RESEARCH ARTICLE

A Proposed Complementary Pairing Mode Between Single-Stranded Nucleic Acids and β-Stranded Peptides: A Possible Pathway for Generating Complex Biological Molecules

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A structure for a heterologous double-stranded molecule consisting of an oligoribonucleotide and a β-stranded oligopeptide, paired through complementary Watson-Crick-type hydrogen bonding, is proposed. The basis for such complementary pairings between oligoribonucleotides and oligopeptides is the close correspondence of the distances between the side-chains attached to the backbones of the two molecules. Both inter-nucleotide spacing and inter-amino acid side-chain spacing are approximately 3.4 Å. These kinds of interactions may have implications in protein-mediated-RNA splicing. Formation of a heterologous duplex through such a pairing mode could provide a simple coding mechanism for a reciprocal information transfer between oligonucleotides and oligopeptides. Because of its simplicity and versatility, allowing both specific and nonspecific coding, interactions via these kinds of pairing may have been relevant for prebiotic molecular evolution and for generating complex biological molecules. © *1995 John Wiley & Sons, Inc.*

Key Words: geometrical complementarity/molecular evolution/protein-dependent-RNA splicing/recognition specificity/structural compatibility.

INTRODUCTION

Complementary pairing of molecules through hydrogen bonds is a fundamental principle in the structural organization of both small molecules and macromolecules [1, 2]. The double helical conformation with paired strands is the commonest structural motif of DNA, and considerable portions of RNA molecules are organized into duplexes as well [3]. Two or more peptide strands arranged into β-sheets constitute an important secondary structural motif in protein folding [1, 4]. Pairings between individual bases and amino acid side-chains are essential for the specificity of the interactions between nucleic acids and proteins. Such specific interactions determine the fidelity of biological information transfer in DNA replication, RNA transcription, protein translation, DNA recombination, protein-DNA and protein-RNA recognition, and consequently genetic regulation. Some of the individual interactions underlying specificity had been predicted on theoretical grounds by Seeman et al. [5]. The au-

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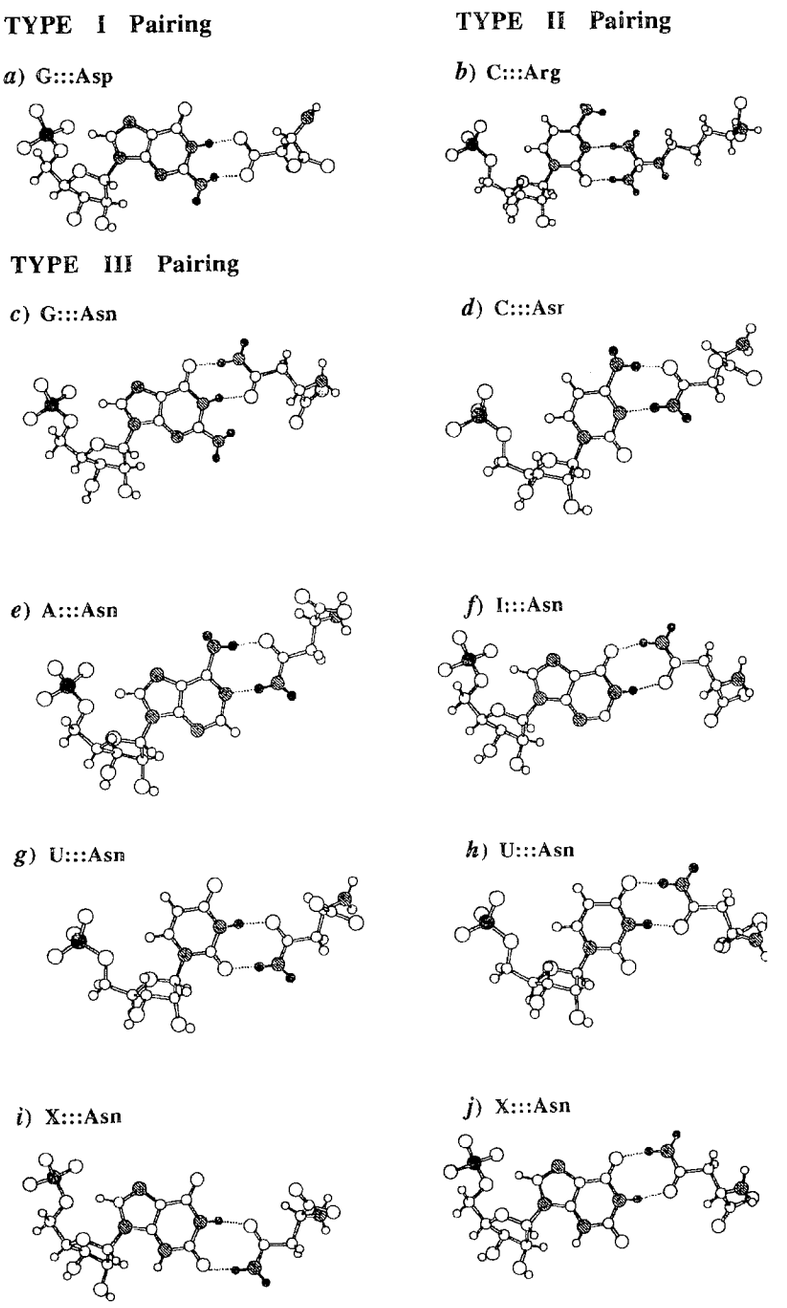
FIGURE 1



