Proliferating cardiac microtubules

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Identifying the mechanisms underlying the transition from adaptive cardiac hypertrophy to maladaptive cardiac failure has long been a central goal of basic and clinical cardiovascular science. Such studies at the level of the cardiocyte have focused largely on the cardiac motor, i.e., the myofilament, as well as the fuel for that motor, i.e., the mitochondrion, and the governor of its activity, i.e., the sarcoplasmic reticulum. Although multiple abnormalities of each of these components have been identified, especially after the transition to heart failure, it has been much less clear that changes in these systems fully account for the earliest, and thus etiologically most important, deterioration of contractile function that prevents the increase in mass of hypertrophied myocardium from compensating indefinitely for increasing loads.

Because the myofilaments function not only within a biochemical setting outlined above but also within a physical setting defined by the extramyofilament cytoskeleton, this latter factor began to attract attention in the 1980s (22). Since cardiocyte ultrastructure during physiological hypertrophy differs very little, if at all, from that during pathological hypertrophy prior to the onset of cardiac failure (19) and since the microtubule component of the extramyofilament cytoskeleton closely invests the myofilaments but is very difficult to discern in striated muscle via standard light or electron microscopy, my colleagues and I decided in 1992 to see if there was a previously unrecognized difference in the microtubule network during an equivalent degree and duration of physiological vs. pathological hypertrophy. Such turned out to be the case, in that we found that pathological pressure overloading, but not physiological volume overloading, produced a dense microtubule network that imposed a viscous load on the shortening sarcomere to cause contractile dysfunction that was reversible on microtubule depolymerization (29, 31, 32). In the years since then, as reviewed elsewhere (9), we have extended this observation to both cardiac ventricles in multiple species at the levels of sarcomere, cell, and tissue in vitro and to the intact heart, including that of humans, in vivo. Apart from these studies of cardiocyte and cardiac mechanics, we found that the increase in microtubule network density and stability is associated with upregulation of α- and β-tubulin (21, 28) and MAP4 (23), a fibrous microtubule-associated protein that stabilizes microtubules. Furthermore, transgenic or hypertrophic MAP4 upregulation itself was shown to cause microtubule network densification and associated abnormalities of contractile function and kinesin-based microtubule transport function (6, 9, 25), and microtubule stabilization via expression of a mutant β-tubulin in the hearts of otherwise normal transgenic mice reproduced the cardiac hypertrophic microtubule phenotype (7).

It is, however, important to point out that not all investigators who have looked for this cytoskeletal alteration in experimental models of pressure-overload cardiac hypertrophy have replicated these findings (2). Although, as reviewed in detail elsewhere (9), there are many factors that might be responsible for this variation, a mechanism-based explanation may now be available. That is, since microtubule network densification in our hands is neither species nor chamber specific, an underlying and unifying reason for interlaboratory variation may well be that, as we have shown (see Fig. 8 and related discussion in Ref. 25), this cytoskeletal change does not happen with modest pressure-overload hypertrophy but, instead, only happens with very substantial pressure overloading leading to increased wall stress and an approximate doubling of ventricular mass. Nonetheless, despite the variable early results, there are now a number of other investigators who have confirmed the basic finding of increased tubulin and microtubules in animal models of clinical heart disease and in clinical heart disease itself (1, 3–5, 10, 11, 13–18, 26, 28, 30, 33, 34), with an extraordinary increase in microtubule protein seen after chronic severe pressure overloading (18).

Our own work has focused tightly on microtubule derangements that selectively affect cardiac growth and function during pathological, high-wall-stress pressure-overload hypertrophy. An especially important example of the broadening, or “proliferation,” of the pathophysiologic setting of this cytoskeletal abnormality has been provided by the work from Jutta Schaper’s laboratory (14, 24) on advanced clinical cardiac disease. For instance, in the hearts of patients with dilated cardiomyopathy, several cytoskeletal proteins, including tubulin, desmin, and vinculin, are found to be upregulated, whereas the myofilament proteins are found to be downregulated. Indeed, in their hands, such cytoskeletal changes are characteristic of end-stage clinical cardiac disease.

In this issue of the American Journal of Physiology: Heart and Circulatory Physiology, Fassett et al. (12) provide at least one new way to begin to understand the selective presence of microtubule network densification in various forms of maladaptive, decompensated cardiac hypertrophy and failure and its absence from physiological, compensated cardiac hypertrophy. Thus they report that adenosine not only prevents the microtubule accumulation that otherwise occurs in isolated cardiocytes in response to specific hypertrophic stimuli, but a lack of extracellular adenosine production induced genetically was found to amplify the degree of microtubule accumulation seen in response to cardiac pressure overloading. These data are especially interesting in the context of the current understanding of myocardial production of the antiadrenergic agent adenosine, where it is increased in compensated cardiac hypertrophy but returns to normal or is decreased in decompensated cardiac hypertrophy (see Fig. 1 in Ref. 20). Thus, Fassett et al. provide important new hints about the upstream signaling events that may be responsible for increased myocardial mi-
crotubules and the potential proliferation of this cytoskeletal abnormality into other settings such as those studied by Schaper’s group (14, 24), wherein persistent myocardial adrenergic activation is quite commonly present.

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REFERENCES


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