Ventricularization of Atrial Gene Expression in the Fibrillating Heart?

Gordon F. Tomaselli

Structural and functional changes in the heart in response to disease or dysfunction are essential compensatory responses to stress. In the context of sustained stress such initially adaptive changes may become maladaptive or contribute to the progression of the pathological phenotype. Understanding the cellular and molecular basis of such remodeling holds the promise of understanding disease mechanisms and identifying novel therapeutic targets and interventions.

Atrial fibrillation (AF) is the most common sustained arrhythmia in man and has justifiably been an area in which remodeling has been intensely investigated. The atria undergo a complex, time dependent series of changes in structure and cellular electrophysiological function in response to rapid atrial activation and heart disease that predispose the development of AF. Canonical individual gene and pathway, transcriptional, translational, and functional studies of animal model and human AF have identified changes in a number of important regulatory pathways in the fibrillating atria that have helped to explain the self-perpetuation of this arrhythmia or why “AF begets more AF”. In this sense, some of the findings of Barth et al benefits from this “cart before the horse sequence of events” and indeed validates some of the findings in the microarray dataset. That is, some of the transcriptional changes in permanent AF identified by microarray analysis have previously been demonstrated in AF.

In particular changes in ion current expression, Ca handling, and profibrotic signaling are consistent with published structural and functional data (for review see). Cross platform consistency, suggests the importance of such changes in the AF phenotype and their regulation, at least in part, at the level of transcription. Notably a number of previously observed changes in atrial structure and function thought to be transcriptional in nature are not altered in this dataset.

Transcriptomic analysis utilizing microarrays has the advantage of being a relatively unbiased approach assessment of expressed RNA. The liabilities are limitations related to the content of the array and the absence of detection of posttranscriptional changes. It is important to keep in mind that expression profiling, regardless of the platform, is the first step in a process of observation, modeling, and hypothesis generation and testing. In this sense the dataset provided by Barth et al is valuable, lending itself to the generation of a number of testable hypotheses. One interesting hypothesis is that of ventricularization of the fibrillating atrial myocardium. Indeed there are commonalities in the expression profiles of non-failing LV myocardium and fibrillating RA myocardium not observed when the RNA from RA appendages of patients in sinus rhythm and AF are compared. It would be interesting to know how the expression profile in the fibrillating RA compares to that of the failing LV. This might help to clarify whether the atrial changes in some way mimic a ventricular phenotype or tend to produce a dedifferentiated “fetal” phenotype in response to stress.

As the authors point out, several notes of caution are warranted. The studies were done on human tissue from a single site in the right atrial appendage. As with all human study controls on the duration of AF, the structural heart disease context, age, gender, pharmacotherapy, and whether the SR controls are truly without atrial arrhythmias are recognized limitations of the work. Spatial heterogeneity of atrial remodeling is characteristic of the changes in both the cellular and interstitial compartments in AF. This may be particularly important in this study as 80% of patients with permanent atrial fibrillation had mitral regurgitation and presumably differential hemodynamic loads between the atria. Alterations in load are characteristic of systolic heart failure which produces substantial remodeling of the left atrium that could predispose atrial fibrillation, even in the absence of the arrhythmia.

One of the principal comparisons was that of the transcriptomes of the nonfibrillating and permanently fibrillating RA. The role of the pathways in the pathogenesis of AF identified in the array analysis is unknown. Indeed, many of these changes may be followers rather than drivers of the pathology associated with AF. Importantly, from the standpoint of identification of appropriate therapeutic targets, it is essential to decide which changes are required for an adaptive response to either AF or the heart disease that predisposes to AF. Interfering with an adaptive pathway may indeed prevent remodeling but the possible liability of compromise of the organism.

Finally, identification of novel therapeutic targets is a promise of gene profiling. Certainly this study has identified a number of candidates involved in transcriptional regulation, elaboration of fibrosis, cell excitability, calcium homeostasis, and energy metabolism. The worthiness of such candidates requires further validation and study, but antiarrhythmic...
drugs have significant liability with considerable limitations in the management of AF (eg,9). It might be preferable to identify genes and pathways that generate the substrate for AF. Although AF begets AF it is not clear what the transcriptome of the permanently fibrillating atrium reflects: a cause of AF; an effect of fibrillation; or both. Further insight into upstream therapeutic targets might be gleaned from studies comparing an appropriate substrate (atrium under hemodynamic stress) that is not fibrillating. In this sense, a comparison of atria from patients with paroxysmal atrial fibrillation, atioventricular valvular heart disease and sinus rhythm, and “normal” atria might provide insight into upstream signaling pathways that are involved in the generation of the substrate that predisposes AF. Aging influences atrial structure and function in ways that resemble the changes that occur in heart failure,10 comparison of the transcriptomes as a function of age may be another way of understanding the molecular mechanisms of generating the substrate for AF.

The work by Barth and colleagues provides an important first step in understanding the molecular basis of the structural and functional changes that predispose human AF and represents a significant advance over previous studies using differential display11 and lower density arrays12 in animal models of AF. The challenge is to now place these expression changes in their appropriate pathophysiological context. The work now begins!

References


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