Complementary pairings via Watson-Crick-type hydrogen bonds between amino acid side chains and nucleotides. Type I pairing: (a) G:::Asp, Type II pairing: (b) C:::Arg, Type III pairing: (c) G:::Asn, (d) C:::Asn, (e) A:::Asn, (f) I:::Asn, (g) & (h) U:::Asn, (i) & (j) X:::Asn. Glu can substitute Asp to pair with G; Lys can substitute Arg to pair with C; Gln can substitute Asn to pair with all nucleotides. U and X can pair with Asn and Gln in two different constellations.

thors pointed out the importance of a number of interactions between bases and amino acid side-chains via two hydrogen bonds for the sequence-specific recognition of double-stranded DNA by proteins. These postulates have been largely confirmed by the accumulated structural data on protein-DNA and a few protein-RNA complexes [6-9]. Several interaction modes of RNA and its binding protein motifs have been described and summarized in a recent review [10]. In many cases, β-stranded motifs are believed to be involved in such interactions. However, at present time there is little detailed structural information available on the interactions between single-stranded DNAs or RNAs and their binding proteins.

We wish to put forward a model (E-Z model) for an interaction between nucleic acids and peptides which is based on a complementary pairing between a single-stranded nucleic acid and a β-stranded peptide through Watson-Crick-type hydrogen bonds. Albeit simple, iterative complementary pairings of the proposed kind between a variety of nucleic acid and oligopeptide fragments could eventually generate a wealth of complex biological molecules for reciprocal information transfers.

THEORY AND MODEL

Complementary Pairings Between Nucleotides and Amino Acids via Two Watson-Crick-Type Hydrogen Bonds

In the individual nucleic acid bases and the side chains of amino acids, the geometrical arrangement of hydrogen bond accepting and donating groups allows the formation of pairs between them through two hydrogen bonds [3 and references therein]. Although there are multiple ways to form hydrogen bonds between the bases and the amino acid side chains, only Watson-Crick-type arrangements will be considered in our model. Moreover, only amino acids with biological relevance are considered, i.e., L-amino acids. Possible pairings with two complementary hydrogen bonds are depicted in Figure 1. There are three types of Watson-Crick-type hydrogen bond pairings between bases and the side chains of several amino acids. In Type I pairing, guanine (G) donates in two hydrogen bonds, and the carboxylic group on the side chains of Asp and Glu, as well as other organic acids found under prebiotic conditions, can accept two hydrogen atoms [Figure 1(a)]. In Type II pairing, cytosine (C) accepts in two hydrogen bonds, and the amino group on the side chains of amino acids, such as Arg and Lys, as well as amino groups found in other compounds, can donate two hydrogen atoms [Figure 1(b)]. Type I and II pairings constitute relatively specific recognition in the sense that Asp and Glu can only

