

Aptamers as Tools in Molecular Biology and Immunology

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1 Introduction

In 1990 TUERK and GOLD introduced the first RNA aptamer for bacteriophage T4 DNA polymerase, obtained by a new combinatorial technique which they designated as SELEX (systematic evolution of ligands by exponential enrichment). In parallel, ELLINGTON and SZOSTAK (1990) showed that it is also possible to select RNA aptamers which are able to specifically complex organic molecules of low molecular weight, thus serving as receptor molecules based on nucleic acids rather than proteins. Since then, considerable progress has been achieved in the field of in vitro selection of combinatorial nucleic acid libraries, which demonstrates its impressive potential as a tool in molecular biology, diagnostics, molecular medicine, drug discovery, and bio-organic chemistry. Today, the SELEX process has been applied to more than a hundred different target molecules, and aptamers are known for almost every kind of targets such as organic dyes, amino acids, biological cofactors, antibiotics, peptides and proteins or even whole viruses (BELL et al. 1998; GAL et al. 1998; ELLINGTON and OSBORNE 1997; KRAUS et al. 1998; YANG et al. 1998; EATON 1997; PAN et al. 1995), showing that aptamers can be obtained for almost any desired target whether complex or small.

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The isolation of specific antagonists for proteins which are involved in disease processes is one of the major goals in pharmacological research. Drug discovery has been greatly facilitated by computer-assisted drug design and various screening strategies of diverse combinatorial libraries of small molecules, peptides, Fab fragments, and antibodies. The SELEX technology provides a powerful method for the screening of large libraries of oligonucleotides, with diversities of up to 10^{15} different molecules, for specific ligand-binding nucleic acids which in many cases have been shown to not only bind a certain target protein, but also to inhibit its biological function. Many isolated aptamers are aimed at possible therapeutic and/or diagnostic applications. Insufficient stability, often cited as the major potential drawback of nucleic acids as therapeutic agents, can easily be overcome by using libraries of chemically modified nucleic acids, such as 2'-fluoro- or 2'-amino-2'-deoxypyrimidine containing nucleic acids. Modifications of that kind have been shown to be compatible with the enzymatic steps of the SELEX process. Other strategies which circumvent the stability problem of RNA or DNA include the so-called mirror-image, or Spiegelmer, approach by exploiting nuclease resistance of the enantiomer of naturally occurring nucleic acids (KLUBMANN et al. 1996; NULTE et al. 1996).

Various recent examples illustrate the potential of aptamers in affecting cellular processes. In this review we will give an overview on recent progress in oligonucleotide selections and applications of aptamers as potential tools in drug discovery, diagnostics, molecular medicine, and for the dissection of cellular processes of immunological relevance (Table 1).

Table 1. Summary of the targeted molecules/viruses used for SELEX experiments

Target molecule	Dissociation constant (nM)	Possible therapeutic and/or diagnostic application	Reference
IgE	10.0	Allergic disease	WIEGAND et al. (1996)
Anti-acetylcholine autoantibodies	60.0	Myasthenia gravis	LEE and SULLENGER (1997)
IFN- γ	6.8	Inflammation and immune response	KUBIK et al. (1997)
L-selectin	3.0	Inflammation	O'CONNELL et al. (1996)
CD4	N/A	Immune response	KRAUS et al. (1998)
bFGF	0.350	Angiogenesis	JELLINEK et al. (1993)
KGF	0.0003	Epithelial hyperproliferative disease	PAGRATIS et al. (1997)
PDGF	0.1	Tumor development	GREEN et al. (1996)
VEGF	0.14	Neovascularization	GREEN et al. (1995)
RSV	40.0	Viral infection	PAN et al. (1995)
HIV-1 RT	1.0	Viral replication	TUERK et al. (1992) SCHNEIDER et al. (1995)
HIV-1 integrase	10.0	Viral replication	ALLEN et al. (1995)
HIV-1 rev	N/A	Viral replication	GIVER et al. (1993)
α -thrombin	25.0	Thrombosis	BOCK et al. (1992), KUBIK et al. (1994), LATHAM et al. (1994)
Activated protein C	110.0	Thrombosis	GAL et al. (1998)
hNE	N/A	Inflammation	CHARLTON et al. (1997)
PTPase	18.0	Oncogenesis, viral and cellular regulation	BELL et al. (1998)
PLA ₂	118.0	ARDS, Septic shock	BRIDONNEAU et al. (1998)

