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Editorial Comment

Adult Myocyte Hyperplasia: Divided They Fail?*

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The mitotic activity of myocytes consistent with cell proliferation, or hyperplasia, generally occurs only in the embryonic or early postnatal periods (1,2). Thereafter, despite the absence of mitotic cell division, the weight of the heart increases by greater than tenfold with normal growth (3). This augmentation of cardiac weight is associated with an increase in the size but not in the number of myocytes (4). Across and within the mammalian species, the growth of the cardiac chambers is directly related to external work load, underscoring a tight coupling between the genetic control of cardiac growth and long-term mechanical stress (5).

When hemodynamic load is chronically elevated, cardiac mass may reach levels that far exceed normal, in which case, further cell enlargement (or hypertrophy) rather than cell proliferation (or hyperplasia) is responsible for this increase in weight beyond that of normal growth (6). Consistent observations of myocyte hypertrophic, but not proliferative, growth have led to the concept that adult myocytes are "terminally differentiated" and are devoid of the capacity of further mitotic division.

The present study. Olivetti et al. (7) performed a detailed morphometric analysis of the myocardium from hearts in an autopsy series of elderly subjects, with and without marked increases in ventricular weight. Their finding of an increase in the total number of myocyte nuclei as well as the cell size per nucleus in the senescent, hypertrophied ventricles challenges the current dogma of the terminally differentiated myocyte. They conclude that the marked increase in ventricular weight is a consequence of an expansion of interstitial area and an increase in the number of myocytes as well as an increase in myocyte volume (7). The authors appropriately acknowledge the limitations of their study, particularly that the histologic assessment of the average myocardial cell volume per nucleus is complicated by the variable population of binucleated myocardial cells. Nonetheless, they conclude that at least a component of the increase in the myocyte compartment in these senescent hypertrophied hearts appears to be attributable to myocyte hyperplasia. When considering the importance of this work, it must not be viewed in isolation, but rather as part of a series of experimental studies by these authors that have demonstrated that under pathologic conditions, the adult myocyte may undergo mitotic division in the late stage of pathologic hypertrophy (8,9).

It has been >30 years since Linzbach (10) published his extensive and now classic morphologic studies of the cardiac components of physiologic and pathologic growth. Although he concluded that most of the increase in chamber mass was a consequence of cell growth without division, he clearly demonstrated that in situations of a marked increase in cardiac weight, there was histologic evidence for an increase in the number of myocardial fibers. More important, he linked this appearance of new cells to a decompensated functional state wherein there was chamber enlargement, or "plastic structural dilatation" (10). The critical feature of the studies of both Linzbach (10) and Olivetti et al. (7) is that myocyte hyperplasia was observed in association with organ failure and structural dilation, not with the more common compensated phase of cardiac hypertrophy. Olivetti et al. do not deny that cell growth is the predominant mechanism of cardiac adaptation to increased work load, but stress that adult myocyte cell division can occur under certain sustained unfavorable loading conditions.

We believe that dilation is an important feature of this unfavorable condition. Dilation has important prognostic implications in that even small increases in ventricular chamber size are associated with a heightened relative risk of death (11–13). Wall tension, which is considered a stimulus for cardiac growth (14,15), becomes markedly increased in the setting of plastic structural dilation. Indeed, unless offset by appropriate wall thickening, the wall tension of the dilated chamber remains increased during the entire cardiac cycle (16,17). The feedback control between work load and cell size would remain an open loop as chamber enlargement begets further dilation (18). Because sarcomere length is not increased even in distended failing ventricles (19), plastic structural dilation requires a major reorientation (remodeling) of both the myocyte and interstitial components. In the aged myocardium under stress, the interaction between the interstitium and the myocyte may lead to an alteration in the genetic expression of the myocytes. Reciprocal cell-to-cell interactions between the microvascular endothelium and adult myocytes in coculture (20) may provide a clue for the unusual finding of latent mitotic activity of the myocyte under a major mechanical stress.

The coupling of cell size and cardiac chamber configuration during normal growth and the compensated phase of hypertrophy underscore the feedback control between mechanical stress and growth. Several possible transducers of mechanical load and myocyte growth have been proposed (21–23). This important work, however, focuses on the acute

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initiation of cellular hypertrophy. The studies of Olivetti et al. (7), Kajstura et al. (8) and Reiss et al. (9) address the more chronic phases of ventricular dysfunction and marked chamber enlargement (7–9). Their conclusion that adult myocytes divide should not be taken as a challenge to the concept of myocyte hypertrophy but as a call for a more open-minded approach to the study of the aged myocyte under pathologic conditions. The reversion of the myocyte under chronic stress to phenotypic expression of fetal isoenzymes is well established (24). Perhaps under the extremes of load and age, the neonatal capacity of the myocyte for mitotic division is also restored. The challenge to the investigative community is to obtain a better understanding of the fundamental biology, not just of the initiation but of the transition from compensated cell growth to dysfunction and chamber enlargement; for once conditions are present for adult myocytes to divide—they fail.

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