Pericardial adhesions and cardiac surgeons' nightmares

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Pericardial layers.

Central Message

Understanding the molecular components of endogenous boundary lubricants at organ interfaces, such as proteoglycan 4, offers new and exciting possibilities to reduce risk of redo cardiac operations.

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Nothing stirs up bad memories for cardiac surgeons like redo operations that are complicated by sternal reentry problems. These problems happen around 10% of the time in redo cardiac procedures.¹ Many of these problems revolve around pericardial adhesions, and the list of interventions aimed at reducing pericardial adhesions is legion. Synthetic materials (treated bovine pericardium, polytetrafluoroethylene patches, etc) to cover the heart after initial operation were probably the first things used to facilitate sternal reentry, only to be followed by notes of caution.^{2,3}

All sorts of chemicals, natural products, and synthetic or autologous tissues have been offered up as initial operative alternatives to facilitate sternal reentry. Modalities as disparate as autologous pericardial flaps,⁴ alcohol consumption,⁵ instillation of various drugs into the pericardium at sternal closure,⁶ nanostructured synthetic films impregnated with steroids,⁷ acellular tissue impregnated with angiogenic agents,⁸ and temperature-sensitive polymer films⁹ have all been suggested as means of limiting pericardial adhesions and facilitating sternal reentry. Perhaps the large number of putative remedies to facilitate sternal reentry is the best evidence that there are no good solutions to limit adhesions and reduce the risks associated with sternal reentry. The missing piece in most of these studies is an examination of the molecular components of postoperative adhesion formation and identification of molecular targets that could reduce these adhesions.

The article by Fedak and coauthors¹⁰ in this issue of the *Journal* presents an analysis of the impact of a mucinlike glycoprotein, glycoprotein 4 (PRG4), on pericardial adhesion formation. Fedak and coauthors¹⁰ characterized PRG4 expression in human pericardium and examined its effects both in vitro on human myofibroblast activity and in vivo on adhesion formation in a pig model. The importance of this research revolves around myofibroblasts, because these cells can secrete collagen and initiate the progression to adhesion formation.¹¹ The experiments of Fedak and coauthors¹⁰ suggest that the loss of PRG4 in pericardial fluid can trigger pericardial adhesion formation, a condition

that depends on myofibroblast activation. Perhaps the most intriguing aspect of the article by Fedak and coauthors¹⁰ is the finding that restoration of PRG4 into pericardial fluid may prevent adhesion formation. They found that PRG4 is expressed by human pericardial mesothelial cells. Recombinant human PRG4 prevented cardiac myofibroblast attachment to pericardium and limited myofibroblast activity. In particular, their in vivo model identified PRG4-associated attenuation of collagen formation from myofibroblast cells. The experiments of Fedak and co-workers¹⁰ have enormous implications for redo cardiac operations. The fact that they considered molecular and biochemical components of pericardial function sets their work apart from most other published putative solutions to limit pericardial adhesions.

PRG4 (or lubricin) is a proteoglycan that is encoded by the *PRG4* gene. It acts as a boundary lubricant and was first isolated in articular cartilage. The same group writing here as Fedak and coauthors¹⁰ was one of the first groups to identify and isolate PRG4 in pericardial fluid and to identify its role in limiting pericardial adhesions.¹² Because of their early work,¹¹ Fedak and coauthors¹⁰ hypothesize that PRG4 is an important component of myocardial adhesion attachment of the heart to the parietal pericardium. There are many details of this interaction that remain to be worked out. The exact target of PRG4 is uncertain. It is likely that PRG4 interacts with myofibroblasts in some way, and the nature of this interaction likely involves receptors on target

cells. Discovering the exact nature of the cellular target for PRG4 is a logical next step for this group. There are intriguing possibilities that include the use of knockout mice (<https://www.jax.org/strain/025737>) and studies of patients with inherited absence of the *PRG4* gene (<http://www.genecards.org/cgi-bin/carddisp.pl?gene=PRG4>). There may be other molecular approaches to preservation of mesothelial cells and limitation of adhesions, so more work needs to be done. Nonetheless, this work of Fedak and coauthors¹⁰ advances the process of dissecting the molecular components of pericardial adhesion formation. The results of this ongoing work could provide patients with safer redo cardiac operations and mean less misery for cardiac surgeons who must deal with these difficult, high-risk procedures.

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