2 Aptamers for Antibodies

IgE antibodies play a key role in allergic responses. Aptamer antagonists, single-stranded DNA and 2'-amino-modified RNA molecules which bind human IgE have been isolated by *in vitro* selection (WIEGAND et al. 1996). Truncated aptamers (designated as IGEL1.2 -2'-amino RNA- and D17.4 -ssDNA-) were shown to competitively inhibit the interaction of human IgE with its FcεRI receptor in rat basophilic leukemia cells transfected with the human IgE receptor. The oligonucleotides block the IgE-mediated release of biogenic amines, such as serotonin, which are important mediators in allergic responses. Because of these properties the selected aptamers may have the potential to serve as a class of new therapeutics for the therapy of allergic diseases.

An aptamer directed against the antibody which plays a decisive role during the development of the autoimmune disease myasthenia gravis was shown to serve as a decoy RNA molecule (LEE and SULLENGER 1997). Myasthenia gravis is a muscular disease which results in progressive muscle weakness. This effect is based on the binding of anti-receptor autoantibodies to acetylcholine receptors in the motor end plate of neuromuscular junctions, affecting failure of muscle response to neuronal impulses (LINDSTROM et al. 1988). The selected aptamer, modified by substitution of the 2'-OH for a 2'-NH₂-group at the riboses of pyrimidine residues to improve its resistance against degradation by nucleases, recognizes anti-acetylcholine receptor autoantibodies present in the serum of patients that suffer from myasthenia gravis. Additionally they inhibit the binding of acetylcholine receptors to the autoantibodies. In this way, the undesired antibody-mediated immune response could be inhibited.

DOUDNA et al. (1995) isolated RNA sequences that mimicked a major autoantigenic epitope of the human insulin receptor. The goal of this approach was to obtain an aptamer which could be used in the treatment of patients with extreme insulin resistance type B. The selection was performed with an anti-human insulin receptor mouse monoclonal antibody (designated as MA20) which recognizes the same epitope of the insulin receptor-like autoantibodies present in the sera of these patients. The selected aptamers showed cross-reactivity with the autoantibodies and were shown to serve as RNA decoys, with the effect that they protected the insulin receptor from antibody binding.

3 The Interruption of Lymphocyte Signal Transduction Pathways by Aptamers

Aptamers targeted against proteins which are involved in inflammatory processes are of considerable medical interest. Interferon γ (IFN- γ) is an immunoregulatory cytokine which is synthesized and secreted by Th1 and NK cells (TRINCHIERI and

PERUSSIA 1985). It is thought to participate in nearly all phases of immune and inflammatory responses (FARRAR and SCHREIBER 1993). IFN- γ plays crucial roles in promoting inflammatory responses by stimulating macrophage cytotoxicity, enhancing adhesion of vascular endothelial cells, and facilitating lymphocyte extravasation. KUBIK et al. (1997) isolated RNA aptamers which bind to IFN- γ with high affinity and specificity. Furthermore, the aptamer inhibits IFN- γ -induced expression of MHC class I and ICAM-1, important proteins in the genesis of inflammatory disease, by human myeloid leukemia cells. The regulation of IFN- γ activity by specific ligands which inhibit the binding of IFN- γ to its receptors may have an important potential for therapeutic applications. This aptamer might be of interest for diagnostic purposes as well.

LEE et al. (1996) reported that several synthetic oligonucleotides can block IFN- γ mediated effects in human cell cultures. Originally these oligonucleotides were designed as antisense-molecules to form a triple helix with the X-X₂ box region of the HLA-DR α gene promoter. Because the oligonucleotide is able to inhibit IFN- γ induced up-regulation of MHC class I and II and ICAM-1 expression, LEE et al. (1996) suggested a mechanism similar to that of aptamers for the inhibitory function of the synthetic oligonucleotide, by dissecting the signal transduction pathway through IFN- γ binding. This is an impressive example for a possible application of an oligonucleotide as an inhibitory drug in medicinal chemistry, in this case for inhibition of undesired immune responses after transplantation.

