Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Learn and Live℠

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

Javier Díez, Arantxa González and Susana Ravassa

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://hyper.ahajournals.org/content/56/6/1045

Subscriptions: Information about subscribing to Hypertension is online at
http://hyper.ahajournals.org//subscriptions/

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
http://www.lww.com/reprints

Editorial Commentary

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

Javier Díez, Arantxa González, Susana Ravassa

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.[1] Cardiomyocyte hypertrophy, apoptosis, and interstitial and perivascular fibrosis are recognized as hallmarks of myocardial remodeling.[1] 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.[1] 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[2] 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.[3] Three c-FLIP splice variants with differences in structure that reflect distinct functional roles have been identified, the 24-kDa form (c-FLIP$_R$), the 26-kDa form (c-FLIP$_S$), and the 55-kDa form (c-FLIP$_L$).[3]

Although most of the research on c-FLIP proteins has been focused on their contribution to the development of tumors, recent data also suggest a role in the heart. On the one hand, it has been demonstrated that these proteins play a particularly important role in the embryonic heart development.[4] On the other hand, Giampietri et al[5] point to a role for c-FLIP$_L$ in the cardiac response to hemodynamic stress. When c-FLIP$_L$ transgenic mice overexpressing c-FLIP$_L$ in the heart were subjected to pressure overload by transverse aortic constriction, they showed normal LV function, reduced LV hypertrophy and fibrosis, and decreased induction of the cardiac fetal gene program compared with wild-type mice. These data have been expanded by Li et al[2] using a cardiac model of hormonal stress, chronic systemic infusion of angiotensin II (Ang II) resulting in systemic hypertension. They show that, after Ang II administration, heterozygous knockout mice for c-FLIP$_L$ exhibit exacerbated cardiomyocyte hypertrophy and myocardial fibrosis and more pronounced LV enlargement and systolic dysfunction compared with wild-type mice.[2] In contrast, the histopathologic, geometric, and functional changes induced by Ang II were attenuated in transgenic mice with cardiac overexpression of human c-FLIP$_L$ compared with control animals.[2] Of interest, the protective effects of c-FLIP$_L$ in transgenic mice were observed despite the persistence of Ang II–induced hypertension. To support these in vivo observations, the authors performed in vitro studies and found that cFLIP$_L$ inhibits hypertrophy in rat cardiomyocytes exposed to Ang II through direct inhibition of mitogen-activated protein kinase kinase-extracellular signal-regulated kinase 1/2 signaling.[2] In addition, they reported that c-FLIP$_L$ blocks collagen synthesis in rat cardiac fibroblasts by disrupting mitogen-activated protein kinase kinase-extracellular signal-regulated kinase ½–dependent transforming growth factor-β-Smad signaling. Collectively, these results suggest that c-FLIP$_L$ can be a key regulator of the myocardial response to mechanical and/or humoral injury.

Additional questions arise, as should be the case for such a provocative study. One major question relates to apoptosis. Li et al[2] provide evidence that cardiac DNA fragmentation and caspase 3, 8, and 9 activation after Ang II treatment increased in c-FLIP$_L$ heterozygous mice compared with wild-type mice. This aspect can be relevant because a dual role of c-FLIP$_L$ 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-FLIP$_L$ ratio. For instance, at low-level expression, c-FLIP$_L$ heterodimerizes with procaspase 8 and caspase 8 autoprocessing, and activation occurs.[6] In this regard, it is important to note that Li et al[2] showed for the first time that c-FLIP$_L$ expression is downregulated during LV remodeling induced by chronic Ang II infusion or transverse aortic constriction in normal mice.

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.[7] Recent evidence has suggested that differentiation of fibroblasts occurs in response to Ang II and other

