CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

A Guardian of the Heartbeat

Nadia Rosenthal, Ph.D.

Of all the bodily functions performed flawlessly without conscious intervention, the steady beat of our hearts is among the most critical. The developing heart is the earliest organ to function in the embryo, generating rhythmic contractions while it is forming, before there is blood to pump. The healthy adult human heart rarely misses a beat, contracting and relaxing some 3 billion times during a normal life span. A reliable heartbeat is the basis of life — if it stops, everything grinds to a halt.

Although the heart is composed of multiple cell types besides muscle cells,[1] keeping a steady heartbeat is the job of specialized cardiomyocytes that ensure coordination of electrical signals throughout the organ. The pacemaker of the heart, the sinoatrial node, generates rhythmic electrical impulses that coordinate atrial contraction and then spread through the atrioventricular node to trigger ventricular contraction. Mutations that compromise cardiomyocyte function invariably affect conduction. This classic view of cardiac conduction has been refined by the revelation that all the cells in the heart are electrically coupled, including fibroblasts that form the stromal support for the heart and the cells of the vascular network that feed the heart muscle itself, presumably to better coordinate the complex wringing action of the cardiac wall.

A recent study by Hulsmans and colleagues[2] implicates a specific population of cardiac support cells — abundant macrophages that reside in heart tissue — as key players in keeping a steady heartbeat. Although changes in macrophage type and number had been documented in various forms of heart disease,[3] it was assumed that cardiac macrophages played a canonical role in immune surveillance, protecting against pathogens and maintaining tissue integrity. The current story starts with a serendipitous observation: mice without properly functioning macrophages had sluggish, irregular heartbeats, which led Hulsmans et al. to look more carefully at clusters of these cells around the atrioventricular node. They found that — like other nonmuscle cells in the heart — macrophages are electrically coupled to the cardiomyocytes. They confirmed in vitro that cardiac macrophages change the electrical properties of coupled cardiomyocytes and determined that the cell-surface protein connexin 43 (which allows ion exchange between cells) is critical to this modulation.

Do macrophages that reside in the heart directly modulate the electrical properties of cardiomyocytes in vivo? Yes. Hulsmans et al. went on to find that in the mouse, macrophage-specific genetic ablation of connexin 43 delayed conduction through the atrioventricular node, whereas body-wide depletion of the macrophage population blocked conduction and caused arrhythmia. The researchers then engineered a mouse with macrophages that expressed a tweaked version of a cation channel, which could be "turned on" through exposure to light and which would increase cellular ionic permeability. When stimulated in isolated hearts, the engineered macrophages became depolarized, resulting in improved conduction in the atrioventricular node. Taken together, these observations show how the membrane potential of cardiac macrophages modulates electrically coupled heart-muscle cells.

The cardioprotective role of cardiac macrophages as guardians of the heart may extend beyond modulating the electrophysiological properties of coupled cardiomyocytes (Fig. 1). The perivascular location of cardiac macrophages

