FGF Induces Hypertrophy and Angiogenesis in Hibernating Myocardium

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For several years there has been considerable interest in stimulating angiogenesis by a variety of growth factors, including the family of fibroblast growth factors (FGF). FGF-5 is a protooncogene known to stimulate cell growth and proliferation in multiple cell types, including cancer. The cardiac myocyte can also produce different isoforms of FGFs, eg, it has been shown that the expression of basic FGF increases in hibernating myocardium, which was the disease state of interest in the current study published in Circulation Research. The most commonly cited effect of FGF-5 in the heart is to promote angiogenesis. Several studies have shown that gene transfer of FGF-5 in the heart increases vessel formation and regional blood flow. This effect is mediated by a production of FGF-5 by the cardiac myocytes, followed by its release in the extracellular space. In addition, FGF-5 can function as an autocrine/paracrine mechanism of cardiac cell growth and as a cytoprotective mechanism against irreversible ischemic damage.

Indeed, most of the prior interest on the role of FGF has been in the field of angiogenesis, where swine models of chronic ischemia have been shown to increase blood flow, presumably through angiogenesis. In contrast, the article by Suzuki et al. concluded that gene therapy with FGF improved function in their swine model of hibernating myocardium, but the mechanism of the salutary effect involved "rather than angiogenesis, stimulation of hypertrophy and re-entry of a small number of myocytes into the mitotic phase of the cell cycle..." The observations are conceptually important in that the focus of prior studies on treating chronically ischemic myocardium has been on angiogenesis, and not directed at improving function through increasing myocardial mass, either by hypertrophy, myocyte proliferation, or other yet to be determined mechanisms. The latter concept of stimulating the cell cycle, is particularly appealing with the current interest in stem cell therapy for myocardial infarction and heart failure. The current article suggests that this type of therapy could also be useful for hibernating myocardium.

There is some prior basis supporting the concept that FGF can induce cellular proliferation. However, those studies were generally not conducted in adult myocytes, which many believe are terminally differentiated. The current study supports the position, proposed most compellingly by the Anversa laboratory, that it is possible to observe myocyte proliferation, under the right conditions. There are several mechanisms by which FGF could stimulate myocyte proliferation. FGF induces myocyte proliferation in fetal and neonatal cardiac myocytes. FGF produced locally in the endocardium and epicardium plays a critical role in mediating myocardial proliferation during midgestation. FGF also causes increases in DNA synthesis as well binucleation in adult cardiac myocytes. The data in the Suzuki study for new myocytes was supported by Ki-67 labeling studies, but was less compelling when comparing the increases in myocyte size and the decrease in myocyte nuclear density. The latter fell by roughly 40%, whereas cell volume only increased 30%. If myocytes had proliferated appreciably, then these numbers should have been reversed.

There is also additional evidence that FGF may stimulate cell growth. FGF is released from cardiac myocytes by mechanical loading as well as contraction-induced wounding, and in turn induces hypertrophy of neighboring myocytes. Systemic application of FGF following acute myocardial infarction induces functional improvement with hypertrophy in surviving myocardium in rats. Mice lacking FGF-2 exhibit dilated cardiomyopathy and impaired hypertrophic responses to angiotensin II, suggesting the importance of endogenous FGF in mediating cardiac myocyte growth. In addition, FGF is an important factor to facilitate muscle regeneration. FGF-6 plays an important role in mediating skeletal muscle regeneration possibly by stimulating satellite cells. FGF not only induces proliferation of myoblasts but also directs differentiation of progenitor cells into cardiac lineages. Pretreatment of myoblast culture cells with FGF increases the efficacy of their implantation.

