A new molecular target for blunting organ fibrosis. Focus on “Secreted Frizzled-related protein 2 as a target in antifibrotic therapeutic intervention”

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Fibrosis is a pathology associated with failure of many different organs, including the heart, lung, kidney, liver, and the vasculature. Fibrosis results from wound healing (and in some cases developmental) processes that become prolonged or dysregulated. Following tissue damage, inflammation at the site of injury produces a gush of cytokines that signal subsequent myofibroblast differentiation and cell proliferation, wound closure and neovascularization, and then tissue matrix deposition that form a fibrous scar. The final step, which accompanies the return to normal tissue function, involves senescence or death of the activated myofibroblasts, which mediate the extracellular matrix (ECM) production, to return to normal organ function (7). Prolonged activation (i.e., inflammation and cytokine production) of these wound healing processes or loss of negative feedback loops that terminate these processes likely underlie the development of pathological fibrosis.

Many studies have investigated the roles of hormones and cytokines in promoting or inhibiting fibrosis (3). Beyond efforts to minimize the insults that produce tissue damage that leads to fibrotic processes, progress has been limited in the development of therapies to slow or reverse these processes. One might be tempted to argue that the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, and aldosterone antagonists, which limit organ damage but also reduce activation of fibroblasts, has attenuated cardiac (and perhaps renal) fibrosis in various cardiovascular conditions. However, use of these drugs for several decades has not ended cardiac fibrosis.

Efforts to treat cardiac fibrosis began with the realization that one needs to target fibroblasts (2). Many investigators focused on fibrogenic stimuli, particularly transforming growth factor-β (TGF-β), angiotensin II, aldosterone, and endothelin-1, which stimulate myofibroblast differentiation (9). Much has been learned about their molecular pathways, and the processes of fibrosis, but no therapies have resulted. Other efforts studied signals that reduce fibrosis, including interleukin-10, interferon-γ, peroxisome proliferator-activated receptor-γ (PPAR-γ), and cAMP signaling (3, 10). Again no druggable targets that lack on-target or off-target effects on basic cellular processes elsewhere in the body have emerged. Certain transcriptional regulators (Sp1, Egr-1, SMADs, Fli-1, p53, p300, and Klotho) and histone deacetylases also appear to contribute to the fibrotic process. Ghosh et al. (3) recently reviewed these and other molecular pathways that regulate fibrosis (3).

However, a novel mediator of fibrosis has recently emerged: secreted Frizzled-related protein 2 (sFRP2), an inhibitor of Wnt signaling. sFRP2 contains a cysteine-rich domain that has homology to the binding site of Frizzled proteins, receptors for Wnt (1). Due to the role of Wnt signaling in embryonic development, carcinogenesis, and diabetes, sFRPs are being actively investigated. sFRP2 was first reported to be profibrotic by Kobayashi et al. (8) based on their findings with sFRP2-null mice, which develop less cardiac fibrosis following myocardial infarction. Soon after, a report by He et al. (5) threw these findings into question by showing that administration of recombinant sFRP2 reduced fibrosis in the postinfarct heart (5). Clearly, this discrepancy needed to be resolved.

In this issue of American Journal of Physiology-Cell Physiology, Mastri et al. (11) show that systemic administration of an sFRP2 antibody to cardiomyopathic hamsters reduces fibrosis and maintains left ventricular ejection fraction (11). These findings support the idea that sFRP2 is a profibrotic mediator. How does sFRP2 work and what underlies the conflicting reports regarding its role in fibrosis? Kobayashi et al. (8) and Mastri et al. (11) found that sFRP2 enhances the procollagen C proteinase activity of mammalian bone morphogenetic protein 1 (BMP1, and likely other Tolloid metalloproteinases), leading to increased procollagen processing and collagen deposition (8, 11) (Fig. 1). This action is independent of the effects on Wnt signaling. On the other hand, He et al. (5) injected recombinant sFRP2 into an infarcted area two days after coronary artery ligation. These authors observed reduced fibrosis, which they related to a reduction in BMP1 activity. The discrepancy between studies appears to be that sFRP2 has biphasic effects on Wnt signaling and BMP1 activity (11, 12); thus a case of different doses determining the effect. A more detailed and complete analysis is needed to understand the concentration-dependency of sFRP2 actions at various effectors.

Mastri et al. (11) make important inroads by using a genetic model of cardiovascular disease rather than the surgical models used previously. They also demonstrate that systemic therapy can alter the course of cardiac fibrosis and improve contractile function. Whether an antibody or other approaches, such as a small molecule inhibitor of sFRP2, are developed, the concept that sFRP2 can be targeted therapeutically is clear, although the safety and efficacy of this approach in humans remain to be demonstrated.

It is too early to ordain sFRP2 as a key target for treating fibrosis. Several critical pieces of information are missing that will require more study. It is clear that sFRP2 (and Bmp1) are upregulated in cardiac fibrosis, but the source of sFRP2 production is not known. Attenuating its production or release may be a more effective therapeutic approach so understanding its formation is essential. The signal(s) that stimulate sFRP2 production and release are also not known but are important to define since the same stimulus might trigger other maladaptive processes or have commonality with fibrotic processes in other organs. Another unknown is if sFRP2 plays varying, or contrasting, roles at different stages of fibrosis or how it regulates...
the complex components of ECM dynamics (4). Given that sFRP2 has actions on Wnt signaling and Bmp1 activity, as well as biphasic responses depending on the concentration, it may play different roles in regulating the disparate aspects of the fibrotic process. Finally, the role of sFRP2 in fibrosis of other organs is not known and needs to be studied so as to expand understanding and the clinical applicability of sFRP2 (13).

As understanding of the fibrotic process in a number of organs has progressed, it has become clear that common mechanisms exist despite the fact that the stimuli that initiate damage in different organs are highly diverse (14). This leads to the hope that scientists with an interest in fibrosis in different organs might collaborate to identify “general” approaches to treat fibrosis. Ultimately, an effective treatment for fibrosis will likely entail the targeting of several different molecules; however, the studies by Mastri et al. (11) provide a strong rationale to add sFRP2 to the list of candidates.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

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REFERENCES


Fig. 1. Bone morphogenetic protein 1 (Bmp1)/Tolloid-like proteinases process procollagen into extracellular matrix (ECM). Bmp1 can also activate transforming growth factor-β (TGF-β) by cleaving latent binding proteins that are then further cleaved by matrix metalloproteinases (MMPs) to release active cytokine. TGF-β, signaling via its receptor and Smads, can upregulate expression of BMP1, procollagen, MMPs, and TGF-β itself, forming a feed-forward loop. Secreted Frizzled-related protein 2 (sFRP2) stimulates Bmp1 activity to initiate this cycle, so an antibody to block sFRP2 binding to Bmp1 can reign in dysregulated extracellular matrix production and reduce fibrosis (6).