(*Hypertension*. 2010;56:1045-1046.)
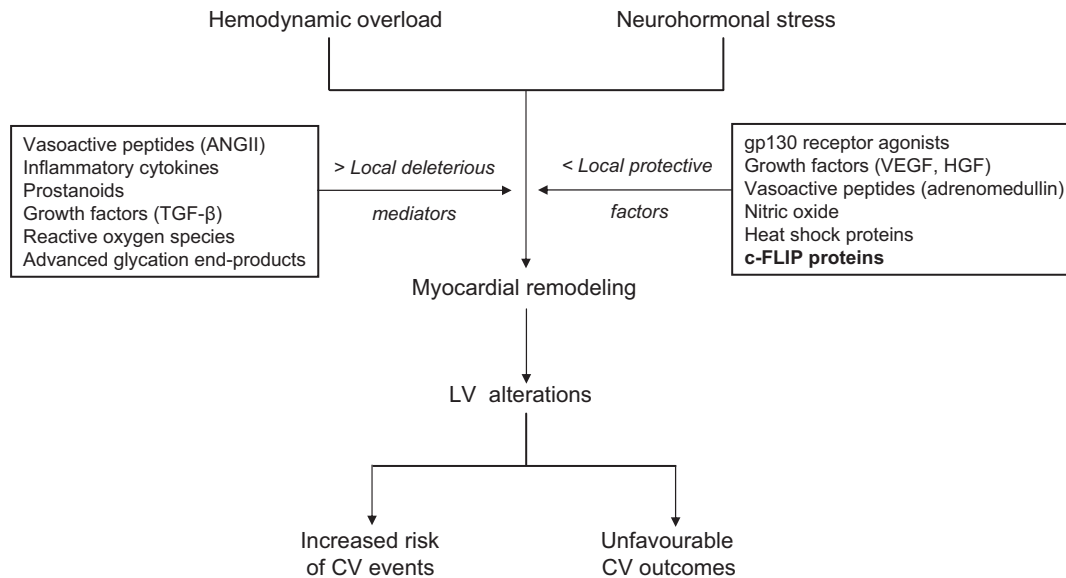© 2010 American Heart Association, Inc.

Figure. The imbalance between an excess of local deleterious mediators and a deficiency of local protective factors (including c-FLIP proteins, eg, the long isoform c-FLIP$_L$) may facilitate the development of myocardial remodeling in conditions of hemodynamic overload or neurohormonal stress. Myocardial remodeling, in turn, can alter LV morphology and function, thus facilitating adverse cardiovascular (CV) events and outcomes. (< means decreased availability and/or activity; >, increased availability and/or activity.)

cytokines and growth factors acting in a coordinated manner.[7] 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 rodents after myocardial infarction,[8,9] 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.[3] Because findings from a number of studies suggest a role for increased ubiquitin-proteasome system activity in the genesis of myocardial remodeling,[10] 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[2] 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.

Sources of Funding

Disclosures

None.

References

1. Swynghedauw B. Molecular mechanisms of myocardial remodeling. *Physiol Rev*. 1999;79:215–262.
2. Li H, Tang Q-Z, Liu C, Moon M, Chen M, Yan L, Bian Z-Y, Zhang Y, Wang A-B, Nghiem MP, Yeh W-C, Liu PP. Cellular FLICE-inhibitory protein protects against cardiac remodeling induced by angiotensin II in mice. *Hypertension*. 2010;56:1109–1117.
3. Bagnoli M, Canevari S, Mezzanzanica D. Cellular FLICE-inhibitory protein (c-FLIP) signalling: a key regulator of receptor-mediated apoptosis in physiologic context and in cancer. *Int J Biochem Cell Biol*. 2010; 42:2010–2013.
4. Yeh WC, Itie A, Elia AJ, Ng M, Shu HB, Wakeham A, Mirtsos C, Suzuki N, Bonnard M, Goeddel DV, Mak TW. Requirement for Casper (c-FLIP) in regulation of death receptor-induced apoptosis and embrionyc development. *Immunity*. 2000;12:633–642.
5. Giampietri C, Petrungaro S, Musumeci M, Coluccia P, Antonangeli F, De Cesaris P, Filippini A, Marano G, Ziparo E. c-Flip overexpression reduces cardiac hypertrophy in response to pressure overload. *J Hypertens*. 2008;26:1008–1016.
6. Yu JW, Jeffrey PD, Shi Y. Mechanisms of procaspase-8 activation by c-FLIPL. *Proc Natl Acad Sci U S A*. 2009;106:8169–8174.
7. Leask A. Potential therapeutic targets for cardiac fibrosis: TGFβ, angiotensin, endothelin, CCN2, and PDGF, partners in fibroblast activation. *Circ Res*. 2010;106:1675–1680.
8. Imanishi T, Murry CE, Reinecke H, Hano T, Nishio I, Liles WC, Hofstra L, Kim K, O'Brien KD, Schwartz SM, Han DK. Cellular FLIP is expressed in cardiomyocytes and down-regulated in TUNEL-positive grafted cardiac tissues. *Cardiovasc Res*. 2000;48:101–110.
9. Steenbergen C, Afshari CA, Petranka JG, Collins J, Martin K, Bennett L, Haugen A, Bsuhel P, Murphy E. Alterations in apoptotic signaling in human idiopathic cardiomyopathic hearts in failure. *Am J Physiol Heart Circ Physiol*. 2003;284:H268–H276.
10. Zolk O, Schenke C, Sarikas A. The ubiquitin-proteasome system: focus on the heart. *Cardiovasc Res*. 2006;70:410–421.