Unexpected Cardiac Hypertrophy by Epidermal Growth Factor Receptor Silencing

To the Editor:

Schreier et al 1 have recently reported a cardiovascular phenotype of mice lacking epidermal growth factor receptor (EGFR) in vascular smooth muscle cells. The mice were created by breeding EGFR\textsuperscript{fl/fl} mice with SM22\textsuperscript{Cre/+} mice resulting in almost complete deletion of vascular smooth muscle cell EGFR and partial deletion of cardiac EGFR. The vascular phenotype of the hybrid mice (lowering of blood pressure and responsiveness to angiotensin II) advances our knowledge regarding the role of vascular EGFR and fits well with a past publication. 2 However, the cardiac phenotype observed in the hybrid mice may deserve further discussion and investigation.

The data 1 clearly indicate that the hybrid mice have severe eccentric hypertrophy at 3 to 4 months of age because neither hypertension nor cardiac fibrosis was evident, which the authors attributed to a physiological hypertrophy response. However, the mice had a similar ejection fraction to the control wild-type mice and seemed to be experiencing hypotension, whereas cardiac output was increased. It is possible to speculate that in the hybrid mice, the heart attempts to compensate against the vascular phenotype (hypotension) by eccentric hypertrophy with limited success, as noted by enormous hypertrophy and onset of increased mortality compared with the control animals.

Under cardiac compensation, hormonal factors, such as angiotensin II, contribute to the pathophysiological hypertrophy associated with fibrosis, extracellular matrix deposition/recomposition, and inflammation with expanding arrays of signal transduction. 3,4 Increased natriuretic peptide expression in the hybrid mice further suggests that the mice are experiencing/progressing toward pathophysiological hypertrophy. Certain amounts of cardiac EGFR may be required for the fibrosis/inflammation associated with cardiac hypertrophy, and although the authors did not observe significantly elevated levels of cardiac fibrosis markers at time of analysis, the trend toward increased fibrosis genes in the hybrid mice suggests that they may be in the early stages of fibrosis development. Whether progression of fibrosis in these mice contributes to the precipitous drop in survival observed >4 months of age would be of interest to discern. Similarly, the potential role for reactive oxygen species dysregulation as a causative factor in the progression of cardiac hypertrophy in response to reduced levels of EGFR would be very important to follow up on.

EGFR has been implicated in pathological cardiac hypertrophy, 5 thus further clarification of the role of cardiac-specific EGFR in this process, distinct from the potential contribution of vascular smooth muscle cell EGFR, seems necessary. The investigation by Schreier et al 1 is an important step in elucidating the impact of EGFR in cardiac homeostasis and disease. Future experiments attaining greater cardiac-selective deletion of EGFR and inducible silencing of EGFR in adult mice will be appreciated.

Disclosures
None.

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