

심혈관질환에서의 유전자치료

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Gene Therapy for Cardiovascular Disease

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서 론

가 가

carrier

delivery system

가

, gene delivery

가 (FH)

심혈관질환에서의 유전자치료를 위한 치료유전자

10

가 , vector ,
가

FH ex vivo

(angiogenesis neorevascularization)

가

2

가

가 (Table 1).¹⁻⁵⁾

: , 120 - 752 134

혈관 재협착의 억제

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Table 1. Cardiovascular targets for gene therapy

Disease	Examples of target gene
Familial hypercholesterolemia	LDL receptor
Critical myocardial/hindlimb ischemia	Vascular endothelial growth factors ; VEGF, FGF, etc
Restenosis after Angioplasty	Suicide gene Cell cycle inhibitors Nitric oxide synthase Angiotensin II type 2 receptor Hirudin
Myocardial Infarction	Tissue inhibitors of metalloproteinase Antioxidant genes Heat shock proteins
Transplant rejection	Transforming growth factor-
Hypertension	Kallikrein
Thrombosis	Tissue plasminogen activator Cyclooxygenase Thrombomodulin

LDL : low density lipoprotein (Adapted from Lafont et al.²)

Table 2. Gene therapy to limit the restenosis after angioplasty

Strategy	Target genes
Antiproliferative strategies	HSV-tk, Rb, p53, p21, H-ras, Cytosine deaminase
Inhibition of SMC migration	TIMP-1, eNOS
Inhibition of thrombosis	Cyclooxygenase, hirudin
Acceleration of Endothelialization	VEGF
Pleiotropic effector molecules	eNOS, C-type natriuretic peptide

HSV-tk : herpes simplex virus-thymidine kinase, Rb : retinoblastoma gene (Adapted from Kullo et al.⁸)

25~30%

remodelling^{6,7)}

(Table 2).⁸⁾

oligodeoxynucleotide

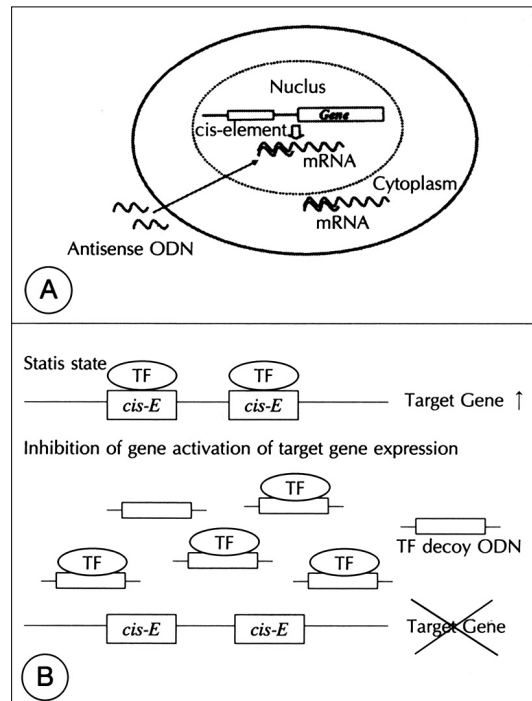


Fig. 1. Gene therapy with oligodeoxynucleotides (ODNs). A : Antisense oligodeoxynucleotide strategy. The antisense ODNs bind to mRNA, resulting in the inhibition of translation. B : Decoy strategy. In statis state, the transcription factor (TF) is bound to cis element, resulting in continuous activation of target gene expression. The TF decoy ODNs bind to TF and inhibit transactivation of TF-promoting target gene expression.

antisense oligodeoxynucleotide strategy가 (Fig. 1).⁹⁾¹⁰⁾ Antisense oligodeoxy-nucleotide c - myb, c - myc, cdc - 2 kinase, PCNA mRNA translation

specificity, oligodeoxynucleotide degradation¹¹⁻¹³⁾ Decoy strategy E2F, NF - B transcription factor (TF) oligodeoxynucleotide TF TF

saphenous vein graft ex vivo¹⁰⁾¹⁴⁾

허혈성 조직에서의 치료적 신생혈관조성

tumor growth, ischemia, inflammation, diabetic retinopathy, rheumatoid arthritis

¹⁵⁾ vascular matrix degradation, , realignment basement membrane

(Table 3).¹⁶⁾ (therapeutic angiogenesis)

, vascular endothelial growth factor(VEGF), fibroblast growth factor(FGF), hepatocyte growth factor(HGF)

Table 3. Factors regulating endothelial cell behavior

Proliferation	Migration	Inflammation	Inhibitors
FGF family	bFGF	IL-1	Angiostatin
VEGF	VEGF	PAF-4	Endothelin
PIGF	PGE ₂	TNF-	IFN-
PDGF	Scatter factor		IL-1
EGF	TNF-		PAF-4
GM-CSF	TGF-		PrRP
Heparin cofactor			TGF
IGF-1			TIMP
Monobutyryn			TNF-
PD-ECGF			TNF-
Pleiotrophin			TSP
Proliferin			
Scatter factor			
TGF-			
Vasculotropin			

FGF : fibroblast growth factor, bFGF : basic fibroblast growth factor, VEGF : vascular endothelial growth factor, PIGF ; placental growth factor, PDGF : platelet derived growth factor, EGF : epidermal growth factor, GM-CSG : granulocyte-macrophage colony stimulating factor, IGF-1 : insulin-like growth factor, PD-ECGF : platelet-derived endothelial cell growth factor, IFN- : interferon- , IL-1 : interleukin-1, PAF-4 : platelet activating factor-4, PGE₂ : prostaglandin E₂, PrRP : proliferation related protein : TGF- : transforming growth factor- , TNF- : tumor necrosis factor- , TGF- : transforming growth factor- , TIMP : tissue inhibitor of metalloproteinase, TSP : thrombospondin (Adapted from Capogrossi & Passaniti.¹⁶⁾).

