mRNA cargo no longer on time

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HEART FAILURE is the most important cause of death in the Western world, and numerous attempts have been undertaken to identify the origin of this disease. Cohn et al. (1) in 2000 defined cardiac remodeling leading to heart failure as “genome expression resulting in molecular, cellular and interstitial changes and manifested clinically as changes in size, shape and function of the heart resulting from cardiac load or injury.” This definition is especially valid for the situation of compensatory hypertrophy after myocardial infarction, in chronic arterial hypertension, aortic valve stenosis, as well as primary and secondary cardiomyopathies. The clarification of the molecular and cellular mechanisms contributing to and finally causing heart failure, however, is still incomplete. In all these cardiac pathological conditions, hypertrophy of different degrees of the cardiomyocyte is the first response to hemodynamic overloading. This is an adaptive process allowing the maintenance of cardiac pump performance at a level necessary and present before overloading.

At the cardiomyocyte level numerous phenomena, such as reduction of the number and responsiveness of β-receptors (11), alterations of Ca sensitivity (15), as well as structural deterioration (14) and other alterations of cardiomyocytes, have been described as part of the cellular mechanisms leading to cardiac failure. Furthermore, several years ago the increased occurrence of oncotic, apoptotic, or autophagic cell death was found to correlate well with the occurrence of cardiac failure (10).

Additionally, changes occur also at the stromal side of the myocardium, because there is an increase in extracellular matrix proteins leading to cardiac fibrosis, resulting in reduced capillary density with disturbed nutrition and alterations in pulse propagation and repolarization.

All of the above-mentioned factors were defined as contributors (acting solely or in concert) to the functional deterioration of diseased hearts, but the question of why the hypertrophic response to hemodynamic overloading shows such a great heterogeneity as stated by Cooper’s group for animals and patients remained unanswered.

This question, however, has been raised in the publication by Scholz et al. (16) in the American Journal of Physiology-Heart and Circulatory Physiology. Here there was an attempt to gain insight into the causes of hypertrophic growth cessation that occurs well before the biological limits of cardiocyte hypertrophy have been reached (3, 6). This work is based on the recent experimental observation by Cooper’s group (17) that during the progression of pressure overload in canine hearts the dogs broke into two groups: one group developed extensive hypertrophy while retaining normal left ventricle (LV) stress and contractile function; the LVs of the second group initially developed hypertrophy but then stopped growing and developed high LV wall stress and very depressed contractile function. On histological examination, differences in the density of the microtubular network were discovered, and it was hypothesized that this might represent an important cellular mechanism involved in growth inhibition. To clarify this point the present study was undertaken. The hypothesis was tested that overdecoration of microtubules (MTs) with microtubule-associated protein 4 (MAP4) may inhibit the transport of mRNA via messenger ribonucleoprotein particles (mRNPs) from the nucleus to the cell periphery, thereby decreasing the translational process at the ribosomal level and inhibiting protein synthesis. This epitomizes a new approach to the identification of the cause of heart failure because even though a densification of MTs in failing myocardium has been described previously (5, 19) the functional significance of this cellular alteration had not been resolved.

The study was carried out in cardiomyocytes from normal and hypertrophied right ventricular cat myocardium. These were isolated and kept under cell culture conditions. The microtubular network was beautifully identified by immunofluorescence techniques, and the previously made observation of MT densification in hypertrophied cardiomyocytes was confirmed. In myocytes, the representation and study of the MT network is especially difficult because of visual interference with densely packed sarcromeric material, and therefore descriptions of the exact localization of the MTs in the heart are scarce in the literature. It is important to know that these are tubules running in the direction of the longitudinal cell axis and that they concentrate around the nucleus as shown here and in work from other groups (9, 12). MTs are the major part of the longitudinal cytoskeleton, while the intermediate filament desmin is their transverse counterpart. Desmin filament surrounds the Z disk of each sarcomere, thereby connecting the contractile units and avoiding slippage of the myofibrils. While desmin is an important factor ensuring cellular stability, the MTs are involved in intracellular transport processes in terminally differentiated cells such as cardiomyocytes (9). In other cell types undergoing mitosis, spindle formation is their major task. There is a rapid turnover by polymerization and depolymerization of individual tubules that grow at the plus end and dissolve at their minus end (see textbooks on cell biology).

Because the extramyofilament cytoskeleton plays a decisive role in mRNP transport, as outlined in the discussion of the present paper, in a next step in this study the dependence of mRNP transport and distribution on the intactness of the MT network was investigated by confocal microscopy. When MTs were reversibly disturbed by the use of nocodazole or colchicine, no mRNP transport occurred. Accordingly, protein synthesis was significantly reduced (~40%) in the absence of an intact MT network.

