Collagen and Transforming Growth Factor-β in Dilated Cardiomyopathy

To the Editor:

The recent article by Pauschinger and his colleagues provides interesting and novel data on the collagen type I/III ratio in patients with dilated cardiomyopathy (DCM). However, the data do not support their conclusion relating to a possible role of transforming growth factor-β1 (TGF). Although the abstract states that the myocardial TGF-β1 and TGF-β2 mRNA levels were elevated in the DCM group, in fact there was only a trend, and the results were not statistically significant. Furthermore, the study suffers from the lack of any control group of normal tissue. The authors have neatly tried to side step this by comparing mRNA levels in those subjects with an ejection fraction <50% and those with an ejection fraction >50%. However, the whole group had a “presumptive clinical diagnosis of dilated cardiomyopathy,” so even those subjects with a relatively normal ejection fraction (presumably a response to treatment) probably did not have a normal myocardium. In a previous study, we demonstrated by immunohistochemistry the presence of TGF in endomyocardial biopsy specimens in patients with DCM. However, recently we have also evaluated gene expression for TGF-β in these biopsy specimens using quantitative (MIMIC) reverse transcription polymerase chain reaction and made a comparison to biopsies taken from subjects with normal left ventricular function (taken at the time of cardiac surgery). There was no statistically significant difference between the DCM group and the normal myocardial specimens. However, we have also demonstrated that there is increased gene expression for TGF in macrophages from patients with DCM compared with normal subjects, and this is associated with a mildly increased plasma level. Kuhl et al showed that there is frequently an increased number of macrophages and lymphocytes in biopsy specimens from patients with DCM, and Hinglais et al demonstrated colocalization of myocardial fibrosis and predominantly T helper lymphocytes and macrophages in spontaneously hypertensive rats. I suggest therefore that on the basis of these results it is more likely that the TGF is being released by circulating and infiltrating macrophages and lymphocytes rather than the myocardium directly. In situ hybridization studies will more directly support or refute this hypothesis.

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Response

We thank Dr Sanderson for his letter. The key topic of our article was characterization of the collagen type I/III ratio in patients with “severe” dilated cardiomyopathy (DCM) (ejection fraction [EF] <50%) compared with patients with “latent” cardiomyopathy (EF >50%). Using histological, immunohistological, and molecular biological methods, we clearly demonstrated a change in collagen type I/III ratio at the mRNA and protein levels. We discussed in the article the fact that one limitation of our study was that it did not include normal myocardium as optimal control, because it was unavailable. However, as the best available approximation, analysis of latent versus severe DCM allowed unequivocal detection of a major change in matrix composition with likely functional relevance.

A minor point of the article was the data on regulatory factors that possibly influence this matrix remodeling. By measuring the abundances of transforming growth factor-β1 (TGF-β1) and transforming growth factor-β2 (TGF-β2) mRNAs using a competitive quantitative reverse transcriptase polymerase chain reaction, we found a trend toward increased abundances of both in patients with severe and those with latent DCM. We nowhere designated this trend as statistically significant. Mere description of RNA abundances cannot provide more than a hint as to possible causal factors, and that is how we assess the described trend. We think that beyond a description of the actual matrix remodeling having occurred in DCM (as in our article), further understanding of the molecular mechanisms causing these changes will require careful analyses of relevant animal models.

To the best of our knowledge, there are currently no data indicating the cellular sources of possibly elevated myocardial TGF-β1 and TGF-β2 levels in DCM. However, the hypothesis of Dr Sanderson that TGF-β1 and TGF-β2 might be released from circulating and infiltrating macrophages and lymphocytes is certainly interesting and should be tested experimentally. Although speculative at the moment, any possible molecular link between immune effector cells and matrix remodeling should be evaluated, since intervention at such molecular links could be therapeutically highly effective.

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Circulation. 2000;102:e66
doi: 10.1161/01.CIR.102.9.e66
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/102/9/e66

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