Many cell-cell interactions in the vascular system are regulated by selectins, a family of cell adhesion molecules subdivided into L-selectin, P-selectin, and E-selectin. Selectins are involved in early steps of tissue injury following hypoxemia, reperfusion, or inflammation (BEVILACQUA and NELSON 1993; BEVILACQUA et al. 1994). Various ligands are known, the most prominent one being sialyl Lewis^x, that block the interaction of L-selectin with other cell surface receptors, such as glycosylation-dependent cell adhesion molecule-1 (GlyCAM-1), but none of these ligands is able to discriminate between the three selectin isoforms. The SELEX technology was used to isolate oligonucleotide ligands for L-selectin (O'CONNELL et al. 1996). Nuclease stabilization was achieved by using a 2'-amino-2'-deoxy-pyrimidine containing oligonucleotide library. The isolated aptamer was shown to bind L-selectin with high affinity and specificity in a calcium-dependent manner and to selectively discriminate between the three selectin isoforms. Furthermore, the aptamer was able to recognize the native protein on cell surfaces.

Another example of aptamers directed against an immunologically relevant target are RNA molecules selected to bind to the CD4 protein. The CD4 antigen interacts with MHC class II on antigen presenting cells (APCs) and plays an essential part in HIV-1 infection (DAGLEISH et al. 1984). In previous studies it was shown that antibodies directed against CD4 can block both MHC II and HIV-1 complex formation. Using a library of 2'-fluoro modified RNAs, randomized at 36 positions KRAUS et al. (1998), isolated aptamers which bind CD4. These aptamers were able to inhibit mixed lymphocyte reactions nearly as well as Fab fragments or IgG antibodies, which may lead to a possible application targeted to manipulations of the immune system.

4 Growth Factors as Target Proteins for In Vitro Selection

Growth factors play an important role in cell proliferation, cell migration, tissue remodeling, and wound healing (FOLKMAN and KLAGSBRUN 1987; GOSPODAROWITZ 1991). Angiogenesis, the development of new blood vessels, is often associated with pathological processes such as cancer development and metastasis. For that reason, there is great interest in obtaining antagonists that inhibit growth factor functions. In the following, we give an overview of nuclease-resistant aptamers that have been isolated by in vitro selection for binding to a variety of growth factors, such as basic fibroblast growth factor (bFGF), human keratinocyte growth factor (hKGF), platelet derived growth factor (PDGF), and vascular endothelial growth factor (VEGF).

JELLINEK et al. (1995) reported the isolation of 2'-amino-modified RNA inhibitors of bFGF. This growth factor initiates angiogenesis by binding to either heparin proteoglycans (low-affinity site) or tyrosine kinase receptors (high-affinity site) on the surfaces of endothelial cells (MOSCATELLI 1987). Overexpression of bFGF is correlated with many malignant disorders. The selected aptamer was extensively characterized, and it could be shown that a minimal aptamer, designated as M21A, is sufficient for binding to bFGF, with a dissociation constant of 350pM. M21A inhibits the binding of bFGF to low-affinity sites on CHO cells with an ED₅₀ of 1nM and the binding to high-affinity sites with an ED₅₀ of 3nM. The bFGF-dependent migration of bovine aortic endothelial cells (BAEs) is inhibited by the aptamer M21A in a dose-dependent manner.

