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Development and Modification of Decoy Oligodeoxynucleotides for Clinical Application

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Abstract Several chemical and structural modifications have been employed to improve the therapeutic effectiveness of oligodeoxynucleotides (ODNs), which largely depends on their stability against nucleases, specificity to the target nuclear factor, and efficient cellular and tissue uptake. Phosphorothioation of ODNs has been used in order to decrease their susceptibility to degradation by exo- and endonucleases. To overcome problems related to safety and the cost of production resulting from the fully chemical modified ODN, we developed a non-chemically modified decoy ODN, the ribbon-type decoy, by ligation of the extremities of two single phosphodiester strands. Moreover, we developed a chimera decoy with binding sequence for two different transcription factors. In this review we also discuss briefly the use of a biodegradable polyester as a carrier of ODN.

ODN act as a decoy for specific transcription factors, and is used to attenuate the authentic *cis–trans* interaction, leading to removal of *trans*-factors from the endogenous *cis*-elements and subsequent modulation of gene expression. We developed an ODN that targets nuclear factor kappa B (NF-κB), which plays a pivotal role in the coordinated activation of inflammatory cytokines and expression of adhesion proteins; and chimera decoys for both NF-κB and Ets, and for both NF-κB and E2F.

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We discuss some studies on NF-κB decoy ODN and chimera decoys in cardiovascular and bone disease in mice, rat, and dog animal models, as well as results from some clinical trials.

Keywords Bone disease, Cardiovascular disease, Decoy oligodeoxynucleotide, NF-κB

Contents

1 Decoy Oligodeoxynucleotides

Decoy oligodeoxynucleotides (ODN) are synthetic double-stranded oligodeoxynucleotides that act as decoy *cis*-elements to block the binding of transcription factors to promoter regions of targeted genes, resulting in the inhibition of gene expression. Decoy ODN strategy is particularly attractive for several reasons: the potential drug targets (transcription factors) are plentiful and readily identifiable; knowledge of the exact molecular structure of the target transcription factor is unnecessary; and the synthesis of the sequence-specific decoy is relatively simple and can be targeted to specific tissues.

Therapeutic effectiveness of synthetic double-stranded ODNs in modulating specific gene expression largely depends on several factors, including stability, specificity, and the efficient cellular and tissue uptake of ODN. One of the obstacles in decoy ODN strategy as a pharmaceutical drug concerns the stability of ODN in cells and blood.

Since the phosphodiester ODN, the natural type (N-ODN), is precluded due to its instability under physiological conditions, chemical modifications such as phosphorothioation (S-modification) and methylphosphonation were employed in order to decrease the susceptibility of ODN to degradation by exo- and endonucleases. The first generation of chemically modified decoy is the phosphorothioated ODN (S-ODN), which consists of the replacement of a nonbridging oxygen for sulfur in the phosphate group of the deoxynucleotide backbone (Fig. 1). Moreover, we developed the phosphorothioated chimera decoy with binding sequences for two different transcription factors.

Although the efficacy of the first generation of phosphorothioated ODN in inhibiting a large variety of transcription factors has been reported [1–3], the use of S-ODN has brought other problems, such as safety and the cost of production

