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EDITORIAL COMMENT

Basic Research on Myocarditis

Superb But Unrequited*

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Considerable progress has been made at the basic research level in our understanding of the molecular pathophysiology of myocarditis, as exemplified by the eloquent report of Weithauser et al. (1) in this issue of the *Journal*.

But, at the clinical level, myocarditis has been strikingly resistant to successful scientific inquiry, as witnessed by the absence of substantial improvements in its treatment. Why the lack of translation?

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Weithauser et al. (1) examined the role of protease-activated receptor-2 (PAR2) in the pathogenesis of viral myocarditis in a murine model exposed to coxsackievirus B3 (CVB3). They observed a stunning reduction of viral load and myocardial inflammation and improved survival in PAR2-deficient mice. Relevance of the observation to clinical myocarditis was suggested by a correlation in patients between PAR2 expression and the severity of myocardial inflammation in biopsy specimens. The investigators concluded by pointing to the therapeutic potential of PAR2 antagonism in myocarditis. Can this potential be met?

Before clinicians knew the basic pathophysiology of viral myocarditis 60 years ago, immunosuppression was recommended and used (2). Today, it is not formally accepted in current treatment guidelines: International expert consensus today only endorses nonspecific treatment of heart failure in patients with known or suspected viral myocarditis (3). Indeed, outside of the investigational setting, there are simply no new generally accepted treatments of myocarditis, and immunosuppression is often used by default. Even the novel observations by Weithauser et al. (1) may have limited therapeutic potential, because patients with viral myocarditis infrequently present early enough in the disease process for an antiviral treatment to be effective.

Paradoxically, one source of translational disappointment is the richness of choices available to the basic investigator. The investigators used a Nancy strain of CVB3 virus to induce myocarditis. This strain is highly myocarditic, but it is also phenotypically diverse (4,5). It is not the only CVB3 virus strain that could be used for inducing experimental myocarditis, and it is only one of many viral species used to study myocarditis. Added to this viral diversity are the assorted and complex determinants of susceptibility of specific viral strains to putative antiviral therapies (6). How can investigators know if their specific virus-induced disease mimics any form of the disease in humans and if it portrays responses to therapy that could be expected in the clinical setting? Which is the right viral strain for discovery of effective treatment?

Weithauser et al. (1) used C57BL/6 mice. This is the most widely used mouse strain for genetic modification (7), but certainly not the only one that could have been used. What is the right mouse strain for the study of viral myocarditis?

There are numerous other animal species that basic investigators have employed to model myocarditis: rat (8); guinea pig (9); hamster (10); rabbit (11); dog (12); pig (13); and monkey (14). Some of these species, especially mice, may be distinctively different in their susceptibility to the effects of steroids (15) and other treatments. Which is the right animal species for mimicking the human disease?

The quest for a therapeutic breakthrough in the treatment of viral myocarditis is further hampered because the disease itself is protean (16), progressing through an initial phase of viral injury, then a period of autoimmune myocardial damage, and finally a phase of adverse remodeling, in which infection, immunity, and autoimmunity may no longer be relevant. This variability complicates the effort to treat myocarditis because the disease phases may overlap or repeat. As a result, new therapies derived from the bench may not get a fair test at the bedside. And, a very basic question is raised: Which phase of the disease is the right therapeutic target?

Even in the scientifically more tractable animal model, mechanistic complexity obscures the path to successful therapy. In their current paper, Weithauser et al. (1) contend that the improvement in myocarditis observed in PAR2-deficient mice is mediated through interferon and Toll-like receptor 3 pathways. Yet, the same Charité group had previously proposed that the effect was a result of inhibition of myocardial expression of the coxsackie-adenovirus receptor. Whereas the evidence presented in favor of the new explanation is strong, and, the investigators are commended for re-examining and revising their previous postulate, the main point is that most relevant receptors present more than one potential downstream therapeutic target. Which is the right therapeutic target?

What are the answers to the numerous questions posed here? What is the solution to the failure of translation from cell to beside in the case of myocarditis?

In fact, the investigators nicely illustrate one promising part of the solution in this, as well as their previous work. They avoided examining molecular mechanisms in an experimental vacuum; rather, they combined their basic findings with

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directly relevant clinical observations. This is an important paradigm for investigation of a disease such as myocarditis that is poorly characterized clinically.