PAGRATIS et al. (1997) selected 2'-amino- and 2'-fluoro-2'-deoxyribonucleotide-modified RNA inhibitors for hKGF. KGF, a member of the FGF family (FINCH et al. 1989), is a basic heparin binding growth factor for epithelial cells (RUBIN et al. 1989). By overexpression of hKGF it was shown that this growth factor participates in diseases like psoriasis and dermatoses with psoriasiform hyperplasia (STAIANO-COICO et al. 1993), inflammatory bowel disease (BRAUCHLE et al. 1996; FINCH et al. 1996), and neoplasia (ISHIL et al. 1994). The isolated hKGF aptamer antagonists bind hKGF with a dissociation constant of up to 0.3pM, which is the tightest binding aptamer reported so far. Compared with the 2'-amino-modified oligonucleotide ligands, the obtained 2'-fluoro-modified RNA ligands showed higher affinities and bioactivities. The aptamers can competitively inhibit hKGF binding to its receptor and inhibits mitogenic activity with k_i values of 92pM. Thus, these nuclease-resistant molecules may be useful for the development of novel pharmaceutical lead compounds for epithelial hyperproliferative disease.

Tumor cell lines produce and secrete PDGF. Therefore, autocrine as well as paracrine effects on tumor stroma and tumor growth can be imagined. Besides the impact of PDGF on tumor development, this growth factor also participates in other proliferative disorders such as glomerulonephritis (IDA et al. 1991) and arteriosclerosis (LINDNER et al. 1995; LINDNER and REIDY 1995). SELEX-derived ssDNA selected for specific complexing with PDGF showed an

5 Anti-viral Aptamers

Aptamers deliver potential tools for dissecting the life cycle of viruses by interacting with proteins essential for viral replication. For human immunodeficiency virus-1 (HIV-1) and Rous sarcoma virus (RSV), oligonucleotides have been isolated that can efficiently interrupt essential steps in the viral life cycle, opening up the potential of treating viral diseases with aptamers.

PAN et al. (1995) selected RNA molecules that neutralize RSV in a concentration-dependent manner. These RNAs were selected by incubation of the random RNA library with whole RSV particles and subsequent separation of the non-virus bound aptamers from those that remained immobilized on the surface of the virus particles. Consequently, the isolated aptamers were shown to interact with the virus surface, unable to enter the virus itself. In a virus-neutralizing activity assay the yield of viral protein could be reduced to 85%–92% at RNA concentrations of 20.0nM. Virus replication was completely blocked at an aptamer concentration of 160.0nM. It was assumed that the presence of the virus-specific aptamers resulted in conformational changes of the glycoprotein structures of viral coat proteins, thereby interfering with the attachment of viruses to the targeted cell and with cell-membrane fusion. Substitution of the pyrimidines with 2'-fluoro-2'-deoxypyrimidine derivatives increased the stability against nucleases but led to a significant decrease in virus neutralization properties.

Various proteins of HIV-1 which are essential for virus replication have been chosen as targets for isolating specific oligonucleotide antagonists. ALLEN et al. (1995) selected RNA aptamers directed against HIV-1 integrase. TUERK et al. (1992) and SCHNEIDER et al. (1995) isolated RNA and ssDNA aptamers which recognize HIV-1 reverse transcriptase (HIV-1 RT). The isolated aptamers were able to inhibit the DNA polymerase activity of HIV-1 RT, with values of K_i as low as 0.3nM (ssDNA aptamer). In addition, the aptamers selectively discriminated between various RTs, showing high affinity and specificity for HIV-1 RT whereas they did not bind to AMV RT or MMLV RT. GIVER et al. (1993) used the HIV-1 rev protein as a target for aptamer selections. SYMENSMA et al. (1996) showed that RNA aptamers, derived against the HIV-1 Rev protein, can mediate Rev function in vivo. This is an impressive example that describes the in vivo functionality of a RNA aptamer.

6 Specific Aptamers with High Affinity Inhibit Enzyme Function

One of the first ssDNA aptamers was directed against human α -thrombin, and ssDNA (BOCK et al. 1992), RNA (KUBIK et al. 1994) as well as 2' modified RNA aptamers (LATHAM et al. 1994) are known for human α -thrombin. BOCK et al. (1992) isolated ssDNA molecules that bind human thrombin and inhibited blood clotting in vitro. They showed that the thrombin-dependent blood clotting activity was blocked up to 50% at an aptamer concentration of 25nM. KUBIK et al. (1994)

selected RNA- and modified RNA aptamers for the same target. For all of these oligonucleotides, mapping of the binding site suggested that they bound to the heparin-binding exo site. The biological role that α -thrombin plays in mechanisms of blood clotting indicates a potential medical application. Indeed, the selected aptamers show inhibitory function of this process in vitro and potential applications as anticoagulants in an ex vivo, whole artery angioplasty model and in pre-clinical studies with dogs (LI et al. 1994; DEAUDA et al. 1994).

