Gelsolin and Cardiac Myocyte Apoptosis
A New Target in the Treatment of Postinfarction Remodeling

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Cardiac remodeling is among the most important problems in patients with heart failure. Ventricular remodeling involves numerous processes, involving molecular alterations, myocardial changes, and the abnormal geometry of the chamber. As a consequence of myocardial infarction (MI), ventricular remodeling occurs immediately as an adaptive response to maintain cardiac output. However, ventricular function and prognosis deteriorate with ongoing remodeling. MI triggers an inflammatory response, including cytokine activation, a cascade of intracellular signaling, and neurohormonal activation. These processes result in scar formation and myocyte loss through necrosis, apoptosis, and autophagy. An MI has been shown to be a prominent inducer of cardiomyocyte apoptosis, which, in turn, may contribute to progressive postinfarction remodeling, as demonstrated by recently reported animal and human studies.

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Mechanisms of Gelsolin-induced Apoptosis
In multiple cell types, gelsolin is cleaved by caspase-3, which is activated during apoptosis. Gelsolin is also cleaved during apoptosis by caspase-8 and tumor necrosis factor. The N-terminal gelsolin fragment loses the Ca2+ control of the severing activity and the capacity to bind monomeric actin, triggering rapid depolymerization of the actin cytoskeleton. Expression of the N-terminal gelsolin leads to upregulation of apoptosis. Conversely, gelsolin has been reported to
inhibit apoptosis. Possible mechanisms have been proposed to explain the inhibitory capacity of gelsolin. Gelsolin in complex with phosphoinositides can competitively inhibit caspase-3.20 Despite all of these data, the effects of gelsolin on apoptosis remain controversial. Li et al16 demonstrated that gelsolin and cleaved gelsolin expression in the wild-type mice was increased and redistributed and that activated caspase-3 and caspase-8 were increased in the wild-type mice post-MI by immunoblotting analysis. In addition, the increase in caspase-3 post-MI functioned only in the presence of gelsolin. These data suggest that gelsolin cleaved by caspase-3 and caspase-8 upregulates MI-induced cardiomyocyte apoptosis (Figure).

Li et al16 noted DNase I was a gelsolin-related endonuclease during apoptosis in the myocyte post-MI. Immunoblotting with a specific anti–DNase I antibody showed less nuclear translocation of DNase I and the biological activity of DNase I was lower in the gelsolin-null mice post-MI. In addition, immunostaining showed the nuclear translocation of DNase I and its involvement in apoptotic cells. Interestingly, gelsolin also translocated into nuclei post-MI, suggesting that gelsolin directly induced the expression of DNase I by transcriptional activation. Indeed, it has been reported that gelsolin enhances the transcriptional activity of androgen receptor in the presence of an agonist.20

How is the transcription of DNase I regulated in cardiac myocytes during apoptosis post-MI? Hypoxia-inducible factor (HIF)-1α is a transcription factor, and is a key regulator of hypoxic conditions.21 Li et al16 demonstrated HIF-1α could bind to the promoter region of DNase I and that HIF-1α was strongly expressed in the wild-type mice post-MI. Immunoprecipitation assays revealed that HIF-1α coprecipitated with gelsolin in vivo and in vitro. Electrophoretic mobility-shift assays confirmed the functional interactions of HIF-1α with the DNase I promoter. In fact, luciferase assays showed that the relative luminescence was significantly increased after cotransfection of HIF-1α and DNase I promoter vectors. These data suggested HIF-1α contributed to the transcription of DNase I in cardiac myocytes during apoptosis post-MI. Interestingly, it has been reported that HIF-1α regulates the transcription of gelsolin gene expression in fibroblasts under hypoxic conditions.22 HIF-1α possibly contributes to the transcription of gelsolin in cardiac myocytes during apoptosis post-MI.

Finally, Li et al16 demonstrated the cleavage of downstream targets of caspase-3 and caspase-8, including the DNA fragmentation factor-45/ICAD, which interacts DNA fragmentation factor-40/CAD. Bid was not significantly different between the gelsolin genotypes. In contrast, the survival signals involving activated Akt and Bcl-2 were preserved in the gelsolin null mice post-MI on immunoblotting analysis. Taken together, the data from the present article suggest that gelsolin may promote apoptosis in vivo through DNase I in collaboration with HIF-1α and that gelsolin may be related to the downregulation of survival factors in cardiomyocytic apoptosis post-MI through the caspase cleavage of PARP, reduction of Akt activation, and decrease of Bcl-2 expression.

**Clinical Application**

These findings suggest that gelsolin is a new target for post-MI and heart failure treatment. However, in terms of clinical application, it must be noted that antiapoptotic therapies may cause carcinogenesis and that the inhibition of gelsolin may lead to diastolic dysfunction.12,13 Indeed, it has been reported that gelsolin expression is downregulated in tumors during carcinogenesis. In addition, a high level of gelsolin expression occurs in early stage non–small cell lung cancer, and it provides highly significant negative prognostic information. However, it has been reported that the gelsolin-null mice showed no increased incidence of tumors.13

In addition, L-type Ca\(^{2+}\) channel activity may be influenced in myocytes isolated from hearts of gelsolin knockout mice.12,23 Li et al16 noted that compared with the wild-type mice, the gelsolin-null mice post-MI had smaller left ventric-
ular end-diastolic volume and nonstatistically increased end-diastolic pressure, which may be attributable to the actin filament stabilization. Left ventricular stiffness may be increased by gelsolin inhibition.

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References

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