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EDITORIAL COMMENT

Tenascin-C in Cardiac Hypertrophy and Fibrosis

Friend or Foe?*

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Tenascin-C (TNC) is a large, hexameric, extracellular matrix glycoprotein. Individual TNC protomers have amino-terminal heptad repeats that promote trimerization, and homotrimers then dimerize to form hexamers. The protomeric heptad repeats are followed by multiple epidermal growth factor-like domains, a string of fibronectin type III repeats, and a carboxy-terminal fibrinogen-like globe (1,2). Because of its modular structure, TNC can interact with diverse molecules, including receptors and extracellular matrix components, giving the protein a wide range of functions during tissue injury (3).

TNC is involved in the early embryonic development of the heart, but it is not expressed in the normal adult myocardium. Expression of TNC reappears in the heart under pathological conditions, including dilated cardiomyopathy, myocardial infarction, myocarditis, and myocardial hibernation (4). Serum levels of TNC correlate with the occurrence and severity of heart failure in patients with dilated cardiomyopathy, hypertrophic cardiomyopathy, and acute myocardial infarction (5-7). However, it has not yet been determined whether high levels of TNC are a cause or a consequence of these cardiac injuries. It is possible that TNC directly triggers the signaling cascades that lead to adverse cardiac remodeling in response to various insults, or alternatively that TNC is up-regulated to counteract cardiac remodeling. Thus, the question remains as to whether TNC is a friend or a foe.

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In this issue of the *Journal*, Song et al. (8) present the results of a loss-of-function approach to investigate the role of TNC during cardiac remodeling in response to mild pressure overload or infusion of angiotensin II. At baseline, the wild-type C57BL/6 mice and *TNC* knockout mice with the same genetic background were indistinguishable in cardiac function and morphology, which is consistent with the lack of TNC expression in normal adult myocardium. However, upon mild pressure overload that was achieved by abdominal aortic banding, *TNC* knockout mice exhibited much greater levels of cardiac hypertrophy and fibrosis than wild-type mice. Similar results were obtained when cardiac remodeling was induced by infusion of angiotensin II. These data suggest that TNC is cardioprotective in pathological conditions. Consistent with the exacerbation of cardiac fibrosis, significant increases in accumulation of Mac-2-positive monocytes/macrophages were observed in the hearts of *TNC* knockout mice in pathological conditions. Further analyses with flow cytometry revealed that levels of Lys6C^{hi}-positive pro-inflammatory monocytes were significantly higher in the hearts of *TNC* knockout mice. Because Lys6C^{hi}-positive monocytes are believed to be of extravascular origin, these results suggest that a lack of TNC increases the cardiac infiltration of monocytes/macrophages from noncardiac sources.

Elegant reciprocal bone marrow transplantation experiments were performed to elucidate the primary site of TNC function (8). When the bone marrow of wild-type donors was transplanted into *TNC*

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knockout recipients, cardiac hypertrophy and fibrosis were significantly reduced under mild pressure overload. However, in the reciprocal experiment, when the bone marrow of *TNC* knockout donors was transplanted into wild-type recipients, adverse cardiac remodeling was not induced. The authors concluded that TNC in the bone marrow (but not in the heart) is relevant to the cardioprotective effects of TNC, which can therefore be pictured as a "friend."

The results of Song et al. (8) emphasize that inflammatory monocytes/macrophages that originate from bone marrow significantly contribute to cardiac hypertrophy and fibrosis, and that TNC in the bone marrow prevents the immune cells from infiltrating to the heart, resulting in the attenuation of cardiac hypertrophy and fibrosis. The function of TNC in the heart is not known, despite its marked up-regulation under pathological conditions. However, we cannot rule out the possibility that expression of TNC in the heart under pathological conditions might affect cardiac function and anatomy, either positively or negatively, but that any such effect is obscured by the more prominent TNC activity in the bone marrow. Alternatively, the induced level of expression of TNC might not be high enough to exert any noticeable effects in the heart. In vivo gain-of-function studies should shed light on this issue. However, the large size of TNC (>2,000 amino acids) limits the options for in vivo studies.

In sharp contrast to the results presented by Song et al. (8), Shimojo et al. (9) have previously reported that cardiac fibrosis induced by angiotensin II is significantly attenuated in *TNC* knockout mice created in the BALB/c background. In addition, treatment with purified TNC protein enhances the migration of macrophages and the expression of pro-inflammatory and pro-fibrotic cytokines in macrophages in vitro. Shimojo et al. concluded that TNC is pro-fibrotic, suggesting that it is a "foe." The results from both these studies highlighted the important roles of immune cells in cardiac fibrosis, but they provided opposing evidence for the role of TNC. Song et al. attributed this discrepancy to the different genetic backgrounds of the *TNC* knockout mice. For example, C57BL/6 mice exhibited predominantly type 1 T helper cell responses, whereas BALB/c mice exhibited predominantly type 2 T helper cell responses to the same antigen (10). It is a considerable challenge to understand how the presence of type 1 or type 2 T helper cell dominance could lead to opposite responses to TNC, but this hypothesis can be tested. For example, it would be interesting to determine whether purified TNC protein induces opposite responses in vitro in monocytes/macrophages isolated from C57BL/6 and BALB/c mice. However, a more important issue is to determine which of these mice is more relevant to human physiology. While this question is being debated, results of in vitro experiments with immune cells of human origin could be illuminating.

The results presented by Song et al. (8) have added a layer of complexity regarding the function of TNC in cardiac hypertrophy and fibrosis. TNC can be either friend or foe depending on the genetic background in a small animal model. We now need to explore this issue in large animal models and/or models with greater relevance to humans.

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