life as a leader in research on muscle contraction. I first met Setsuro 50 years ago in October at a meeting organized by Professor Kumagai, the then Chief of the Department of Pharmacology, School of Medicine, University of Tokyo, and then Assistant Professor Ebashi at the International House in Tokyo. The 1957 meeting led to many friendships, scientific interactions and visits between Japanese scientists and the West. Koscak Maruyama, whom I met at that meeting, became the first Japanese visiting fellow in my laboratory. The work that my colleagues and I have carried out in Boston has been very much influenced by the discoveries of Dr. Ebashi and his colleagues. On a personal note, I greatly enjoyed Setsuro's gracious hospitality on my many visits to Japan.

The work of B.B. Marsh and J.R. Bendall had shown [1–3] that a fraction of a homogenized muscle, to become known as the relaxing factor was able to reverse contraction of myofibrils or their ATPase activity, the relaxation being reversible by Ca^{2+}. This was followed by numerous papers suggesting that this relaxing factor was identical with some known enzymes in muscle, such as creatine kinase or myokinase. Ebashi became known to those in the field of muscle research in 1955 when a paper by Kumagai, Ebashi and Takeda, the latter to become Mrs. Ebashi, on the true nature of the relaxing factor appeared in Nature [4]. The Kumagai/Ebashi paper showed that the relaxing factor appeared to be identical with an ATPase previously reported by Kielley and Meyerhof [5,6]. Ebashi with his colleagues [7], as well as Annemarie Weber [8], using known Ca^{2+} and Mg^{2+} binding constants of the chelating agent EGTA and ATP, respectively, firmly established Ca^{2+} as a regulator of the ATPase activity. In 1959 Ebashi joined Fritz Lipmann at the Rockefeller Institute for a year or so. They established that the ATPase in the particulate fraction of the relaxing factor acts as a pump to accumulate Ca^{2+} ions inside lipid vesicles [9–10]. Independently Hasselbach and Makinose also discovered this ATP-dependent Ca^{2+} pump [11].

An important event in our story was the Ebashi group's discovery of a component of muscle first named native tropomyosin, which eventually became known as troponin and recognized as a Ca^{2+} binding protein [12]. Originally troponin was considered as a single entity but it soon became clear that there were several components, at least one carrying Ca^{2+} binding sites and the other being responsible for the inhibitory effect on contraction and ATPase activity. A notable finding was that troponin is bound to thin filaments of muscle at regular intervals [13]. In the late 1960s, owing to possible impurities or proteolytic breakdown, the number of components in troponin was somewhat uncertain, but at a conference held in 1972 at the Cold Spring Harbor Laboratory on Long Island it became generally accepted that troponin was a complex of three subunits known as TnI, TnC, and TnT, responsible for actomyosin ATPase inhibition, Ca^{2+} binding, and tropomyosin binding, respectively [14].

In the period through the mid eighties the chemistry of the troponin components, their interaction with each other, with actin and with tropomyosin has been explored by a number of investigators utilizing biochemical and biophysical techniques including the determination of the amino acid sequence of the proteins involved. Studies using fish proteins led to the identification of the Ca^{2+} binding sites in the primary structure and led to the first X-ray crystal structure of the Ca^{2+} binding protein, parvalbumin, This protein, roughly half the size of TnC, provided some clues to the structure of TnC [15–17]. For reviews of this period see [18,19].

The full atomic level structure of troponin C was revealed by the work of two groups independently publishing a two lobe structure of troponin C, the two lobes

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being connected by an alpha helix [20,21]. James and his colleagues [22] proposed a model in which the activation of the actomyosin system and initiation of contraction would be the result of the opening of the N-terminal lobe by Ca^{2+}. They further proposed that the open site binds TnI, thus removing the inhibitory region from actin. Shortly thereafter experimental evidence supporting this model was produced [23,24]. The following years saw the exploration of structural changes within TnC and the effect on interactions among the various components utilizing X-ray, NMR, fluorescence and optical rotation techniques. The studies in various laboratories were further helped by the use of genetically engineered mutants permitting the placement of so-called donor and acceptor molecules in order to apply Forster's resonance energy transfer (FRET) method, making it possible to determine intra- or intermolecular distances (for additional reviews [25–29]).

Maeda and his colleagues [30] carried us significantly forward in the field opened up by Ebashi. They reported a crystal structure of the TnC complex with a fragment of TnI shortly to be followed by the solution of the structure of a complex including a larger fragment of TnI and a fragment of TnT [31]. Work from other laboratories [32–34] further expanded our knowledge in these areas, and no doubt the collection of papers in this issue will bring us to the most recent developments.

Ebashi's work has opened a whole new field of research. It brought new knowledge, not only in what is known as basic science, but has laid the foundations for studies of pathophysiology of troponin and other components of the muscle machinery, which are well represented in this memorial issue. Ebashi's memory will be with us for a long time.

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