GAL et al. (1998) selected RNA ligands that inhibit activated protein C (APC) function, an essential protein in thrombosis and hemostasis regulation. The activation of protein C is induced by thrombin complexed to thrombomodulin (ESMON and OWEN 1981). GAL et al. showed that the selected aptamer, designated as APC-99, inhibits APC function with a k_i of 137 nM and do not interact with related serine-proteases like thrombin, human neutrophil elastase, or hepatitis C virus NS3 protease.

Human neutrophil elastase (hNE) plays a crucial role in several inflammatory diseases, such as septic shock, myocardial ischemia-reperfusion injury, emphysema, and especially in acute respiratory distress syndrome (ARDS) (DORING 1994; REPINE 1992). Inhibitors for proteases are well known but they generally react unspecifically with the active site (EDWARDS and BERNSTEIN 1994). Valyl phosphonate is an unspecific and irreversible inhibitor for serine proteases (OLEKSYSZYN and POWERS 1991). To aim towards a specific interaction with one particular protease, this small molecule was covalently attached to every pool member of a randomized ssDNA library. This selection method, designated as blended-SELEX (GOLD et al. 1995), was used to isolate specific RNA (SMITH et al. 1995) as well as ssDNA (CHARLTON et al. 1997) inhibitors of hNE. The aptamers that best promoted the covalent reaction of the reactive moiety inactivated elastase with a k_{obs} around $2 \times 10^8 \text{M}^{-1}$ per min, almost two orders of magnitude faster than peptide-based inhibitors. In a parallel study, the aptamer inhibitor was also shown to reduce lung injury in a rat alveolitis model (BLESS et al. 1997). By using the $^{99\text{m}}\text{Tc}$ -labeled anti elastase aptamer and, as a control, a $^{99\text{m}}\text{Tc}$ -labeled rat anti-elastase IgG, which is clinically used during in vivo imaging of inflammatory sites, it was shown that the aptamer achieved a significantly higher target-to-background (T/B) ratio in less time than the IgG (Fig. 2).

This example indicates that in some cases specific ligand binding nucleic acids might be advantageous over antibodies; in the present case the superior T/B ratios were attributed to the more rapid clearance of the aptamer from the peripheral circulation compared to the IgG.

High concentrations of human nonpancreatic secretory phospholipase A_2 (hnsP-PLA₂) are associated with various diseases such as acute pancreatitis, ARDS, bacterial peritonitis, and septic shock (RINTALA and NEVALAINEN 1993). Antagonists with high affinity and specificity are proposed to block the biological role of phospholipase A_2 (PLA₂). One such antagonist is LY311727, a small molecule indol-based inhibitor of PLA₂ (SCHEVITZ et al. 1995). BRIDONNEAU et al. (1998) have chosen a SELEX approach for new drug design and isolated 2'-amino-modified RNA aptamers as PLA₂ antagonists. One of these ligands, designated as