I see an opportunity to improve translation through a renewed effort to characterize the clinical disorder. The cart has gotten in front of the horse. We need to step back and carry out a large, multinational observational study so that the superb basic science we already have can be translated and can become more informed by reverse translation. This suggestion may seem backward, simplistic, uninteresting, and tedious. But, in most cases, clinicians managing patients with myocarditis do not know what they are dealing with. Myocarditis is most often a presumptive diagnosis, and even if an endomyocardial biopsy is done, there is considerable argument over diagnostic criteria, no matter how sophisticated the histological and molecular probes that are applied. Diagnosis aside, our inability to confidently identify individual or overlapping phases of the disease is a crippling deficiency that must be corrected before science and clinical care can come together.

The proposed observational study might enroll 1,000 patients to be followed for 3 years. Each would undergo the most astute clinical observation, endomyocardial biopsy, and magnetic resonance imaging, serially. The most promising analyses would be applied to the tissue and blood samples, and outcomes would be systematically documented. Therapy would not be directed but would be carefully monitored. Analysis of the data might help to answer many of the questions posed here and break the block between bench and bedside. Cost? About $10M.

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REFERENCES

1. Weithauser A, Bobbert P, Antoniak S, et al. Protease-activated receptor-2 regulates the innate immune response to viral infection in a coxsackievirus B3–induced myocarditis. J Am Coll Cardiol 2013; 62:1737–45.
2. Garrison RF, Swisher RC. Myocarditis of unknown etiology (Fiedler's?) treated with ACTH; report of a case in a 7-year-old boy with improvement. J Pediatr 1953;42:591–9.
3. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2009;119:1977–2016.
4. Lee C, Maull E, Chapman N, Tracy S, Wood J, Gauntt C. Generation of an infectious cDNA of a highly cardiovirulent coxsackievirus B3(CVB3m) and comparison to other infectious CVB3 cDNAs. Virus Res 1997;50:225–35.
5. Tracy S, Tu Z, Chapman N, Hufnagel G. Genetics of coxsackievirus B3 cardiovirulence. Eur Heart J 1995;Suppl O:15–7.
6. Schmidtke M, Hammerschmidt E, Schüler S, et al. Susceptibility of coxsackievirus B3 laboratory strains and clinical isolates to the capsid function inhibitor pleconaril: antiviral studies with virus chimeras demonstrate the crucial role of amino acid 1092 in treatment. J Antimicrob Chemother 2005;56:648–56.
7. Wikipedia. C57BL/6. [Online encyclopedia]. Available at: http://en.wikipedia.org/wiki/C57BL/6. Accessed May 26, 2013.
8. Ito M, Kodama M, Masuko M, et al. Expression of coxsackievirus and adenovirus receptor in hearts of rats with experimental autoimmune myocarditis. Circ Res 2000;86:275–80.
9. Tominaga M, Matsumori A, Horie M, Yoshida H, Okada Y. Activation of Ca-permeable cation channels by myocarditis-associated antibody in guinea pig ventricular myocytes. J Clin Invest 1993;91: 1231–4.
10. Morita H. Experimental coxsackie B-3 virus myocarditis in golden hamsters: light and electron microscopy findings in a long-term follow-up study. Jpn Circ J 1981;45:713–29.
11. Edwards S, Small JD, Geratz JD, Alexander LK, Baric RS. An experimental model for myocarditis and congestive heart failure after rabbit coronavirus infection. J Infect Dis 1992;165:134–40.
12. Zhang J, Andrade ZA, Yu ZX, et al. Apoptosis in a canine model of acute Chagasic myocarditis. J Mol Cell Cardiol 1999;31:581–96.
13. Gwathmey JK, Nakao S, Come PC, et al. An experimental model of acute and subacute viral myocarditis in the pig. J Am Coll Cardiol 1992;19:864–9.
14. Paque RE, Gauntt CJ, Nealon TJ. Assessment of cell-mediated immunity against coxsackievirus B3-induced myocarditis in a primate model (Papio papio). Infect Immun 1981;31:470–9.
15. Claman HN. Corticosteroids and lymphoid cells. N Engl J Med 1972; 287:388–97.
16. Liu PP, Mason JW. Advances in the understanding of myocarditis. Circulation 2001;104:1076–82.

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