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Review

Janus-like role of fibroblast growth factor 2 in arteriosclerotic coronary artery disease: Atherogenesis and angiogenesis

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ABSTRACT

Angiogenic stimulation is a promising new strategy for treating patients with arteriosclerotic coronary artery disease. This strategy aims to ameliorate cardiac function by improving myocardial perfusion and lowering the risk of myocardial infarction. However, angiogenesis may contribute to the growth of atherosclerotic lesions. Atherogenesis is also a potential side effect of angiogenic therapy. Early clinical trials were performed using fibroblast growth factor 2 (FGF2) protein, which enhances the formation of new collateral vessels to reduce ischaemic symptoms. Conversely, angiogenic stimulation by FGF2 is a dilemma because it could cause negative angiogenic effects, such as atherosclerosis. Thus far, clinical trials in patients with recombinant FGF2 protein therapy have not yet yielded undisputable beneficial effects. Future trials should determine whether an improvement can be obtained in patients with coronary artery disease using a combination of FGF2 and other growth factors or a combination of the FGF2 gene and stem cell therapy. This review summarises the multiple roles of FGF2 in the progression of atherosclerosis, its effect on pro-angiogenesis and improvement of cardiac function in coronary artery disease, and the potentially unfavourable effect of angiogenesis on the prevention and treatment of atherogenesis.

Contents

1. Introduction

Atherosclerosis, a chronic disease that affects large- and medium-sized arteries, is characterised by smooth muscle cell proliferation, endothelial dysfunction, lipid and macrophage accumulation [1].

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This disease is also the most frequent cause of coronary artery disease (CAD) [2]. CAD is a major cause of ischaemic heart disease (IHD), which is one of the leading causes of death and morbidity in western societies [3]. Early treatment by revascularisation strategies, such as coronary artery bypass graft (CABG) surgery, percutaneous coronary intervention and drug therapy, significantly reduces cardiac mortality [4]. Despite the improved scope of effective treatments, several patients with CAD still experience extreme chest pain daily and have low quality of life.

Treatment strategies that aim to reduce myocardial injury and ameliorate blood supply to the myocardium in CAD are still barriers in clinical research. Angiogenic induction using fibroblast growth factor 2 (FGF2) is a promising new treatment method for atherosclerosis-related diseases, especially for patients with severe CAD. FGF2 regulates numerous cellular functions in multiple cell types, including cell proliferation, differentiation, survival, adhesion and migration. FGF2 also regulates processes such as vasculogenesis, angiogenesis and blood vessel remodelling [5]. Nevertheless, the results from animal experiments and clinical studies in patients with IHD are incongruent. The results of initial studies on FGF2 are encouraging, as shown by clinical improvement and evidence of angiogenesis. However, the initial high efficacy of FGF2 could not be confirmed in subsequent larger trials. Whether FGF2 can aggravate atherogenesis by promoting angiogenesis, which lowers the therapeutic effect, remains uncertain. This article aims to determine the underlying roles of FGF2 in the progression of atherosclerosis and to identify the effects of FGF2 in angiogenesis and in improving cardiac function in CAD. The unfavourable effects on FGF2-induced atherogenesis and the therapeutic potential of FGF2 for IHD intervention are also discussed.

2. FGF2 and receptors

The FGF family includes 23 members, of which 18 are FGF receptor (FGFR) ligands. FGF2 is widely expressed and exists in 18 kDa, low-molecular-weight and 20 kDa–34 kDa, high-molecular-weight isoforms. FGF2 lacks a signal peptide but is believed to be released by damaged cells or through pathways that are independent of the endoplasmic reticulum–Golgi route. FGF2 receptors are single-pass transmembrane proteins that consist of an extracellular part that binds FGF ligands, a transmembrane domain and an intracellular tyrosine kinase domain that transfers the signal to the cell interior. The extracellular part is composed of three immunoglobulin (Ig)-like domains (I–III) with an acidic, serine-rich region between domains I and II, which is called the acid box. Together with the acid box, the first Ig-like domain participates in receptor autoinhibition [6]. Domains II and III constitute the FGF ligand-binding site. Heparan sulphate proteoglycans (HSPGs) are critical components of the FGF signalling system in vitro and in vivo [7]. HSPGs protect ligands from degradation and promote the binding of FGF2 to the receptors, causing the dimerisation of a ternary complex consisting of FGF2, FGFRs and heparan sulphate [8,9].