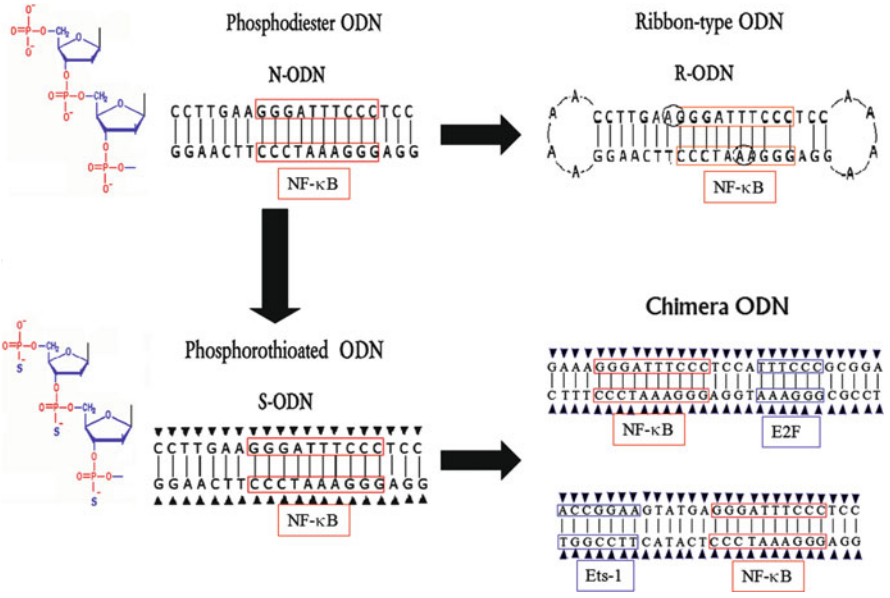

Fig. 1 Non-modified ODN (*N-ODN*), phosphorothioated ODN (*S-ODN*), ribbon-type ODN (*R-ODN*), and chimera decoy. The NF-κB, Ets-1, and E2F binding sequences are marked by *rectangles*. *Filled triangles* in the S-ODN represents the phosphorothioation, and *circles* in the R-ODN indicate the bases involved in the ligation reaction

resulting from that chemical modification [4–7]. One of the major concerns is the generation of nonspecific effects, particularly those attributed to the polyanionic nature of S-ODN. Non-sequence-specific inhibition may operate through blockade of cell surface receptor activity or interference with other proteins [8]. The toxicity of S-ODN may also be relevant. Although low dosage administration does not seem to cause any toxicity, bolus infusions could be dangerous. High doses over prolonged periods of time may cause kidney damage, as evidenced by proteinuria and leukocytes in urine in animals; liver enzymes may also be increased in animals treated with moderate to high doses [9]. Several S-ODN have been shown to cause acute hypotensive events in monkeys [10, 11], probably due to complement activation [12]. More recently, prolongation of prothrombin, partial thromboplastin, and bleeding times has been reported in monkeys [13].

Although those effects are transient if managed properly, and are relatively uncommon, a new construction called ribbon-type ODN (R-ODN) was designed to overcome nonspecific effects caused by chemical modifications. This is a non-chemically modified decoy ODN with a dumbbell-shaped structure formed by ligation of the extremities of two single phosphodiester strands. Such construction significantly increased the stability of the phosphodiester backbone against nucleases compared to N-ODN, and was as efficient as S-ODN in binding to the transcription factor NF-κB [14]. Even though phosphorothioation has been considered to decrease the S-ODN specificity, it increases the stability against nucleases.

On the other hand, the dumbbell-shaped structure does not interfere with the specificity of R-ODN, but is still less stable in serum than S-ODN; incubation with 5% fetal bovine serum for 24 h completely degraded R-ODN, while S-ODN remained almost intact [14].

The development and optimization of ODN construction is a growing field, with new constructions emerging fast and with justified expectations for therapeutic applications. Partially chemically modified R-ODN is expected in the near future.

Transcription factors are key players in disease pathology. They recognize a specific sequence relatively near the site where gene transcription starts, and switch the target gene expression on or off. Therefore, inhibition of a specific transcription factor may prevent the expression of multiple genes responsible for the disease development. In this section we introduce the transcription factors NF-κB, Ets-1, and E2F, and some successful uses of decoy ODN targeting NF-κB in animal models.

2 NF-κB Decoy ODN

2.1 NF-κB

NF-κB (nuclear factor-kappa B) is a transcription factor so named because its first identified binding site is located within an enhancer in the Ig κ light chain gene in mature B cells. The functional NF-κB is a homo- or heterodimer of homologous proteins that share a common structure motif called the Rel domain. The Rel family in the vertebrate includes five cellular proteins: p50 (NF-κB1), p52 (NF-κB2), p65 (RelA), RelB, and c-Rel. The most common NF-κB consists of a p65:p50 heterodimer, but there exists a variety of homodimers and heterdimers, each of which activates its own characteristic set of genes.

NF-κB activation is triggered by signal-induced phosphorylation of specific serine residues in the inhibitor κB (IκB) proteins by an enzymatic complex called IκB kinase (IKK), which is activated by TNFR (tumor necrosis factor receptor), TCR (T cell receptor), or cytokines receptors and involves TRAF (TNFR-activated factor) family adapter proteins. The phosphorylation targets the inhibitor for ubiquitylation and rapid degradation by proteasome and, as a consequence of the release from IκB, NF-κB translocates into the nucleus and binds to specific sequences in the promoter region, called κB-sites, which regulate the expression of target genes. The gene expression controlled by NF-κB regulates cell growth and differentiation, inflammatory responses, apoptosis, and neoplastic transformation.

NF-κB is activated by a variety of stimulants: reactive oxygen intermediates, hypoxia, hyperoxia, cytokines, protein kinase C activators, mitogen-activated protein kinase (MAPK) activators, dsRNA, UV radiation, and bacterial or viral products such as lipopolysaccharide.

