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Commentary

Dysfunction of microtubules induces cardiac dysfunction

Masafumi Kitakaze

Department of Clinical Medicine and Development, National Cerebral and Cardiovascular Centre, 5-7-1 Fujishirodai, Suita 565-8565, Japan

Microtubules, the highly dynamic polar filaments composed of α/β-tubulin dimers, play an essential role in cell survival and function by providing dynamic instability and reflecting the active polymerisation and depolymerisation indicative of microtubule growth and shortening [1]. Microtubules also target focal adhesions to regulate the cell to extracellular matrix adhesion, and the attachment of microtubules to special cortical regions of the cells is essential for cell polarisation [2]. Therefore, the growth, catastrophe, shortening, and rescue, which are the components of dynamic microtubule instability, induce cellular homeostasis, division, and movement. Moreover, inside the cells, microtubules contribute to the movement of intracellular organelles, such as mitochondria, using the motor proteins. Therefore, from the perspective of cell survival, microtubules exclude the unfavourable stimuli from the cells and propel the cells to more favourable stimuli as well as adjust each of the intracellular organelles to appropriate forms and positions to ensure cell survival.

These concepts can be extended to cardiomyocyte survival, thereby suggesting that microtubule dysfunction causes cardiac dysfunction. Indeed, many researchers have investigated the role of microtubule dysfunction in cardiac hypertrophy/heart failure [3,4], myocardial ischaemia–reperfusion injury [5], and catecholamine-induced myocardial injury [6]. However, these investigations have only provided the phenomenological insight into the role of microtubules in cardiovascular injury; the molecular perspective regarding its role has not been investigated. In this regard, the most pertinent questions are regarding the mechanisms underlying microtubule impairment and whether this impairment causes cardiovascular dysfunction.

In a study in *EBioMedicine* [7], the authors have attempted to address these fundamental questions by focusing on microtubule associated proteins (MAPs). Though microtubule instability is regulated by MAPs and GTP-tubulin, the authors have focused specifically on the role of MAP4. MAP4 promotes the microtubule assembly and has been shown to counteract the destabilisation of interphase microtubule catastrophe promotion. Interestingly and importantly, the authors suggested an interaction between MAP4 phosphorylation and cardiac apoptosis in hypertrophic right ventricular tissues in patients with hypoxemia having tetralogy of Fallot. Therefore, the authors extended their idea that MAP4 phosphorylation is related to cardiac disease aetiologies, such as cardiac hypertrophy, hypoxia/reoxygenation injury, and catecholamine-induced myocardial injury. The authors further examined this by developing murine models that carried mutations of MAP4 (S667A, S737E, and S760E) to simulate the aberrant MAP4 phosphorylation and assessing these mice for age-dependent cardiac phenotypes including hypertrophy, fibrosis, remodelling, and dysfunction. The development of cardiomyocyte apoptosis along with the microtubule disassembly and mitochondrial translocation of phosphorylated MAP4 prior to the onset of hypertrophy, fibrosis, and remodelling was observed in these transgenic mice. Moreover, it was revealed that p38/MAPK was possibly the key signalling molecule that mediated myocardial apoptosis and *in vivo* hypertrophy through MAP4 phosphorylation and enhanced extracellular matrix production by isoproterenol-stimulated fibroblasts *in vitro*. The authors concluded that MAP4 is related to pathological cardiac hypertrophy and remodelling through its phosphorylation.

The fascinating aspect of this investigation is the direct clinical utility of the findings. Specifically, the present hypothesis is not only generated from the *in vitro biological* observations but also *via* clinical observations, which makes the MAP4 observations clinically relevant. This direct bench-to-bedside utility of these findings would likely not have occurred if observations were based on *in vitro* experiments alone. This interaction among clinical practice, basic research, and clinical medicine is crucial in understanding the biological findings from the clinical point of view termed 'Back-and-Forth Loop between Clinical Data and Basic Research' [8,9]. The verity and accuracy of a concept in the clinical settings would largely contribute to the innovation of new drugs for cardiac hypertrophy/heart failure or myocardial ischaemia–reperfusion injury. However, before the authors translate these findings to the clinical field, they should clarify several crucial biological issues including the mechanism underlying MAP4 phosphorylation in cardiomyocytes. Although we understand that under several stressed circumstances, MAP phosphorylation is important to determine the severity of cardiac injury and the authors suggested P38MAP kinase as a candidate kinase, a definite answer is not provided in the present study. We had a chance to show that CLIP170, one of the most popular plus-end tracking protein of microtubules, is phosphorylated by AMPK [10], and this was tested in GFP and *in vivo* monitoring of CLIP170. Such a strategy would have been relevant to the investigation of MAP4 phosphorylation. Another issue pertains to determining the mechanism by which MAP4 phosphorylation followed by microtubule dysfunction affects the severity of the myocardial injury in several stressed circumstances. Addressing these unanswered questions would increase the quality of the present novel findings and add to the translational utility of this investigation.

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E-mail address: kitakaze@zf6.so-net.ne.jp.

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Finally, we are fortunate and happy to learn the importance of MAP4 phosphorylation in cardiovascular diseases from Li and colleagues in *EBioMedicine*.

Disclosure

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