Prof. Anthony Rosenzweig: exercise can benefit the cardiovascular system and help prevent heart failure

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Expert introduction

Prof. Anthony Rosenzweig, MD, is the chief of cardiology at Massachusetts General Hospital and co-director of the Corrigan Minehan Heart Center. He practices cardiology at Mass General, where he studies causes of heart failure and previously served as the director of the Cardiovascular Gene Therapy Program. From 2006 to 2015, Dr. Rosenzweig served as the director of cardiovascular research and associate chief of the Cardiovascular Division at the Beth Israel Deaconess Medical Center. His clinical interests include noninvasive clinical cardiology and cardiovascular disease prevention (*Figure 1*).

Prof. Rosenzweig has held various leadership roles, including American Coordinator for a Leducq Foundation Network of Research Excellence, comprising 11 laboratories in Europe and the United States. He was also an associate editor of the *New England Journal of Medicine* from 2003 to 2013 and has served on numerous editorial boards including *Cell Metabolism*, *Circulation*, and *Circulation Research*.

I got the chance to meet and interview Prof. Rosenzweig during his recent visit to China (*Figure 2*). It's my great honor and pleasure.

Figure 1 Prof. Anthony Rosenzweig, MD.

Figure 2 Prof. Rosenzweig and Molly, taken after the interview.

Interview questions & responses

NCRI: You are a widely published expert on mechanisms of heart failure and the benefits of exercise. Looking back, how did you get started with heart failure research?

Prof. Rosenzweig: I had trained as a postdoctoral fellow in the laboratory of Jonathan and Christine Seidman who study the genetics of cardiomyopathy that was really the start of my interest in mechanisms of heart failure. But obviously genetic cardiomyopathy is only one part of a larger syndrome of heart failure. I think it was a combination of the growing clinical need that is represented by heart failure and a number of interesting scientific questions which intersect in the context of heart failure that drove me to focus my laboratory's research in this area.

NCRI: What's the relationship between heart failure and exercise? Can you talk a bit about the benefits of exercise?

Prof. Rosenzweig: Exercise appears to protect against a broad range of cardiovascular and other diseases. It

obviously has a large impact on cardiometabolic diseases like diabetes and insulin resistance. There may even be an impact on things like cancer development. For heart failure, in particular, the strongest inverse association seems to be with heart failure with preserved ejection fraction or what we call HFpEF. Physical inactivity is a significant risk factor for the development of heart failure, and the strongest signal for that is for HFpEF. Exercise does lots of wonderful things. It not only changes your metabolism, skeletal muscle and vasculature but also changes your intrinsic pathways in your heart. So I think it's a combination of all of those things that benefits the cardiovascular system and helps prevent heart failure.

NCRI: In 2015, your team has published the paper "miR-222 is necessary for exercise-induced cardiac growth and protects against pathological cardiac remodeling". For what reason did you choose to study the role of miR-222 in heart disease? Can you talk more about this study?

Prof. Rosenzweig: Dr. Xiao (Junjie Xiao) was visiting at the laboratory at that time, and he did a screen of the microRNAs that change in two different models of exercise, a voluntary running model and a swimming model, with the hypothesis that the most robust mechanisms of protection would be conserved in both models. MiR-222 was one of the most interesting microRNAs that was at that intersection. It really was Dr. Xiao's working that led to the discovery of miR-222 and our interest in studying this microRNA in exercise. Subsequent studies show that it's absolutely necessary for the growth of the heart in response to exercise but also protects against pathologic stress like an ischemic injury.

NCRI: What about down the road?

Prof. Rosenzweig: It's an interesting question. I think there are a couple of different approaches one could take to thinking about enhancing that particular microRNA. But one potential concern is that miR-222 seems to drive proliferation and growth of a number of tissues. So I think one would want to be cautious about giving a systemic treatment that would enhance miR-222 across all tissues because there's the concern that it might potentiate malignancy. More appealing alternatives would include either delivery specifically to the heart or some molecular control that restricted expression to the heart. In some of those studies involved in that paper, we went on and identify downstream targets, and two of the targets are kinases. MiR-222 decreases the levels of these two kinases and to the extent that the benefits accrue from that, those kinases might be druggable targets, because there's been a success in inhibiting kinases and other contexts, such as cancer therapies. So I think that's another potential therapeutic avenue that one could pursue.

NCRI: In terms of difficulties you're encountered, can you talk about that?

Prof. Rosenzweig: In the United States, the major difficulty is there's never enough funding for research, particularly for junior people starting out and establishing their laboratories. The United States over the last few years has been investing less and less of the gross domestic product in research. China has been very forward-thinking in this regard and investing substantially in research which is wonderful to see, but I think that's been rare in the United States. Our biggest challenge is getting enough funding to support the research we want to do and particularly for the junior people starting out.

NCRI: What's your view on the role of non-coding RNA in the treatment of cardiovascular disease?

Prof. Rosenzweig: Many Studies have shown that non-coding RNAs are the critical determinants of cardiovascular physiology development and disease pathogenesis. I think that they're very important first in providing some insight into the pathophysiology of these diseases. Although as we talked about with miR-222, you would have to look at each one in detail and think about what the risks and benefits of targeting that particular non-coding RNA, which might be depending on how you're going to target. And then because some of these circulate in the blood, they are also potentially useful biomarkers that might enable you to identify either clinically meaningful subpopulations that might respond preferentially to a specific kind of treatment. So I think they have a number of potentially useful clinical applications as well as just being a really interesting window into understanding the pathophysiology of these diseases.

NCRI: When it comes to cardiovascular research in China, what would you say?

Prof. Rosenzweig: I've been so impressed with so much of the work that I've seen. In particular, Dr. Xiao, who I'm

very familiar with, is really doing wonderful and exciting research on non-coding RNAs and the pathologic and physiologic growth of the heart. As a window onto the larger scientific enterprise in China, it's wonderful to see so many thriving laboratories and exciting work going on here.

NCRI: You have been an associate editor of the New England Journal of Medicine from 2003 to 2013. How do you look at the role of journal editor?

Prof. Rosenzweig: As an associate editor for those years, my role was pretty narrowly defined to handle some of the cardiovascular papers that came in. For me, it was a very humbling experience because there were so many wonderful papers and really we could only publish a small fraction of them. I took some consolation knowing that even things the *New England Journal of Medicine* couldn't publish generally wound up published in very good journals. And I learned a tremendous amount from the authors, other editors and the statisticians at the journal, so it was really a wonderful and humbling experience.

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