가 .¹⁷⁻²⁰⁾ VEGF family VEGF A, B, C, D, E placenta growth factor

가 , 가 .¹⁸⁾²¹⁻²³⁾ FGF family FGF - 1, FGF - 2, FGF - 4, FGF - 5

가 , 가 .³⁾¹⁹⁾²⁴⁾

유전자전달체(Vector System)

가 , 가 ,

Table 4
Plasmid DNA, , Hemagglutinating virus of Japan(HVJ) - liposomes

Plasmid DNA
Plasmid DNA transduction (<1%)
DNA vaccine
, Wolf plasmid DNA

²⁵⁾ Plasmid DNA 가 ,

Isner angiogenic factor naked plasmid DNA , delivery system

plasmid DNA ,
²⁶⁾²⁷⁾

가²⁹⁻³²⁾
 HVJ-liposomes
 가
 hybrid vector가
 HVJ-liposomes
 (Sendai virus)
 some
 DNA가 liposome
 HVJ
 liposomes sialic acid receptor
 lipid F
 liposome
³³⁾ Liposome phagocytosis
 lysosome
 liposome
 Liposomes
 oligodeoxynucleo-
 tide DNA
 liposomes

³²⁾
 immunomodulatory gene
 transfection^{36/37)}
 유전자발현기간
 promoter
 attenuation
 조직특이성
 Cell-specific promoter cell tropism
 promoter thrombom-
 odulin, vWF, tie-2
 promoter SM22 가³⁸⁻⁴¹⁾
 Cell tropism

가³⁴⁾
 유전자전달체의 개발
 가 가

유전자발현의 조절
 promoter
 가
 cytokine-inducible
 promoter hypoxia responsible element
 (HRE)

바이러스성 유전자전달체의 염증 및 면역성 유발
 가
³⁵⁾
 transcriptional coding
 region

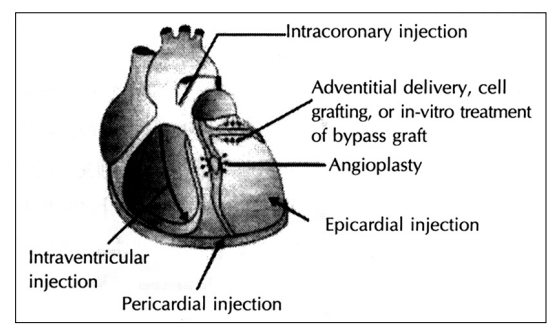


Fig. 2. Gene therapy route for treatment of myocardium and coronary artery disease.

가 ⁴²⁾⁴³⁾ direct myocardial in-
 jection, coronary vasculature , peri-
 cardium 가 ,
 ultrasonography, microbubble
 가 ⁴⁸⁾⁴⁹⁾

Delivery System

심혈관계 유전자치료의 임상시험

가
 Fig. 2

microporous, hydrogelcoated, channel balloon,
 dispatch balloon catheter ^{44 - 46)} (Table 5). plasmid
 DNA plasmid
 connective tissue, lipid content가 가 DNA 가
 , needle catheter
 catheter가 가
⁴⁷⁾ Silastic collar, biodegradable collar,
 biodegradable gel adventitia 가

Table 5. Clinical gene therapy trials in cardiovascular disease and hyperlipidemia

Disease	Target gene	Delivery route	Vector	Investigator/company
FH	LDL receptor	Ex vivo to hepatocyte	Retrovirus	Wilson JM et al
PAOD	VEGF-A	Intramuscular injection	Naked DNA	Baumgartner I, Isner JM et al
Burger's disease	VEGF-A	Intramuscular injection	Naked DNA	Isner JM et al
CAOD	VEGF-A	IM thoracotomy	Naked DNA	Isner JM et al
PAOD	LacZ	Infusion-perfusion	Adenovirus	Yla-Herttuala S et al
PAOD/post PTA restenosis	VEGF-A	Infusion-perfusion catheter after angioplasty	Liposome-adenovirus	Yla-Herttuala S et al
CAOD	LacZ/VEGF	Infusion-perfusion	Liposome-adenovirus	Yla-Herttuala S et al
End-stage ischemic heart disease, restenosis	VEGF	Via thoracotomy catheter after angioplasty	Naked DNA	Sylven et al
CAOD	VEGF ₁₂₁	TMR	Adenovirus	Rosengart T et al/GenVec Inc
CAOD	FGF-4	Intracoronary injection	Adenovirus	Engler R et al/Collateral therapeutics Inc.
PAOD	VEGF-A	Adventitial delivery with biodegradable reservoir	Plasmid-liposome	Eurogene ltd
PAOD	FGF-1	Intramuscular injection	Plasmid (pCOR)	RPR gencell
PAOD	VEGF-C	Intramuscular injection	Naked DNA	Isner JM et al/Vascular genetics Inc
CAOD	VEGF-C	Catheter-based myocardial injection	Naked DNA	Isner JM et al/Vascular genetics inc
PAOD	FGF-4	Intramuscular injection	Adenovirus	Collateral therapeutics inc/Schering AG
Vein graft stenosis	E2F decoy	Pressure ex vivo delivery	Oligonucleotide	Mann M, Dzau V et al

FH : familial hypercholesterolemia, CAOD : coronary artery obstructive disease, PAOD : peripheral artery obstructive disease (Adapted from Yla-Herttuala & Martin.⁵⁰⁾

결 론

가

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