Letter to the Editor

Does growth hormone reduce fibrosis?

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In the article by Grimm et al. [1] dealing with the action of growth hormone on left ventricle remodeling after myocardial infarction in rats, the authors have concluded that growth hormone enhanced cardiomyocyte hypertrophy and reduced adaptive fibrosis in the noninfarcted part of the wall. Inter alia, they document their findings in Fig. 3. While Fig. 3B visualizes the untreated myocardium, in Fig. 3C the myocardium has been treated with growth hormone. The problem is that the fibrosis in the untreated ventricle (Fig. 3B) is not purely adaptive but corresponds to a mixture of adaptive and reparative fibroses. It is generally accepted that adaptive fibrosis is present in the interstitial space and reparative fibrosis consists of scars in the places previously occupied by dead cardiomyocytes [2, Fig. 1]. In adaptive fibrosis, most collagen fibers run parallel to the long axis of cardiomyocytes, while in reparative fibrosis they are arranged in an irregular crisscross pattern.

In Fig. 3B [1], there are large and irregularly shaped gaps between cardiomyocytes occupied previously by dead parenchymal cells. These gaps are filled by the collagenous tissue which is quite heterogeneous in comparison with the adaptive fibrosis in Fig. 3C. Note that the cardiomyocytes in Fig. 3B manifest irregular shapes with moth-eaten margins. This is clear evidence of their injury. Even though both Figures present the same amount of myocardium, there are about twice as many cardiomyocytes in Fig. 3C (treated myocardium) than in Fig. 3B. If there had been only adaptive fibrosis in Fig. 3B (i.e., if there had not been any cardiomyocyte death), one would expect that untreated left ventricles would be heavier (owing to extensive fibrosis) than treated ones (in spite of the increased width of their cardiomyocytes). The opposite is true, however: the mean weight of untreated ventricles is 0.835 g and of treated ones 1.233 g in large infarction and 0.878 g and 0.977 g respectively in moderate infarction.

All above facts may be reconciled by the hypothesis that a great number of cardiomyocytes in the untreated left ventricles died, were eliminated, and replaced by scars during the experiment. This conclusion brings up two important questions: (a) what was the mechanism of cardiomyocyte death, and (b) how has growth hormone influenced the remodeling of the noninfarcted ventricular wall?

Accidental death (often called necrosis) and apoptosis are two mechanisms of cell death usually recognized today. Cheng et al. [3] have described apoptosis in the noninfarcted myocardium in rats. Apoptosis does not provoke inflammation and scarring unless secondary factors such as interstitial haemorrhage intervene [4]. Since bleeding is extremely rare in the noninfarcted myocardium, another pathological phenomenon which would explain scarring after apoptosis must be postulated.

Edema is an increased accumulation of interstitial fluid. If it appears in consequence of increased microvascular permeability, it contains high amount of plasmatic proteins, including fibrinogen. This protein allows interstitial fluid to clot in the same way as blood does in contact with extravascular tissues. The clots provoke inflammation and stimulate wound healing reaction leading to their organization. If high-protein edema lasts long enough, it leads to fibrosis [5]. The most notorious examples of this process are chronic inflammation, lymphatic obstruction, and long-lasting venostasis.

Myocardial edema is present in numerous cardiac diseases, including myocardial infarction [6] in which it affects both infarcted and noninfarcted parts [7]. Myocardial infarction leads to high-protein edema [8] able to elicit fibrosis. Thus, the origin of the adaptive fibrosis described by Grimm et al. [1] may be explained in this way.

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Myocardial defects formed by cardiomyocyte apoptosis either collapse [4] or become filled with interstitial fluid. If this contains a high amount of plasmatic proteins, it will clot, provoke inflammation, and will lead to the healing of myocardial defects by scars. It is most plausible that this process led to the formation of the scars present in Fig. 3B [1].

The action of growth hormone in the heart is mediated by insulin-like growth factors (IGF-I, IGF-2). Both are cardioprotective [9,10] and manifest antiapoptotic action [11]. The growth hormone IGF-I axis is also known as a potent wound healing stimulator [12]. It is not probable, therefore, that growth hormone would manifest an antifibrotic action. On the other hand, it is apparent from the experiments of Grimm et al. [1] that growth hormone treatment led not only to enhanced cardiomyocyte hypertrophy and the improved function of the heart but also to the reduction of cardiomyocyte death mediated by apoptosis. All these actions resulted in less myocardial injury followed by inflammation, wound healing, and fibrosis. Consequently, one may conclude that growth hormone rather prevents than reduces fibrosis.

References