Due to the role of NF-κB as a convergent point for the pathways of different stimulants, this transcription factor has a key role in many pathologies. Therefore, strategies to specifically inhibit NF-κB in a certain organ or tissue, and consequent suppression of multiple gene expression have been pursued.

2.2 NF-κB Decoy ODN in Cardiovascular Diseases

2.2.1 Myocardial Infarction

Myocardial reperfusion injury develops mostly as a result of severe damage to myocytes and endothelial cells, induced by the complex interaction of multiple cytokines and adhesion molecules activated by reperfusion. Increased NF-κB binding activity was confirmed in hearts with myocardial infarction. Transfection of NF-κB decoy ODN into rat coronary arteries before left anterior descending coronary artery occlusion markedly reduced the damaged area of myocytes 24 h after reperfusion, whereas no difference was observed between scrambled decoy ODN-treated and non-transfected rats. The therapeutic efficacy of this strategy via intracoronary administration immediately after reperfusion, similar to the clinical situation, was also confirmed. The selectivity of the NF-κB decoy ODN effect was shown by the reduction of the damaged myocardial area, which was not observed in rats treated with antisense ODN directed against the rat gene encoding inducible nitric oxide synthase. The specificity of the NF-κB decoy in the inhibition of cytokine and adhesion molecule expression was also confirmed by in vitro experiments using human and rat coronary artery endothelial cells (ECs). Transfection of NF-κB decoy ODNs markedly inhibited the protein expression of cytokines [interleukin (IL)-6 and IL-8] and adhesion molecules (VCAM, ICAM, and E-selectin) in response to TNF-α stimulation in human aortic ECs. In contrast, the control scrambled decoy ODN failed to inhibit the induction of these protein expressions. Cell numbers after transfection were not changed, indicating that the NF-κB decoy induces a specific inhibitory effect rather than nonspecific cytotoxicity [2].

2.2.2 Vascular Bypass Graft Occlusion

Autologous vein is commonly used for the surgical treatment of coronary artery disease and peripheral artery disease. Although bypass grafts are highly successful in relieving symptoms in patients with severe ischemic arterial disease, the long-term survival of vein grafts is still a crucial problem. Acute vein graft failure is mainly due to thrombosis, and late failure is associated with progressive graft atherosclerosis. Another important process involved is the progression of neointimal hyperplasia. It is mainly caused by endothelial injury and subsequent migration and accumulation of blood-derived cells such as macrophages. These cells express numerous growth factors, cytokines, and proteases regulated by

NF-κB activation, ultimately leading to vascular smooth muscle cell (VSMC) migration and proliferation from media into intima. In the vein graft of a rabbit hypercholesterolemic model, transfection of NF-κB decoy ODN, but not scrambled ODN, significantly inhibited the migration and accumulation of macrophages in the subendothelial layer, and inhibited VSMC growth by induction of VSMC apoptosis. Moreover, there was an inhibition of the transformation of matrix metalloproteinase (MMP)-9 into active MMP-9, and reduced MMP-2 activity. Transfection of NF-κB decoy ODN resulted in the preservation of acetylcholine-mediated vasorelaxation [15]. Taken together, the inhibition of NF-κB activity by decoy ODN in vein grafts protected the surviving endothelial cells from hemodynamic stress and ischemic injury at the time of surgery.

2.2.3 Restenosis After Angioplasty

NF-κB decoy ODN has also been reported as a potential device in the treatment of restenosis after balloon angioplasty. Intimal hyperplasia, as mentioned above, develops largely as a result of VSMC proliferation and migration induced by the complex interaction of multiple growth factors activated by vascular injury. Transfection of NF-κB decoy ODN into balloon-injured rat carotid artery or porcine coronary artery markedly reduced neointimal formation, whereas no difference was observed between scrambled decoy ODN-treated and untransfected blood vessels [16, 17]. In addition to VSMC proliferation, endothelial damage also contributes to the development of restenosis. Interestingly, transfection of NF-κB decoy ODN inhibited EC death, and consequently decreased vascular inflammation because ECs play an important role in suppression of VSMC growth, maintenance of vascular tonus, and protection from monocyte and platelet adhesion.

On the basis of the therapeutic efficacy of this strategy, we obtained permission for a second clinical trial (starting in 2002) using the decoy strategy to treat restenosis. In this trial, NF-κB decoy ODN was delivered to the vessel wall through a hydrogel-coated catheter without any viral or nonviral vector. Efficient ODN transfection was confirmed with fluorescein isothiocyanate (FITC)-labeled ODN. The hydrogel-coated catheter was able to deliver the ODN not only to the coronary endothelium, but also to the vascular wall [18].