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pair with guanine. Similarly, Arg and Lys can only pair with cytosine. Conversely, in Type III pairing, the nucleic acid bases as well as the side chains of the amino acids Asn and Gln act as both, hydrogen bond donors and acceptors [Figure 1(c-j)]. Type III pairing is nonspecific and Asn and Gln can pair with any of the four genetically relevant nucleic acid bases, adenine (A), guanine (G), cytosine (C) and uracil (U)/thymine (T) as well as with the metabolic intermediates inosine (I) and xanthine (X). The nonspecific pairing behavior between Asn or Gln and the bases, especially U and X, is based on the geometrical arrangement of the hydrogen bond accepting and donating functions. In both U and X, the donor nitrogen is flanked by the two acceptor oxygen atoms [Figure 1(g-j)]. Because Type III pairing allows pairing variations, it is plausible that such pairings may have contributed, to some extent, to molecular diversity in prebiotic evolution. In addition to three Watson-Crick-type hydrogen bond pairings, there exist Hoogsteen-type complementary pairings between bases of nucleic acids and side chains of amino acids [5]. In this case, O6 and N7 of guanine/inosine/xanthine act as two hydrogen bond acceptors and the guanidinium group of Arg and the amino group of Lys act as hydrogen donors, therefore two hydrogen bonds exist in such pairs. Similarly, N6 and N7 of adenine can form two complementary hydrogen bonds with Asn/Gln where both adenine and Asn/Gln act as hydrogen bond donors and acceptors [5]. Furthermore, N2 and N3 of guanine may also form two hydrogen bonds with Asn/Gln. However, it is not known if this kind of pairing can produce a heterologous complementary pairing structure with continuity. Additional model constructions and structural analyses will be carried out in a separate communication.

A number of side chains of amino acids, such as Ser, Thr, Tyr, and His, can form a single hydrogen bond with the bases and Phe, Tyr, Trp, and His can stack with the bases of nucleotides. However, because the formation of a single hydrogen bond lacks the structural stability and specificity necessary for a coding system, these kinds of pairings are not considered in our current model. Nevertheless, it is possible that these amino acids may have also played an important role in interacting with RNA and in reciprocal information transfer during prebiotic molecular evolution.

Geometrical Complementarity and Structural Compatibility Between Nucleic Acids and Peptides

The basis for the complementary pairings between oligoribonucleotides and oligopeptides is the close correspondence of the distances between the side-chains attached to the backbones of the molecules. The distances, namely, inter-nucleotide spacing and inter-amino acid side-chain spacing, measure approximately 3.4 Å in both cases [4, 11]. It is possible that such a close relationship may not be merely an arithmetical coincidence. Rather, it could have been the result of rigorous prebiotic molecular selection and evolution.

MODEL BUILDING

In the proposed structural model for a heterologous oligoribonucleotide and oligopeptide duplex, alternating repetitive sequences were utilized to demonstrate the geometrical complementarity and structural compatibility between nucleic acids and peptides. However, alternating repeats are not a prerequisite for formation of such a duplex. Rather, a wide variety of complementary oligonucleotides and peptides may form such duplexes (data not shown).

Construction of a Plastic Model

Initial model building trials using Maruzen Biochemistry Molecular Models (Maruzen Co., LTD, Tokyo, Japan) indicated that an unwound single strand of RNA and a peptide in a slightly bent β-stranded conformation could be easily joined to a complex by forming pairs of hydrogen bonds between the nucleic acid bases and the side chains of the amino acids. To construct the heterologous duplex we used a hexa-ribonucleotide with sequence 5′-GUGUGU-3′, and a hexapeptide with sequence N-Asp-Val-Asp-Val-Asp-Val-C. The length of the peptide was chosen in accordance with the finding that the average number of residues in the single strands of β-sheets in proteins is in the range of 4 to 12, with an average of 6 to 7 [4]. Also, an oligopeptide composed of alternating hydrophilic and hydrophobic residues very likely adopts a β-sheet conformation in water [12, 13] and under physiological salt conditions [14-17]. Furthermore, only the two oxygen atoms from the carboxylic group of the side chains of Asp and Glu can accept two hydrogen atoms from the N1 and N2 positions of guanine, and thus form sequence-specific pairs. The side chain of Asp is negatively charged, thus preventing it from interacting with the phosphodiester backbone of nucleic acids. In addition, Val residues form strong hydrophobic interactions due to the branched isopropyl side chains, oriented on one side of the β-strand in an alternating sequence [14] such as the one chosen for our model.

Heterologous duplexes between nucleic acids and peptides constitute a very simple coding system for reciprocal information transfer between oligonucleotides and oligopeptides with possible relevance for prebiotic molecular evolution.