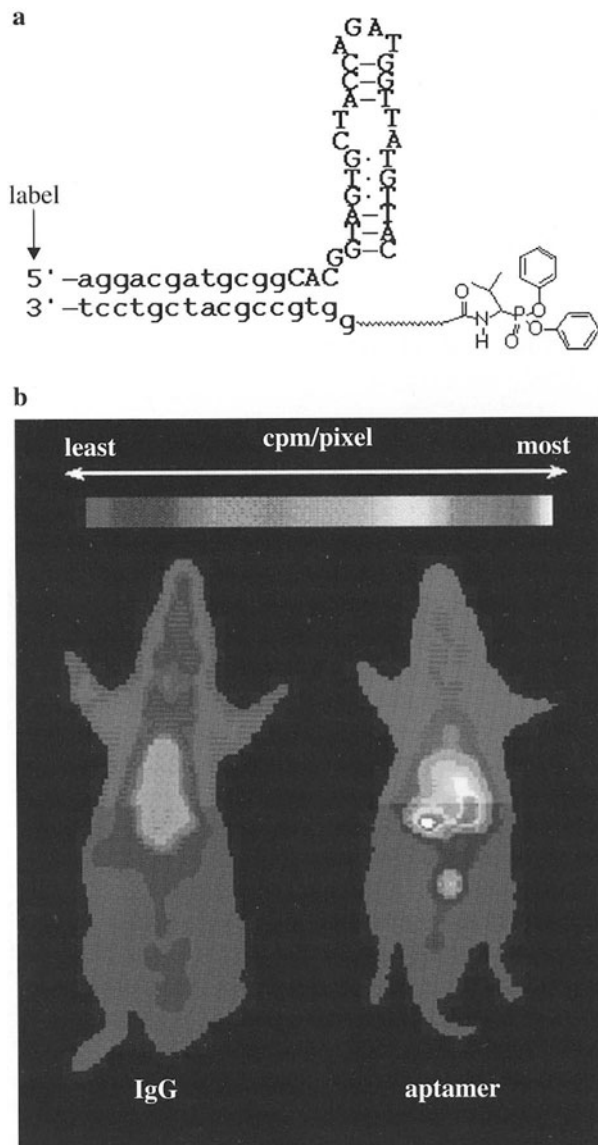


Fig. 2a,b. In vivo imaging with an aptamer. **a** DNA aptamer that binds to neutrophil elastase and acts as an irreversible inhibitor via the attached valine derivative. **b** Inflammation imaging by aptamer NX21909 (*right*) and IgG (*left*) after 10 min; *cpm*, counts per minute. (From CHARLTON et al. 1997)

aptamer 5, showed a k_i of 0.14 nM and 93% inhibition in the chromogenic hnp-PLA₂ enzymatic activity assay (REYNOLDS et al. 1992). In tissue-based contraction assays, the truncated version of aptamer 5 showed higher apparent dissociation constants ($k_B = 118 \pm 26$ nM) than the non-oligonucleotide based antagonist LY311727 (270 ± 50 nM) (SNYDER et al. 1993).

Protein tyrosine phosphatases (PTPases) play important roles in oncogenesis, pathogenesis and the regulation of cellular and viral replication. Common antagonists show little specificity and cannot discriminate between various PTPases. Two different random pools, varying in length, have been exploited to isolate more specific ligands that bind and inhibit the PTPase active site (BELL et al. 1998). The selected aptamers shared a 21-residue conserved sequence independent of the pool they were isolated from and were shown to inhibit the *Yersinia* PTPase used in the selection protocol by IC_{50} values of 10.0 and 35.0nM.

7 Aptamers Against Various Target Molecules

An impressive example for the application of combinatorial RNA libraries to identify natural RNA binding sites for a given target protein was provided by BUCKANOVICH and DARNELL 1997. They selected RNA aptamers which bind to the neuron-specific RNA binding protein Nova-1, an autoantigen in a neurologic disorder associated with breast cancer and dysfunction of brainstem or spinal motor systems (BUCKANOVICH et al. 1996). Although it was known that Nova-1 contained three RNA binding domains, a particular RNA motif recognized by Nova-1 was unknown. To identify such motifs, an in vitro selection for Nova-1 binders was performed using a library of 10^{15} different 52-mer RNAs. Isolated aptamers contained a conserved 15-mer consensus motif [UCAU(N)₀₋₂]₃ which was found to be absolutely necessary for Nova-1 binding. Remarkably, a GenBank search for this consensus sequence identified natural Nova-1 binding sites in two neuronal pre-mRNAs. One sequence lies within an intron of the glycine receptor $\alpha 2$ (GlyR $\alpha 2$) pre-mRNA. The other sequence was the pre-mRNA which encodes for Nova-1 itself. Both natural pre-mRNAs specifically interact with authentic Nova-1 protein. These studies established that Nova-1 functions as a sequence-specific nuclear RNA binding protein in vivo. It was one of the first SELEX experiments that identified previously unknown, naturally occurring, nucleic acid binding sites of a RNA binding protein. The authors suggested that the mechanism of the neurologic disease involves disruption of Nova-1 binding to GlyR $\alpha 2$ pre-mRNA by the autoantibody.

