CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Cardiac Repair after Myocardial Infarction

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Heart failure, a leading cause of death in industrialized nations, is caused by damage to or loss of contracting cardiac muscle cells known as cardiomyocytes. Wei and colleagues[1] recently described a strategy to restore these cells. They reported that increasing the levels of follistatin-like 1 (FSTL1) derived from the epicardium, which are depleted after myocardial infarction, promotes myocardial repair and regeneration by stimulating the proliferative capacity of existing cardiomyocytes (Fig. 1).

Normally, cardiomyocytes in adult mammals

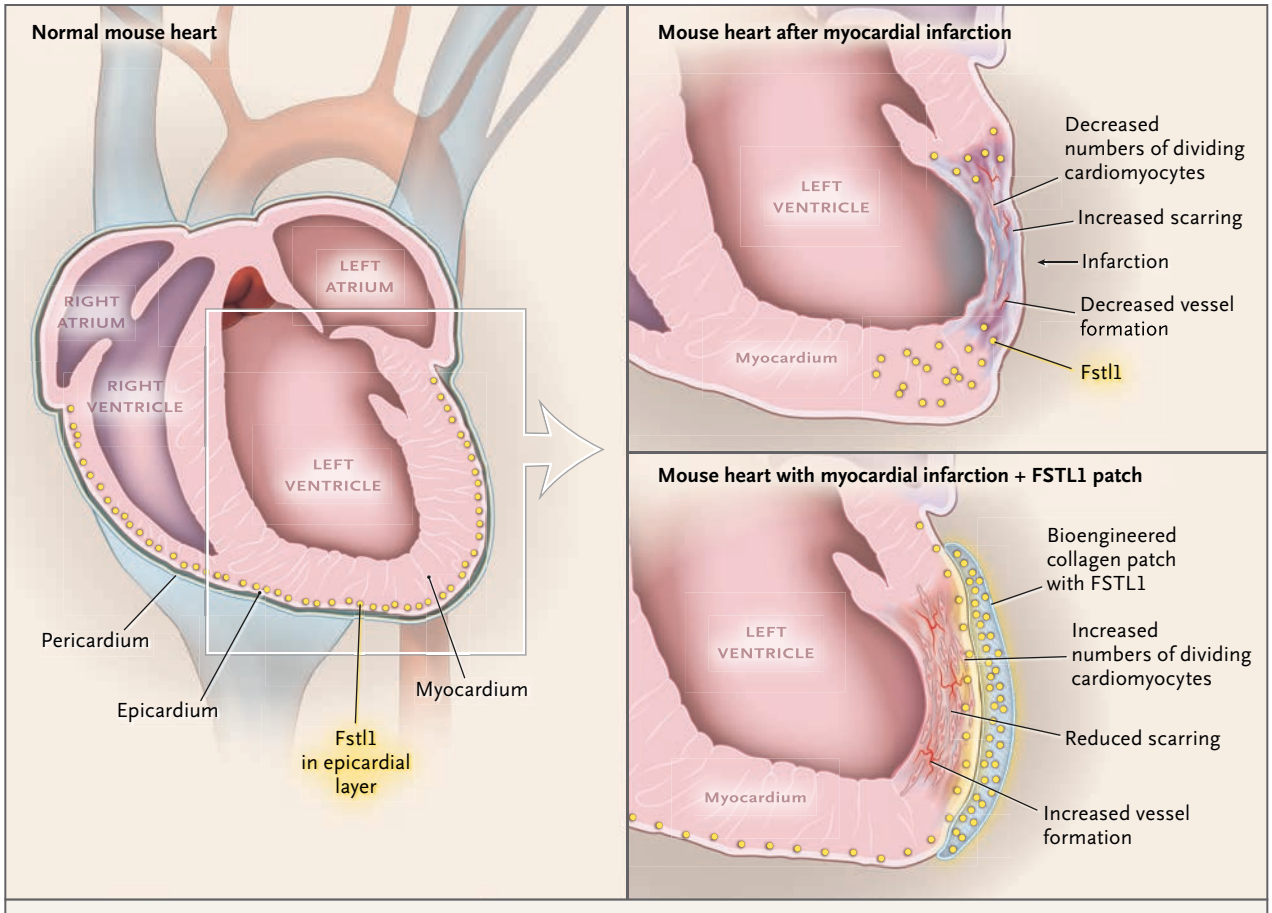

Figure 1. The Folly of Myocardial Infarction.