We have recently prepared an open-label phase I/IIa clinical trial (the INDOR study; a phase I/IIa open-label multicenter study to assess the inhibitory effects of NF-κB decoy ODN on restenosis after stenting in coronary artery) to evaluate the safety and efficacy of NF-κB decoy ODN. Seventeen patients were treated with NF-κB decoy ODN after percutaneous coronary intervention (PCI) using bare metal stents. As a result, the stenosis improved to $1.4 \pm 5.9\%$ after the intervention. Serum monocyte chemotactic protein-1 (MCP-1) levels were significantly suppressed in NF-κB decoy ODN-treated patients on day 3 after the PCI. Significant restenosis was found in only one of the 17 patients after 6 months, and the average restenosis rate was $39.6 \pm 22.3\%$. No in-stent thrombosis was found and no

significant systemic adverse effect occurred in any of the patients during this observation period [19].

Although further placebo control trials are required, the aforementioned results suggest the clinical usefulness and safety of the NF-κB decoy ODN to prevent restenosis.

2.2.4 Cardiac Transplant Rejection and Vasculopathy

Acute rejection and graft arteriopathy limit the long-term survival of recipients after cardiac transplantation. Acute rejection is enhanced by several cytokines, adhesion molecules, and myosin heavy chain expression, and the arteriopathy is characterized by intimal thickening comprised of proliferative VSMCs. NF-κB decoy ODN was infused into donor hearts in a complex with HVJ (Hemmagluttinating virus of Japan)-AVE-liposome and transplanted into murine recipients. Nontreated ($n = 6$; 7.8 ± 0.4 days) or scrambled decoy-transfected ($n = 6$; 8.0 ± 0.6 days) allografts were acutely rejected, whereas NF-κB decoy transfection significantly prolonged allograft survival ($n = 6$; 13.7 ± 2.4 days, $P < 0.05$). In addition, NF-κB decoy not only attenuated myocardial cell infiltration, but also inhibited arterial neointimal formation in cardiac allografts [20].

2.2.5 Chimera Decoy ODN Against NF-κB and Ets-1 in Abdominal Aorta Aneurism

NF-κB inhibition by decoy ODN has also been reported in a rat model for abdominal aorta aneurism (AAA) using a chimeric decoy ODN with binding sites for two transcription factors: NF-κB and Ets. Destruction of elastin is considered to be one of the major causes of abdominal aortic aneurysm (AAA). Elastic fibers normally maintain the structure of the vascular wall against hemodynamic stress. Proteolytic degradation induces remodeling of the extracellular matrix, resulting in aneurysmal development and, finally, ruptures in the vascular wall. MMP secreted by invasive macrophages, migrating VSMCs, and ECs play important roles in such mechanisms of AAA. NF-κB regulates the transcription of MMP-1, MMP-2, MMP-3, and MMP-9. The Ets family activates the transcription of genes encoding MMP-1, MMP-3, MMP-9, and urokinase plasminogen activator; all of which are proteases involved in extracellular matrix degradation.

AAA was induced in rats by transient aortic perfusion with elastase, and the decoy ODN was transfected by wrapping a delivery sheet containing the chimeric decoy ODN around the aorta. The prevention of aortic dilatation was confirmed by histological studies, and the progression of AAA was inhibited by the chimeric ODN, even 4 weeks after transfection. There was marked inhibition of elastin proteolysis and macrophage migration, and a decrease in MMP gene expression as compared with scrambled decoy ODN and the non-transfected group [15].

2.2.6 Chimera Decoy ODN Against NF-κB and E2F in Anastomotic Intimal Hyperplasia

Prosthetic grafts are commonly used for infrainguinal bypass grafting to treat arterial occlusive disease, but long-term patency remains a crucial problem. One major limitation of prosthetic bypass grafting is the usage of small diameter vessels, such as tibial or peroneal artery bypass, and the graft failure is mainly due to the progression of anastomotic intimal hyperplasia, which causes significant lumen narrowing. The luminal lining of the prosthetic graft is composed of pseudointima and lacks ECs. The lack of an endothelial monolayer disrupts the homeostatic regulation of thrombosis, platelet activation, and leucocyte adhesion, resulting in VSMC proliferation and migration. Therefore, inhibition of VSMC proliferation is thought to prevent progression of intimal hyperplasia, and E2F has attracted attention in this process because it is a pivotal cell-cycle transcription factor.

