**Editorial Commentary**

**Is the Deficiency of the Long Isoform of Cellular FLICE-Inhibitory Protein Involved in Myocardial Remodeling?**

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**See related article, pp 1109–1117**

The term “myocardial remodeling” is used to describe a variety of changes in cardiomyocyte and noncardiomyocyte compartments of the myocardium that alter the geometry and architecture of the left ventricular (LV) chamber and occur in response to hemodynamic and neurohormonal stress. Cardiomyocyte hypertrophy, apoptosis, and interstitial and perivascular fibrosis are recognized as hallmarks of myocardial remodeling. Because myocardial remodeling may result in deterioration of both diastolic and systolic function, propensity for arrhythmias, and compromise of intramyocardial perfusion, it can be a key determinant of the clinical course and outcome of a number of cardiac diseases. Therefore, there is a growing interest in gaining new insights into the mechanisms responsible for cardiac remodeling, as well as developing novel strategies aimed at prevention and treatment.

In this conceptual framework, the study by Li et al published in the present issue of the journal provides new information of great interest related to the cellular Fas-associated death domain-like interleukin-1 converting enzyme (FLICE)-inhibitory protein (c-FLIP). This protein is a catalytically inactive procaspase 8/10 homologue that associates with the signaling complex downstream of death receptors, negatively interfering with apoptotic signaling. Three c-FLIP splice variants with differences in structure that reflect distinct functional roles have been identified, the 24-kDa form (c-FLIP S), and the 55-kDa form (c-FLIPL). This protein is a caspase-8:c-FLIPL ratio. For instance, at low-level expression, c-FLIPL heterodimerizes with procaspase 8 and caspase 8 autoprocessing, and activation occurs. In this regard, it is important to note that Li et al showed for the first time that c-FLIPL can be a key regulator of the myocardial response to mechanical and/or hemolytic injury. Additional questions arise, as should be the case for such a provocative study. One major question relates to apoptosis. Li et al provide evidence that cardiac DNA fragmentation and caspase 3, 8, and 9 activation after Ang II treatment increased in c-FLIPL heterozygous mice compared with wild-type mice. This aspect can be relevant because a dual role of c-FLIPL as either inhibitor or activator of caspase 8 has now been established, which may depend on a variety of parameters, including cellular context and caspase 8:c-FLIPL ratio.

Another major question concerns fibrosis. Myofibroblasts are differentiated fibroblasts that express the highly contractile protein α-smooth muscle actin and exhibit increased migratory, proliferative, and secretory properties, thus being currently considered as the cell type responsible for the excessive synthesis and deposition of collagen fibers leading to fibrosis. Recent evidence has suggested that differentiation of fibroblasts occurs in response to Ang II and other...
cytokines and growth factors acting in a coordinated manner. Thus, it could be of interest to explore whether c-FLIP L downregulation facilitates the differentiation of resident fibroblasts into myofibroblasts in the fibrotic myocardium.

From the above considerations, it can be hypothesized that deficiency of c-FLIP proteins, in particular, the c-FLIP L isoform, may facilitate myocardial remodeling in conditions of hemodynamic overload or neurohormonal stress (Figure). Interestingly, reduced c-FLIP expression has been described in the myocardium of patients with end-stage heart failure and rodent after myocardial infarction, suggesting 2 conditions characterized by severe myocardial remodeling. Therefore, altered regulation of c-FLIP proteins can be of major importance for determining their contribution to myocardial remodeling. Although c-FLIP expression can be regulated at multiple levels, c-FLIP proteins have a short half-life in normal cells, because their turnover is tightly controlled by the ubiquitin-proteasome system. Because findings from a number of studies suggest a role for increased ubiquitin-proteasome system activity in the genesis of myocardial remodeling, the possibility exists that increased ubiquitin-proteasome system–dependent degradation of c-FLIP L and other c-FLIP isoforms may lead to diminished availability of these proteins which, in turn, would facilitate the remodeling process.

In summary, Li et al should be congratulated for shedding new light on the potential role of c-FLIP L in the development of myocardial remodeling. Nevertheless, additional research is required to achieve greater knowledge on the nature of myocardial actions of this protein, as well as on its regulation during cardiac diseases and its potential usefulness as a target for therapeutic strategies aimed at preventing or repairing myocardial remodeling.

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Disclosures

None.

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