Construction of the Computer Model

The above skeletal model was then used to construct a computer model of the duplex. The starting components consisted of a single strand of oligoribonucleotide, i.e., an RNA with a conformation adopted in an ideal A-form duplex and the hexapeptide in an ideal β-strand arrangement. The duplex was assembled by unwinding the RNA, without chang-

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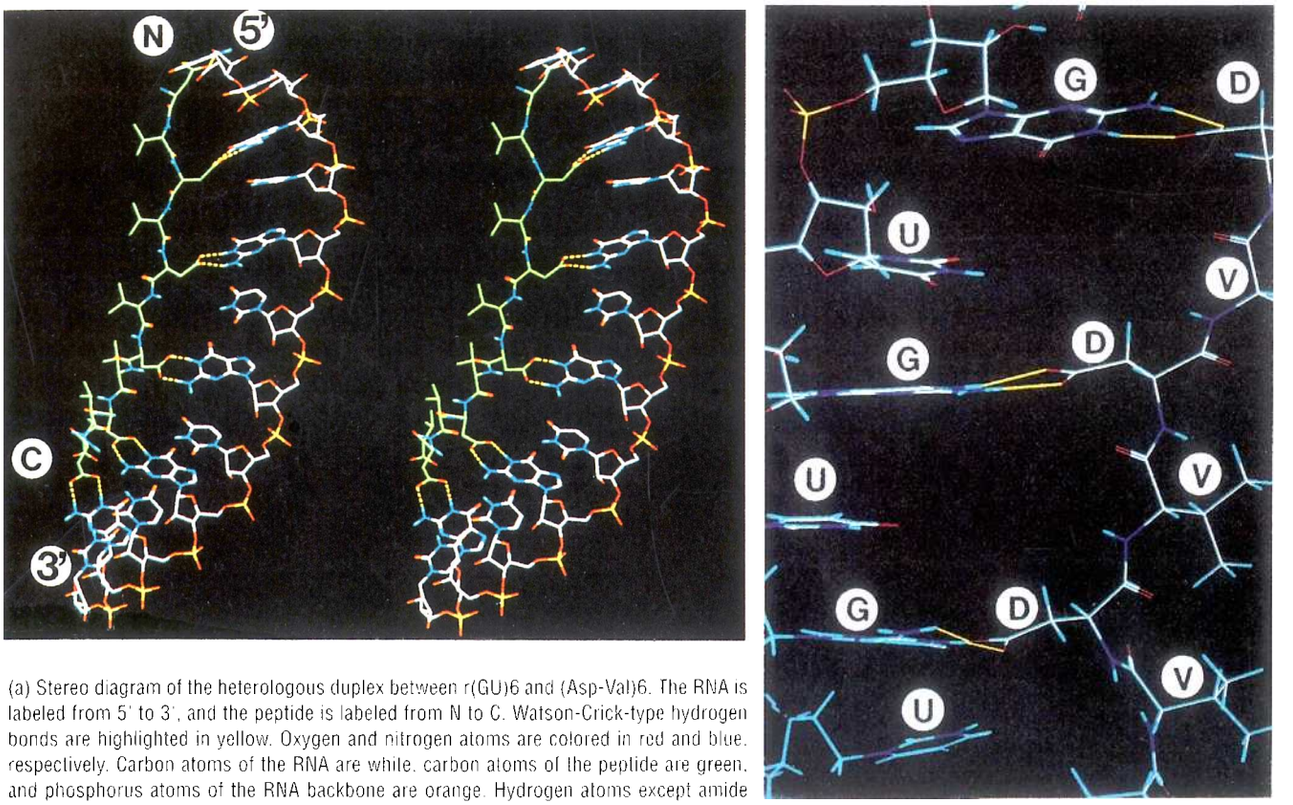
FIGURE 2



(a) Stereo diagram of the heterologous duplex between r(GU)6 and (Asp-Val)6. The RNA is labeled from 5' to 3', and the peptide is labeled from N to C. Watson-Crick-type hydrogen bonds are highlighted in yellow. Oxygen and nitrogen atoms are colored in red and blue, respectively. Carbon atoms of the RNA are white, carbon atoms of the peptide are green, and phosphorus atoms of the RNA backbone are orange. Hydrogen atoms except amide hydrogens in the peptide, and those participating in hydrogen bonds have been omitted for clarity. (b) Stacking interaction of the paired molecules. The stacking interactions between the bases are visible and enlarged for clarity. Guanine (G) forms two hydrogen bonds (colored yellow) with Asp (D). Uracil (U) does not directly form hydrogen bonds with Val (V), but may form hydrogen bonds with the backbone of the peptide via water molecules.