We developed a chimera decoy strategy to inhibit both NF-κB and E2F simultaneously. Treatment with chimera decoy ODN could reduce the inflammatory response as well as VSMC proliferation and migration in the process of neointimal formation of anastomotic intimal hyperplasia in the prosthetic graft placement in a rabbit hypercholesterolemia model. Chimera decoy ODN also accelerated re-endothelialization. Expression of platelet-derived growth factor (PDGF)-BB and PDGF receptor-β were also suppressed and resulted in a reduction of VSMC accumulation. In addition, chimeric decoy ODN treatment inhibited macrophage accumulation, which was accompanied by a reduction in gene expression of vascular cell adhesion molecule-1 and monocyte chemoattractant protein-1 [21].

2.3 NF-κB Decoy ODN in Bone Disease

2.3.1 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by articular inflammation in which the osteoclasts generated within the synovial membrane are probably involved in bone destruction in vivo. Osteoclasts are activated by both macrophage colony-stimulating factor (M-CSF) and receptor activator of NF-κB ligand (RANKL). A crucial target of RANKL is the activation of NF-κB, and transfection of R-ODN decoy against NF-κB into osteoclasts decreased the RANKL-induced activation, as measured by TRAP staining and pit formation assay. The transfection also decreased the expression of the NF-κB target gene *NFATc1*, which is a master switch for regulating the terminal differentiation of osteoclasts. Using the collagen-induced arthritis animal model, we found that transfer of R-ODN into rat ankle joints resulted in marked improvement in arthritis score compared to S-ODN and control groups, and significantly decreased the osteoclast number and activity in the joint as measured by hematoxylin and eosin staining and TRAP staining [22].

2.3.2 Periodontal Diseases

As previously mentioned, NF-κB is involved in osteoclast differentiation and activation, and the blockade of the NF-κB pathway is a potential therapeutic strategy for treating bone diseases such as periodontitis, which is a subgingival inflammation caused by bacterial infection. NF-κB decoy ODN was topically applied for experimental periodontitis in a debris-accumulation model and for wound healing in a bone-defect model of beagle dogs. Application of S-ODN significantly reduced IL-6 activity in crevicular fluid and improved alveolar bone loss, as shown by analysis of dental radiographs and dual-emission X-ray absorptiometry (DEXA) scans. Direct measurement of exposed root that had lost alveolar bone support revealed that NF-κB decoy treatment dramatically protected bone from loss through the inhibition of osteoclastic bone resorption, and promoted the healing process as compared with scrambled ODN, as shown by micro-computer tomography (CT) analysis [23].

2.3.3 Osteoporosis

Exaggerated osteoclast activation leads to another bone disease – osteoporosis. In an ovariectomized rat model, the estrogen deficiency induces osteoporosis, which was reversed by continuous administration of NF-κB decoy using an osmotic pump. The reversal was indicated by attenuation of TRAP activity, significant increase in calcium concentrations in the femur and tibia, and a decrease in urinary deoxypyridinoline. In agreement, NF-κB decoy ODN infusion in an osteoporosis model of vitamin C-deficient rat dramatically improved the bone length, weight, and mineral density, as assessed by DEXA [24].

3 Perspectives for Decoy ODN Strategy

Decoy ODN-based therapy still shows some unsolved issues. Further modifications of ODN will facilitate the potential clinical utility of these agents by, for example, (1) increasing its half-life, which will allow a shorter intraluminal incubation time to preserve organ perfusion and prolong the duration of biological action; (2) improvement of uptake of ODN by a specific target cell using efficient vehicles or innovations in the gene transfer methods, in a way that the nonspecific effects of high doses can be avoid; and (3) improvement of ODN resistance against nucleases by chemical or structural modifications, because the site of decoy ODN effects is the nucleus and because bypassing the endocytotic pathway and translocation from the cytoplasm are crucial for therapeutic efficiency.

Recently, studies with the biodegradable polyester poly(DL-lactide-*co*-glycolide) (PLGA) showed that PLGA microspheres encapsulating NF-κB decoy ODN were

able to release the ODN at a constant rate for about 40 days [25]. In the chronic inflammation induced by a sponge implant model in rats, injection of decoy ODN–microspheres into the sponge significantly decreased leukocyte infiltration and granuloma formation for up to 15 days after implantation, through inhibition of NF-κB activation. The authors argue that the combination of long-term release and efficient protection of the encapsulated decoy ODN against nucleases could explain the effect obtained [26].

More studies concerning the release rate, ODN loading density, and control of local concentrations at delivery sites are expected, as well as further studies on biodegradable polymers and additional modifications of the ODN itself. In the future, ODN-based gene therapy might overcome present limitations and offer an alternative for treatment of unmet diseases.

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