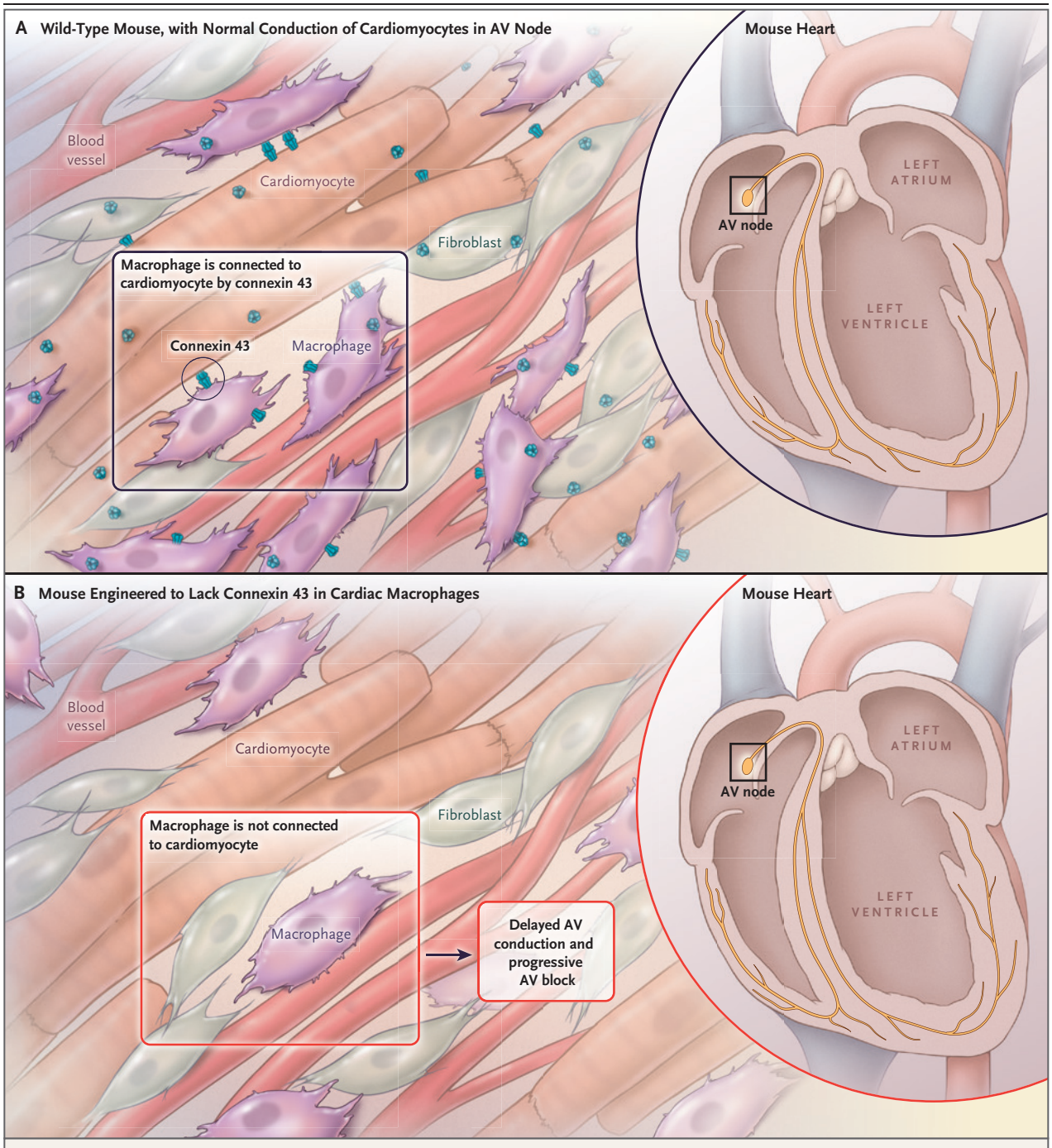

Figure 1. The Role of Macrophages in Helping the Heart to Keep the Beat.

Hulsmans et al.[2] recently reported a series of experiments in mice that implicate modulation of the depolarization of cardiomyocytes by macrophages. They showed that connexin 43, a molecule that makes up gap junctions, connects macrophages to myocytes (Panel A) and that macrophage-specific ablation of connexin 43 results in delayed atrioventricular (AV) conduction and progressive AV block (Panel B). It is plausible that the connections of macrophages to other cell types, such as fibroblasts and the epithelial cells of blood vessels, serve to link cardiac conduction to other essential functions of the heart.

renders them uniquely positioned to interpret systemic signals in the bloodstream.[4] They would therefore seem well positioned to facilitate a rapid cardiac response to injury. In other tissues, interaction of macrophages with activated fibroblasts and the matrix that they produce is indispensable for the promotion of a constructive remodeling response after injury. Their modulation of conduction in specialized cardiac fibroblasts[5] to which they are electrically coupled may serve to link the changing heart rate to structural requirements.

It is temping to hypothesize that targeting macrophage modulation of cardiac conduction may be a more effective means by which to tackle arrhythmias than targeting the cardiomyocytes themselves. High on the list of "next steps" is to determine whether macrophage dysfunction results in atrioventricular block in humans, the cause of which is often unknown. Another possible scenario is one in which macrophages contribute to the arrhythmic complications of diabetes and infectious disease, contexts in which their inflammatory responses could interfere with their role in modulating conduction of the cardiomyocyte. Age-related changes in macrophage populations may render the geriatric heart more susceptible to arrhythmias or other cardiovascular disease. If defects in macrophage function are linked to these clinical conditions, reprogramming macrophages in situ with antibodies could be a viable form of immunotherapy that could be applied to ensure a steady heartbeat in patients with arrhythmia.

Disclosure forms provided by the author are available at NEJM.org.

From the Jackson Laboratory, Bar Harbor, ME, and Imperial College London, London.

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