ing the ribose C3'-*endo* puckers, and introducing a slight right-handed twist with the peptide. This model was refined with force-field methods using potentials for bond lengths, bond angles, torsion angles and nonbonded contacts. Initial restraints were applied for hydrogen bonding distances (2.7 Å) and angles (C-N-O-values of 120°), as well as to generate coplanarity between the guanine bases and the carboxylic group of Asp residues. No charges for the RNA backbone or the carboxylic groups of Asp were used throughout the refinements. Two hexamer duplexes were then assembled into a dodecamer and refined in a similar way. Subsequently, the relaxed duplex was rebuilt by adjusting the torsion angles of the joined backbones of RNA and peptide, and shifting the complete peptide with respect to the RNA by superimposing the positions of the carboxylic oxygen atoms of Asp side chains onto idealized positions of acceptors. The model was then further refined and during the terminal refinement cycles, only soft distance restraints between the hydrogen bonding partners were retained. In the final model, the hydrogen bond lengths fall into a range between 2.45 Å and 3.1 Å. The heterologous hexamer duplex was also immersed in a "water bath" and subjected to molecular dynamics for several pico-seconds with program AMBER [18]. The two strands did not separate and there were no drastic conformational changes in either the RNA or the peptide. The calculated energies for the model suggested a stable arrangement. Coordinates for both duplex models may be obtained from the authors.

RESULTS AND DISCUSSION

We reasoned that interaction modes of single-stranded nucleic acids and motifs in proteins are likely to be significantly different from those of motifs in proteins with double-stranded nucleic acids. Nevertheless, such interactions could utilize the standard structural motifs of nucleic acids and peptides, either in their canonical forms or involving subtle conformational alterations. For construction of the heterologous duplex, only pairing modes involving the acceptors and donors of bases normally engaged in Watson-Crick-type hydrogen bonds were considered as hydrogen bonding partners for the side-chains of the peptide. An oligoribonucleotide strand was used as the nucleic acid component of the duplex, and the standard C3'-*endo* conformation of its riboses was not altered during model building. A stereo diagram of a computer model of such a duplex between $r(GU)_6$ and $(Asp-Val)_6$ is depicted in Figure 2(a).

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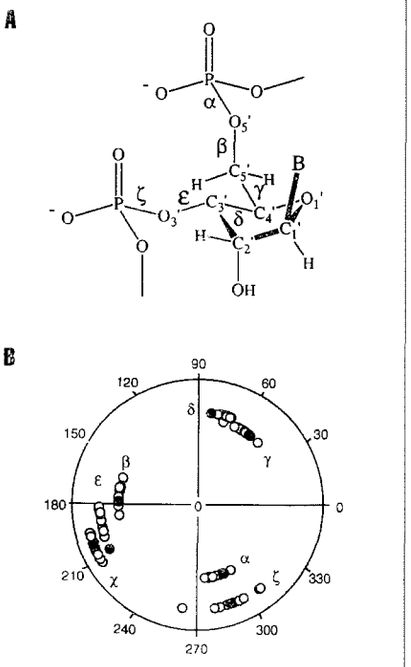
Structure of the Oligoribonucleotide

