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Genetic coding algorithm for sense and antisense peptide interactions

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ABSTRACT

Sense and antisense peptides, i.e. peptides specified by complementary DNA and RNA sequences, interact with increased probability. Biro, Blalock, Mekler, Root-Bernstein and Siemion investigated the recognition rules of peptide—peptide interaction based on the complementary coding of DNA and RNA sequences in 3′ → 5′ and 5′ → 3′ directions. After more than three decades of theoretical and experimental investigations, the efficiency of this approach to predict peptide—peptide binding has been experimentally verified for more than 50 ligand—receptor systems, and represents a promising field of research. The natural genetic coding algorithm for sense and antisense peptide interactions combines following elements: of amino acid physico-chemical properties, stereochemical interaction, and bidirectional transcription. The interplay of these factors influences the specificity of sense—antisense peptide interactions, and affects the selection and evolution of peptide ligand—receptor systems. Complementary *mRNA codon—tRNA anticodon complexes*, and recently discovered Carter-Wolfenden *tRNA acceptor-stem code*, provide the basis for the rational modeling of peptide interactions based on their hydrophobic and lipophilic amino acid physico-chemical properties. It is shown that the interactions of complementary amino acid pairs according to the hydrophobic and lipophilic properties strongly depend on the central (second) *purine base* of the mRNA codon and its *pyrimidine* complement of the tRNA anticodon. This enables the development of new algorithms for the analysis of structure, function and evolution of protein and nucleotide sequences that take into account the residue's tendency to leave water and enter a nonpolar condensed phase considering its mass, size and accessible surface area. The practical applications of the sense—antisense peptide modeling are illustrated using different interaction assay types based on: microscale thermophoresis (MST), tryptophan fluorescence spectroscopy (TFS), nuclear magnetic resonance spectroscopy (NMR), and magnetic particles enzyme immunoassay (MPEIA). Various binding events and circumstances were considered, e.g., in situations with—short antisense peptide ligand (MST), L- and D-enantiomer acceptors (TFS), in low affinity conditions (NMR), and with more than one antisense peptide targeting hormone (MPEIA).

1. Introduction

The standard genetic code defines rules for the transcription of biological DNA and RNA information, and related protein synthesis, namely translation rules. It is often described as a translation table by which nucleic acid sequence information is interpreted as polypeptide (Carter and Wolfenden, 2016). The natural property of the genetic code is the "complementarity principle", defined by the physicochemical nucleotide interaction, i.e. pairing, of uracil (U) or thymine (T) with adenine (A), and cytosine (C) with guanine (G) (Table 1A).

A large body of theoretical and experimental evidence over the last three decades supports the thesis that peptides specified by the complementary DNA and RNA sequences, i.e. sense and antisense peptides, interact with increased probability (Root-Bernstein, 2015; Root-Bernstein, 2005; Biro, 2007; Siemion et al., 2004; Miller, 2015; Blalock, 1995; Štambuk et al., 2014). The idea of

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Table 1
(**A**) Standard genetic code Table. Sixty-four 3-letter codons specifiy 20 amino acids and 3 stop codons for the protein synthesis. (**B**) The number of complementary (sense – antisense) amino acid pairs depends on the direction of translation (3′ → 5′ = left → right or 5′ → 3′ = right → left).

A

First (5′) letter	Second letter				Third (3′) letter
	U	C	A	G	
U	F	S	Y	C	U
	F	S	Y	C	C
	L	S	stop	stop	A
	L	S	stop	W	G
C	L	P	H	R	U
	L	P	H	R	C
	L	P	Q	R	A
	L	P	Q	R	G
A	I	T	N	S	U
	I	T	N	S	C
	I	T	K	R	A
	M	T	K	R	G
G	V	A	D	G	U
	V	A	D	G	C
	V	A	E	G	A
	V	A	E	G	G