3. Role of FGF2 in atherogenesis

FGF2 and its receptors have a dual role in the cardiovascular system because their expression in a normal vessel wall is beneficial for vascular homeostasis, vascular protection and endothelial survival. In atherosclerotic lesions, FGF2 and its receptors contribute to inflammatory processes, intimal thickening and intra-plaque angiogenesis. Therefore, the risk of vulnerable plaque formation, plaque rupture and thrombus formation is increased. Conversely, FGF2 could lead to collateral vessel growth, which improves blood circulation into the hypoxic or ischaemic areas of the heart in CAD. The potential pathophysiological roles of FGF2 in atherosclerotic lesions are summarised in Table 1.

3.1. Expression of FGF2 in atherosclerotic lesions

In human atheromatous plaques, FGF2 is produced by endothelial cells (ECs), vascular smooth muscle cells (VSMCs) and macrophages [10]. FGFR1, FGFR2 and FGFR3 are released by intimal smooth muscle cells. Given that FGFR1 and FGFR2 are highly expressed in atheromatous lesions, these receptors are related to intimal macrophage foam cells and microvessels [11]. FGF2 has high affinity for FGFR1 and FGFR2 [12], suggesting that FGF2 and FGFRs could be involved in the development of atheromatous lesions.

3.2. Mitogenic effects of FGF2 on VSMCs

VSMCs have an indispensable role in the atherosclerosis and restenosis of arteries, the development and progression of atherosclerotic lesions associated with the proliferation of VSMCs and their migration from the arterial tunica media to the intima [13]. FGF2 and FGFRs expressed in VSMCs are upregulated during vascular injury and are involved in atherosclerotic plaque formation [14,15]. In human primary vascular smooth muscle cells, FGF2 and FGFRs increase the expression level of p53-induced thrombospondin (TSP)-1, which is a VSMC growth and motility factor that stimulates the proliferation and migration of VSMCs, further providing a molecular mechanism for FGF2 pro-atherogenic activity [16]. The presence of matrix metalloproteinases (MMPs) in plaques [17] may lead to extracellular matrix degradation, including collagens I, III, IV, V and XI; gelatins I and V; and elastin. Thus, VSMC migration is increased. Kenagy et al. [18] reported that MMP-2 and MMP-9 are involved in regulating the stimulatory effect of FGF2 in the migration of smooth muscle cell out

Table 1
Potential pathophysiological role of FGF2 in atherosclerotic lesions.

Target cells/model	Potential pathophysiological consequences	Signalling molecules explored	Ref.
Femoral artery cuff injury mice model	VSMC proliferation and neointima formation	TRAIL	[19]
Human primary vascular smooth muscle cells	VSMC proliferation and migration	Thrombospondin-1	[16]
Rat aortic smooth muscle cells	Osteogenic differentiation	Runx2	[26]
Human carotid atherosclerotic plaques	Contribute to the vulnerability of atherosclerotic plaques	MMP-9 and iNOS	[45]
	Carotid plaque instability	MMP-2 and -9	[36]
ApoE deficient mice	Protective effects in early atherosclerosis	Fibroblast growth factor receptor signalling	[34]
	Accelerates plaque progression	Vasa vasorum	[40]
FGF2 deficient microvascular endothelial cells	Involved in vascular remodelling	MMP-3	[90]
Tie2-FGFR2-Tg/ApoE deficient mice	Accelerates atherosclerosis	FGFR2 signalling	[33]
Rabbit atherosclerotic model	Improves endothelial function and decrease macrophage content	Unknown	[31]

VSMCs: vascular smooth muscle cells; TRAIL: tumour necrosis factor-related apoptosis-inducing ligand; Runx2: osteoblastic transcription factor; iNOS: induced nitric oxide synthase; MMP: metalloproteinase; Tie2-FGFR2-Tg/ApoE deficient mice: endothelial cell (EC)-targeted constitutively active FGFR2-overexpressing and apolipoprotein E (ApoE)-deficient mice.