Vasopressin is known as an important peptide hormone which regulates water balance in the body (NIELSEN et al. 1995). This peptide plays a key role in various states of disease including diabetes insipidus as well as hyponatremia and polydipsia in schizophrenic patients (GOLDMAN et al. 1997). WILLIAMS et al. (1997) used the SELEX method to isolate L-ssDNA ligands to vasopressin. In their approach D-DNA ligands have been selected using D-vasopressin as a target molecule. The enantiomer of the winning D-ssDNA aptamer, designated as L-ssDNA aptamer, has been synthesized and its ability to bind L-vasopressin was demonstrated. Importantly, this approach led to enhanced nuclease stability by mirror-image ssDNA (KLUSSMANN et al. 1996; NOLTE et al. 1996). The L-ssDNA-aptamer inhibited cAMP release mediated by vasopressin, but the cAMP release induced by oxytocin was not affected.

Human thyroid stimulating hormone (hTSH) belongs to a family of glyco-hormone proteins such as leutinizing hormone (hLH), follicle stimulating hormone (hFSH), and chorionic-gonadotropin (hCG) (PIERCE and PARSONS 1981). The measurement of serum hTSH levels, secreted by the pituitary gland, is important for diagnosis of pituitary and thyroid disorders such as hyperthyroidism and hypothyroidism (LABRIE 1990). LIN et al. (1996) isolated specific ligands for hTSH that do not interact with the other members of the same protein family. They showed that selected oligonucleotides could be used in diagnostic assays.

HALLER and SARNOW (1997) isolated RNA molecules that show a 1000-fold higher affinity for N-7 methylguanosine than for nonmethylated guanosines. A remarkable feature of the selected RNA is that binding to the 5' terminal cap structure leads to the inhibition of cap-dependent processes such as mRNA translation initiation. The cap structure plays an important role in many different biological processes, e.g., pre-mRNA splicing, nuclear transport, and mRNA stabilization. Haller and Sarnow showed that the isolated aptamer R8-35 not only displaces human cytoplasmic cap-binding complex, but also inhibits the formation of human nuclear cap-binding protein complexes like CBP20 and CBP80. This aptamer is an impressive example for selective discrimination between two highly related molecules with only small structural differences. In the reported case, aptamers provide useful tools to investigate and understand biological processes in living cells.

Another example indicating that remarkably specific aptamers can be isolated by SELEX was reported by YANG et al. (1998), who selected DNA ligands that bind to cellobiose, the disaccharide of cellulose. The selected motifs are able to discriminate sugar epimers, anomers, and other disaccharides. Oligosaccharides play an important role in cellular adhesion, inflammation and molecular recognition. Commonly, antibodies are used for diagnostic purposes but they often cannot discriminate between various sugar tags of cell surface receptors.

8 Summary

We have listed and described recent promising developments in the field of aptamer research. The properties and the application potential of aptamers propose an exciting future for aptamers either in the clinic or as research tools for various purposes. We have reviewed exciting examples in which the SELEX technology was applied to obtain promising tools that may help to facilitate our understanding of biological processes and to interfere at distinct points in signal transduction cascades. High affinities and specificities of aptamer/target-interactions can now routinely be achieved. Furthermore, a wide spectrum of chemical modifications of nucleotides is known which greatly increase the stability of RNA molecules in biological materials, considerably enhancing their application potential. The aptamer technology shows that the combination of organic synthesis and molecular biology can contribute to interesting and promising new drug leads, which may

very soon find their way into daily clinical practice or onto the laboratory benches of many researchers in the life sciences.

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