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Evidence for Myocyte Apoptosis in the Heart

G. Olivetti, E. Cigola, N. Bertani, G. Graiani

In the heart myocyte loss is an important factor in the genesis, development and progression of end-stage failure. Myocyte apoptosis has been seen in a variety of experimental and human conditions and it seems to play an important and unrecognized role in the loss of contractile material explaining, at least in part, functional deterioration. Since apoptosis is an active process regulated by several genes efforts have to be made to control the phenomenon with appropriate interventions. J Clin Basic Cardiol 2000; 3: 201–3.

Key words: apoptosis, necrosis, myocyte, heart failure

Apoptosis or programmed cell death is a form of cell death that was described several years ago and has been found relatively recently in different cardiac disorders and has been considered of primary importance in the onset and progression of cardiac dysfunction and failure in animals and men. This is because the loss of contractile cells in the heart poses an additional workload on the remaining viable myocytes that may be unbearable, resulting in pathologic stimuli and death signals. The evidence that supports this view is derived from several data, mostly quantitative, collected under different conditions that will be reviewed here.

Since 1994, the only form of myocyte death in the myocardium has been attributed to the well known process described as necrosis [1]. However, several studies have demonstrated that myocyte apoptosis may also be present in the heart. Apoptotic myocyte cell death has been found in embryogenesis [2], during postnatal growth [3], hypoxia in vitro [4], after ischaemic and reperfusion injury [5, 6], stretching of the papillary muscle in vitro [7], myocardial infarction in animals [8] and humans [9–12], in congenital heart defects [13], normal aging [14], rapid ventricular pacing [15], heart failure after coronary embolization [16], and more recently, in hearts in end-stage failure [17, 18], arrhythmogenic right ventricular dysplasia [19, 20], cardiac allograft rejection [21] pressure overload cardiac hypertrophy [22] and acromegaly [23].

Myocyte Apoptosis

Apoptosis is activated by an endogenous endonuclease able to cleave DNA in the linker region resulting in single or multiple DNA fragments of 200 bp [24, 25]. At this relatively early stage of the process there are minor morphological changes in the nuclei described as chromatin margination [24], not always detectable in the heart. In order to visualize in the tissue nuclear DNA strand breaks specific methods are needed [3, 7, 8, 10, 11, 14, 17]. In later stages, when DNA is fully compacted, the morphologic recognition of the residual apoptotic bodies is much easier [15]. Such a pattern of DNA cleavage can also be seen by agarose gel electrophoresis after extraction of DNA from the tissue which results in a typical nucleosomal laddering [7, 8, 14, 17]. Although both techniques have inherent limitations they have been used in combination to demonstrate the occurrence of the apoptotic process in the heart.

In contrast to apoptosis, the morphological criteria indicative of necrotic myocyte cell death have been extensively described [11]. Initially, the damage is limited to the mitochondria, then to the cytoplasmic components and finally to the sarcolemma compartment. In this scheme, the appearance of sarcolemma discontinuities is the landmark of an irreversible damage [1]. Unfortunately these structural changes are difficult to be seen by standard morphologic techniques and are apparent ultrastructurally only at the completion of the irreversible biochemical events, limiting their use in the detection of the process.

Myocyte Necrosis

A more direct approach to recognize necrotic myocytes has been developed by injecting monoclonal antibody specific to cardiac myosin in vitro and detecting its localization in the tissue with fluorescein labeled secondary antibody [26, 27]. It has been shown that the anti-myosin IgG binds to myofibrillar myosin only in myocytes with ruptured plasma membranes, whereas intact myocytes remained unlabeled. With this technique the presence of irreversible damaged myocytes after the infusion of isoproterenol [27] or angiotensin II [28] has been established and finally, the relative contribution of myocytes necrosis and apoptosis during the evolution of myocardial infarction has been quantified [8]. Indium-111-labeled antimyosin monoclonal antibody has also been applied in the noninvasive detection of myocardial damage in different pathologic conditions in humans [28–31].

Mechanisms of Myocyte Cell Death

The possibility that myocyte cell death may be elicited either by necrosis or apoptosis raises some considerations on the mechanisms responsible for these processes. The appearance of apoptosis before necrosis in a carefully planned experiment [8] supports the notion that a decrease in oxygen tension may activate the suicide program of myocytes. This possibility has been described in neonatal myocytes in culture [4], after ischaemic-reperfusion injury [5, 6] and after myocardial infarction in rats [8] and humans [11, 12]. In the infarcted myocardium, however, the affected and surviving muscles are both subjected to a significant elevation in diastolic overload [32, 33] and a direct relationship between mechanical forces and apoptotic myocyte cell death has been clearly demonstrated in vitro [7]. A diastolic overloading was also seen with aging [34], during rapid ventricular pacing [15], and in end-stage cardiac failure [17], all conditions in which apoptotic myocyte cell death has been documented.

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In summary, there are convincing evidences that myocyte cell loss may be induced by apoptosis and necrosis. Ischaemia and overload are essential in the generation of the cell death signal although changes in the induction of genes promoting or opposing apoptosis may modulate the total amount of myocyte damage. However, there is still a need to clarify the role played by different genetic and environmental factors implicated in cell death or survival.

Conclusion

References


Bcl-2 and Apoptosis

Apart from the described morphologic characteristics, apoptosis differs from necrosis because several genes are activated during apoptosis. This is important since apoptosis is an active process and could be prevented or modified by appropriate intervention. The expression of some members of the Bcl-2 family has been studied recently in the myocardium. During postnatal maturation of the heart, the expression of Bcl-2, which prevents apoptosis [42], is up-regulated in myocytes when apoptotic cell death is decreased and vice versa [3]. Aclutely, after experimental myocardial infarction, myocyte expression of Bcl-2 is enhanced in correspondence of the onset and peak of apoptotic myocyte cell death. At the same intervals, Bax, which promotes apoptosis [43], is unchanged [8]. Furthermore, Bcl-2 expression is moderately increased in human hearts with end-stage failure, where apoptosis is present in a large number of myocytes [17]. In infarcted ventricles in men [9, 44] apoptosis is accompanied by myocyte expression of Bcl-2 with overexpression of Bax. These contrasting findings can depend upon the interaction of different genes with Bcl-2.

Defects in Bcl-2 production in Bcl-2 deficient transgenic mice are coupled with cell death in different organs [45]. However, the interaction of Bcl-2 with other members of the same family may originate different results. For example, Bcl-2 forms heterodimers with Bax [46]. If Bax homodimers predominate cell death will occur, but when Bcl-2 and Bax heterodimerization prevails cells can survive [47]. Bcl-2 production may also interfere with the apoptotic process induced by Fas antigen [8]. In fact, it has been demonstrated that Fas protein is upregulated in more than 50 % of myocytes present in the area at risk after the occlusion of the left coronary artery despite the overexpression of Bcl-2 [8].
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