B

Amino acid	Antisense 3′ → 5′	Antisense 5′ → 3′
F	K	K, E
L	D, E, N	E, Q, K
I	Y	N, D, Y
M	Y	H
V	H, Q	H, D, N, Y
S	S, R	G, R, T, A
P	G	G, W, R
T	W, C	G, S, C, R
A	R	R, G, S, C
Y	M, I	I, V
H	V	V, M
Q	V	L
N	L	I, V
K	F	F, L
D	L	I, V
E	L	L, F
C	T	T, A
W	T	P
R	A, S	A, S, P, T
G	P	P, S, T, A

sense and antisense peptide binding, mediated by specific through-space amino acid paired interactions, was first proposed by Mekler (Biro, 2007; Tropsha et al., 1992; Mekler, 1970; Mekler and Idlis, 1981). Biro, Blalock, Root-Bernstein and Siemion investigated different aspects of peptide—peptide interaction based on the coding of antisense DNA and RNA sequences in 3′ → 5′ and 5′ → 3′ directions (Table 1B). Critical examination of the concept has confirmed the relevance and applicability of antisense peptides to *in vitro* and *in vivo* research (Root-Bernstein, 2015; Root-Bernstein, 2005; Biro, 2007; Siemion et al., 2004; Miller, 2015; Blalock, 1995; Štambuk et al., 2014).

Until recently, most discussions related to the physico-chemical properties of antisense peptides relied on the concept of classic hydropathy (Miller, 2015; Blalock, 1995) based on the fact that the second base of the messenger RNA (mRNA) codon specifies amino acid hydropathy as an important factor regarding protein interactions. The hydropathy index of an amino acid was proposed in 1982 by Jack Kyte and Russell F. Doolittle (Kyte and Doolittle, 1982) as a number representing the hydrophobic or hydrophilic properties of amino acid side chains.

In this study we investigate sense-antisense peptide relationships using a new transfer RNA (tRNA) acceptor-stem code, introduced by Carter and Wolfenden (Carter and Wolfenden, 2015). This acceptor-stem code, related to amino acid size and lipophilicity, is distinct from the code in the anticodon that is based on amino acid hydrophobicity or hydrophilicity, and preserves key properties of stereochemically-encoded peptides.

2. Results and discussion

2.1. Antisense peptides and complementary nucleotide coding

The purposeful design of specific bioactive complements is related to the theory that antisense peptides or proteins bind with high affinity to each other (Root-Bernstein, 2015; Root-Bernstein, 2005; Biro, 2007; Siemion et al., 2004; Miller, 2015; Blalock, 1995; Štambuk et al., 2014). According to Siemion et al. there are three main hypotheses concerning the interaction of sense—antisense peptides based on complementary coding principles (Siemion et al., 2004):

1. the Root-Bernstein approach to the interaction of complementary peptides, which is based on the stereochemical interaction of sense—antisense amino acids coded by anticodons read in parallel with the coding DNA strand (3′ → 5′ translation).
2. the Mekler-Blalock antisense hypothesis, which is based on the hydropathic complementarity principle of the sense—antisense interaction that is independent of the direction of triplet reading (5′ → 3′/3′ → 5′), since the central base of the coding triplet specifies the hydropathy of the amino acid.
3. the Siemion hypothesis of sense—antisense peptide interaction, which is based on the periodicity of the genetic code, i.e. *the Siemion one-step mutation ring of the code*, that is related to: a) *the Argyle amino acid similarity ring* (residue replacement during evolution), b) *the Pieber-Tohác amino acid ring*, i.e. codon replacement probability matrix, and c) the Chou-Fasman conformational parameters and amino acid compositional frequencies in proteins. The resulting sense—antisense amino acid pairs are in most cases similar to 3′ → 5′ translation according to Root-Bernstein.

2.1.1. Rules and patterns of complementary peptide coding

The algorithms for the antisense peptide design based on complementary peptide binding in the 3′ → 5′ and 5′ → 3′ translation direction were introduced in the 1980s by Root-Bernstein (Root-Bernstein, 2015; Root-Bernstein, 2005; Root-Bernstein, 1982) and Blalock et al. (Blalock, 1995; Blalock and Bost, 1986; Zull and Smith, 1990), and their efficiency has been experimentally verified for more than 50 ligand—receptor systems (Root-Bernstein, 2015; Root-Bernstein, 2005; Biro, 2007; Siemion et al., 2004; Miller, 2015; Blalock, 1995; Štambuk et al., 2014).

Simple transformations of complementary (sense—antisense) peptide coding in both directions (*left → right* and *vice versa*) define pivotal aspects of the natural code presented in Table 1:

1. two of the basic types of sense—antisense amino acid hydropathy patterns (neutral-neutral, nonpolar-polar) are *symmetric*, i.e. of identical pattern type, with respect to *left → right* and *right → left* translation of the coding table (Fig. 1);
2. two of the basic types of sense – antisense amino acid hydropathy patterns are *assymetric—chiral*, i.e. of different pattern number, with respect to *left → right* and *right → left* translation of the coding table (Fig. 1).

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