Myocardial infarction causes the loss of viable cardiomyocytes, which leads to a loss of heart function. Wei et al. found that cells located at the epicardial surface of the heart normally express a factor called follistatin-like 1 (Fstl1), which is lost in response to an infarction. Restoration of this loss with the use of a bioengineered collagen patch loaded with purified human FSTL1 improved survival and cardiac function in mice after myocardial infarction.

proliferate at an extremely low rate (approximately 1% of cardiomyocytes per year undergo cell division). During ischemic injury — for example, a myocardial infarction — the rate of cardiomyocyte division increases, but it remains insufficient to compensate for the loss of cardiomyocytes, and tissue damage results. The scarred area of tissue gradually expands, and the expansion (termed remodeling) ultimately leads to heart failure.[2] Therapeutic approaches directed at restoring the lost myocardium with the use of adult stem cells or pluripotent stem cells have garnered interest, but the ineffective homing of these cells to the heart and their lack of differentiation into cardiomyocytes have led to disappointing results. Efforts to stimulate endogenous mechanisms of regeneration represent an attractive alternative therapeutic strategy.

It has been established that epicardial-derived signals have a major effect on cardiac regeneration. Among these signals are secreted factors known as cardiokines, which effect cardiac repair in an autocrine or paracrine fashion.[3] FSTL1 is a glycoprotein cardiokine and a member of the follistatin family of proteins. It is normally expressed in cardiomyocytes, vascular cells, and fibroblasts, and its expression is increased during ischemic injury and heart failure. It binds to and inhibits members of the transforming growth factor β superfamily of proteins.

It was previously shown that increasing the level of FSTL1 in the heart induces a cardioprotective effect against ischemic injury, because FSTL1 increases cardiomyocyte survival and stimulates angiogenesis (blood-vessel formation) through the phosphorylation of a factor called AKT, without increasing the formation of new cardiomyocytes.[4,5] However, the study by Wei et al. showed that cells located at the epicardial surface of the mouse heart express and secrete Fstl1, which can subsequently trigger an increase in the rate of cardiomyocyte division. Because epicardial Fstl1 expression disappears from the infarcted area in response to ischemic damage, the authors hypothesized that reconstitution of epicardial Fstl1 would restore function by increasing the number of cardiomyocytes. When a bioengineered collagen patch loaded with purified human FSTL1 was sutured to the epicardial surface of the infarcted heart of mice, it resulted in improved survival and cardiac function (Fig. 1). These effects coincided with a reduction in scarring, an increase in the formation of new vessels, and an increase in the number of dividing cardiomyocytes, as compared with hearts without a collagen patch.[1] These data indicate that epicardial delivery of FSTL1 can partially restore injured heart tissue after myocardial infarction by enhancing multiple aspects of cardiac regeneration and repair.

The epicardial origin of Fstl1 appears key for inducing this cardioprotective effect. Neither the naturally occurring increase in Fstl1 in other cell types in response to myocardial infarction nor the transgenic overexpression of Fstl1 in cardiomyocytes had a similar effect on heart regeneration. A potential explanation for this phenomenon that is proposed by the authors is cell-type–dependent posttranslational glycosylation. The glycosylation status, which is determined by the type and quantity of sugar residues attached to Fstl1, differs between epicardial-derived and cardiomyocyte-derived Fstl1, which might affect protein function.

Biomaterial-based strategies are emerging for the treatment of heart injuries, either as standalone therapies or in combination with regeneration-inducing signals or cells. After myocardial infarction, these biomaterials can strengthen the damaged tissue and prevent pathologic remodeling and progression to heart failure. In addition to providing biomechanical support, these patches can be loaded with regeneration-inducing factors to promote the regeneration of myocardial tissue in infarcted hearts. Wei and colleagues used a collagen patch that delivers FSTL1 and then degrades over time. Although the FSTL1-loaded patch has beneficial effects on fibrosis, angiogenesis, and cardiomyocyte division, as compared with the patch alone, the biomechanical support provided by the patch itself has some benefit after infarction injury, perhaps by rendering the site more amenable to regeneration.

Further insights into the down-regulation of epicardial Fstl1 in response to myocardial infarction, the regulation of Fstl1 in cardiac tissue from species that can regenerate their hearts (like amphibians), or the cell-specific glycosylation state of Fstl1 may aid in the interpretation of the results described by Wei et al. Meanwhile, their report, which also includes a description of

preliminary data obtained on the delivery of FSTL1 in a porcine model of myocardial infarction, points to an intriguing opportunity.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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