Normally, MAP4 decorates and stabilizes the MTs (13), but in hypertrophied myocytes it occurs in elevated amounts and
“overdecorates” the MTs (16). Experimentally, the same phenomenon can be provoked in nonhypertrophied cardiomyocytes by adenoviral transfection, and in both situations of MAP4 overdecoration mRNP was significantly reduced. Furthermore, its centrifugal distribution was disturbed by MAP4 overdecoration: in the control cardiomyocytes a vortical long-range and progressive movement of mRNP was observed, whereas in the presence of MAP4 overdecoration the mRNP oscillated in place. These elegant studies were completed by measurements of velocity and distance of mRNPs showing on a quantitative level the impediment of movement of mRNP caused by MAP4 overdecoration. It was stated that “the net effect of MAP4 interference with microtubule-based motor protein transport resembles a viscous impediment to vectorial motion”. Finally, and as expected, slowing of the mRNA movement into the sites of structural protein synthesis in hypertrophied cardiomyocytes as opposed to normal cells was evident.

From this study it was concluded that the dense MAP4-decorated microtubular network may cause contractile dysfunction and prevent fully compensatory growth response to hemodynamic overloading. Thus the conclusion is twofold in stating that there may be a direct effect, i.e., a viscous impediment to contraction, as well as an arrest of protein synthesis limiting the hypertrophic response. It is concluded that microtubular densification may be the cause of “decompensated failure” characterized by elevated LV wall stress and systolic myocardial and chamber dysfunction. This was found in the “decompensated” group in the canine study (17) and in patients with aortic stenosis (19). The most important finding is the fact that compensatory hypertrophy stops in the presence of a dense, MAP4-decorated MT network, resulting in decompensation and heart failure.

This is an interesting statement, especially in view of the fact that a dense MT network was found by immunoblotting in a subset of human patients with aortic stenosis (19). This was confirmed by a study from our group showing an increase in tubulin protein and its mRNA in failing hearts from patients with dilated cardiomyopathy. In our work, however, in addition to tubulin other proteins such as desmin and vinculin were found to be augmented while the contractile proteins actin and myosin and the major component of the sarcomeric skeleton titin were significantly reduced (5, 14). This indicates that changes in the microtubular system certainly are important, especially for the rate of protein synthesis as shown in the paper under discussion, but that other molecular changes occur as well and may significantly influence the course of hypertrophy and heart failure. This certainly applies for proteins such as vinculin and desmin, but also for the sarcomembran protein dystrophin. The latter has shown irregularities in human cardiomyopathic hearts (18), and it might very well be that dystrophin and the different members of the dystrophin complex are affected in the pressure overload situation as well. It has been shown that microtubule stability is necessary for gap junction formation (7), and therefore the more specified regions of the sarcolemma, i.e., the intercalated disks, were investigated by our group in patients with aortic stenosis. It was evident that the quantity and spatial distribution of Cx43 differed markedly between compensated and decompensated LV hypertrophy. Uprogulation of Cx43 in compensated hypertrophy may represent the immediate adaptive response to increased load, whereas diminished and heterogeneous Cx43 distribution in decompensated hypertrophy may play maladaptive roles culminating in heart failure and ventricular arrhythmias (8).

In failing hearts, as seen in the electron microscope or with immunofluorescent confocal techniques, cardiomyocyte degeneration occurs, which means reduction of the contractile material, increased size of the nucleus, and disappearance of mitochondria. Autophagic vacuoles were evident, and that led us to determine the rate of cell death in the transition from well-compensated to decompensated hypertrophy with heart failure in patients with aortic stenosis (4). We found that the occurrence of oncosis (formerly called necrosis) and autophagic cell death was significantly higher whereas apoptosis played a minor role. A direct correlation was found between these myocyte changes and LV function, and it was therefore concluded that both degenerative changes and the rate of cell death significantly contribute to systolic heart failure (4).

Diastolic dysfunction also needs to be considered in the course of the transition to heart failure. We found that the increase in fibrosis correlated directly with the elevation of LV end-diastolic pressure and that it occurred before myocyte alterations and systolic dysfunction (4). Thus the transition from compensated hypertrophy to heart failure is a multifaceted process in which most of the components of the cardiac tissue, cellular and extracellular, are involved and must be investigated. This, however, constitutes a huge program requiring well-funded laboratories, ingenious researchers, suitable experimental models, and access to human tissue.

Animal models will help to elucidate the enigma of intracellular signaling cascades and to separate the very early adaptive and maladaptive changes that occur in LV hypertrophy due to chronic pressure overload. In the clinical setting, the way out of the dead-end street of maladaptation is not easy to manage and usually not only leaves some scratches at the finish but unfortunately often leads to severe or irreversible myocardial damage (2).

Reversible and irreversible cardiac remodeling is a highly complex process, and the publication by Scholz and colleagues (16) now clarifies the role of one particular molecular-cellular mechanism. Its great progress can be seen in the fact that one of the phenomena found to be typical in human failing hearts was taken beyond the descriptive phase and has been studied in detail and in depth.

In conclusion, the work by Cooper’s group presented here is an important example for future studies regarding the problem of transition from compensated hypertrophy to decompensation. Findings from in vitro studies and experimental work should be taken to the human situation, and their true importance for the situation of long-standing cardiac disease in human patients, in contrast to myocardial injury inflicted on normal healthy animal hearts, must be determined. Such intense efforts will finally lead to the knowledge of the cause of decompensatory hypertrophy and heart failure and will permit the development of drugs effective in the treatment of this life-threatening disease.

REFERENCES

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