In contrast, this finding that gene therapy with FGF induced myocyte hypertrophy was based solidly on left ventricular (LV)/body weight measurements as well as myocyte size. The authors proposed that FGF could be a novel therapy for hibernating myocardium, because it upregulated LV function. However, not all the data in their article support the conclusion that LV function is improved following the FGF therapy. In patients with hibernating myocardium with coronary artery bypass therapy, regional function is improved in the areas of the heart, which are chronically ischemic and hibernating. Importantly, this enhanced regional function was...
associated with an improvement in global LV function, eg, LV ejection fraction or fractional shortening.\textsuperscript{24–26} In the present study, a major increase in LV function occurred in the hibernating myocardium, as reflected by an almost doubling of wall thickening. The question of why such a marked improvement in regional function is not manifested by enhanced global LV function arises. Because LV fractional shortening did not improve with FGF therapy in this article,\textsuperscript{3} it is difficult to conclude that a salutary effect on LV function was observed. Their findings contrast sharply, not only with studies in patients with hibernating myocardium treated with bypass, but also with those of Simons’ laboratory where FGF showed significant increases in fractional shortening as well as wall thickening in their ischemic swine model.\textsuperscript{8–10}

More curious is why their catecholamine stimulation with epinephrine, which improved function in the remote area and in the initial hibernating myocardium (supplemental Table 2); as it should), no longer improved regional LV function in hibernating myocardium after myocyte hypertrophy and potentially proliferation had enhanced baseline wall thickening. Is it conceivable that the hypertrophied or new myocytes in the hibernating zone were not functional? Or is it possible that the blood flow response to epinephrine differed before and after FGF? Apparently the supplemental data do not support the latter hypothesis in that blood flow to hibernating myocardium in response to epinephrine responded similarly before and after FGF therapy, but regional LV function increased before, but not after FGF therapy. If therapy for hibernating myocardium, as in this study, or in cases of stem cell therapy for ischemic heart disease, results in new myocytes or larger myocytes, which cannot increase their function in response to catecholamines or to exercise, then the success of this therapy will be less than optimal. Suzuki et al, also makes a major point of their disappointment with the amount of angiogenesis observed with FGF. Again, their data contrast sharply with those of Simons’ laboratory and colleagues,\textsuperscript{8–10} demonstrating increased angiogenesis in another swine model of chronic ischemia. One limitation of the current study\textsuperscript{1} was that the duration of therapy was only 2 weeks between gene injection and assessment of collaterals. First of all, some time must elapse between gene delivery and sufficient FGF protein generated to stimulate angiogenesis. Secondly, Schaper’s laboratory has shown that collaterals in swine models are most pronounced 4 to 8 weeks after the inciting stimulus.\textsuperscript{27,28} Perhaps, if longer time had elapsed, angiogenesis would have been more pronounced.

However, it is also possible to take the position that significant angiogenesis did occur in the present study.\textsuperscript{3} It is well known that angiogenesis occurs in LV hypertrophy, where LV mass increases and blood flow per gram of myocardium remains constant.\textsuperscript{29,30} Quantitation of capillary and resistance vessels demonstrated that capillary and resistance vessel densities were maintained in LV hypertrophy, whereas baseline blood flow remained at control levels,\textsuperscript{29,30} as was observed in the current study. Because cell volume increased \textasciitilde30%, coupled with formation of additional myocytes, for blood flow to remain at baseline values, when normalized to a given weight of myocardium, indicates that angiogenesis must have occurred. Of course, baseline levels could be maintained by vasodilation. This explanation is not likely in view of the normal maximal vasodilator response to adenosine. Finally, it would have been informative to examine the effects of a temporary, complete coronary occlusion on regional myocardial blood flow before and after FGF therapy to determine whether collateral vessels had formed and exerted a functional effect, ie, whether the blood flow during temporary disruption of antegrade flow was improved following FGF therapy.

Thus, it appears that FGF could be a novel therapeutic approach, which results in myocyte hypertrophy, potentially new myocytes, and a corresponding increase in angiogenesis. This interesting study\textsuperscript{1} may provide further understanding for why so many clinical trials with growth factors have failed,\textsuperscript{31} and suggest new directions to pursue to optimize this therapy.

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