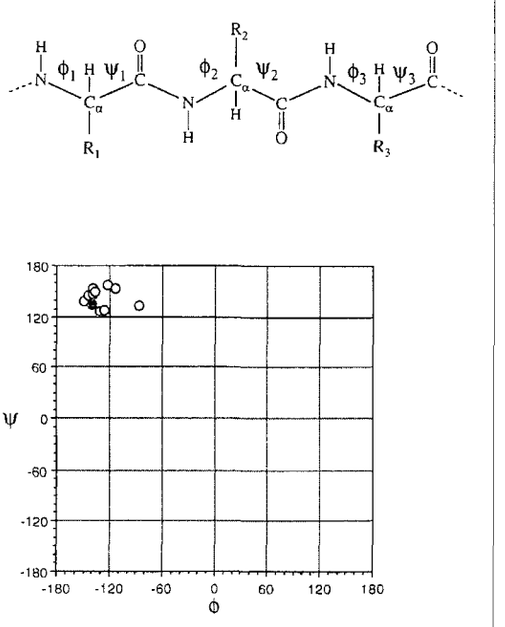
In the duplex, the C 5′-end of the RNA strand is arranged opposite the N-terminus, and the C 3′-end is opposite the C-terminus of the oligopeptide. This relative orientation of the RNA and peptide strands is somewhat arbitrary, and modeling shows (data not shown) that RNA-peptide duplexes with opposite orientation of strands can also be constructed. Moreover, it should be noted that although an RNA strand was chosen to build the heterologous duplex, a DNA strand can be paired with a peptide strand in a similar way. The 12 nucleotides of the RNA strand in the modeled duplex constitute a single-helix half-turn, and compared to a standard double-helix A-RNA backbone, about twice as many residues are thus required to form a complete turn. Despite of the unwinding of the RNA strand, its backbone and glycosidic torsion angles still lie in the conformational ranges observed for those parameters in standard RNA A-form duplexes (Figure 3). Furthermore, this conformation allows stabilizing hydrogen bonding between the ribose 2′ hydroxyl group and acceptors such as the O 4′ and O 5′ oxygen atoms of the adjacent residues [3, 19]. Although the stacking interactions between bases in the RNA strand of the RNA-peptide duplex are somewhat reduced compared to standard nucleic acid duplexes, inspection of the model shows that significant stacking still exists [Figure 2(b)]. From the model building studies, it appears that there is a potential water-mediated hydrogen bonding contact between uracil N3 and the carbonyl oxygen form the opposite located residue in the peptide backbone. Similarly, only minor conformational deviations are necessary in the peptide to pair it with the RNA.

FIGURE 3



Structural parameters of the oligoribonucleotide (GU)6 in the heterologous duplex pairing model. (a) Definition of torsion angles in an oglionucleotide backbone [3, 19]. The backbone torsion angles are defined as follows: O3′-P-_-O5′-β-C5′-_-C4′-∂-C3′—O3′—P, and the glycosidic torsion angles are defined as O4′-C1′-N9-C4 (guanine) and O4′-C1′-N1-C2 (uracil), respectively. (b) Backbone and glycosidic torsion angles of the oligoribonucleotide (GU)6 strand. Open circles represent the angles in the model and the solid circles correspond to the averaged values in the X-ray fiber structure of double helical A-RNA [3].

FIGURE 4



Structural parameters of the oligopeptide (VD)6. (a) Definition of torsion angles in the peptide backbone. The torsion angles are defined as N'>i-Ø-C_ and C_—C'>i. (b) Ramachandran diagram for the oligopeptide strand. Open circles represent the angle pairs in the dodecapeptide (omitting residues Asp[13] and Val[24], the residues in the oligonucleotide strand are numbered 1-12, and those of the oligopeptide strand are numbered 13-24), and the solid circle corresponds to the angle pair of a strand in an antiparallel β-sheet with ideal conformation [1].

Structure of the Oligopeptide

A peptide in β-stranded form was chosen for the pairing model construction [Figure 4(a)]. A Ramachandran diagram [20] for the dodecapeptide illustrates that its backbone angles fall well within the ranges normally associated with β-stranded conformations [Figure 4(b)]. Moreover, the pairing with the RNA requires the peptide to assume a right-handed twist, which is quite common with β-strands arranged in sheets [21, 22]. Combining an RNA strand and an oligopeptide to form a duplex, in which the residues along the strands are paired via hydrogen bonds, does not seem to require conformational adaptations which exceed those normally observed in structural arrangements of the individual duplex components. Oligopeptides usually do not have stacking interactions between the side-chains as in the case of nucleic acids. However, when the sequences of amino acids are alternating, with every other residue being aromatic (Tyr, Phe, Trp), their stacking may contribute significantly to the overall stability. In addition, amino acids with hydrophobic residues, Ile, Leu, Val, Ala and Met, oriented on one side of the β-strand, can contribute substantially to peptide stability. From Figure 2, it is apparent that the side-chains of Val residues, all pointing to the same side of the duplex, form close hydrophobic contacts to one another. Although our model combines two single strands into a duplex, one can also imagine an RNA strand interacting with the outermost peptide strand of an extended

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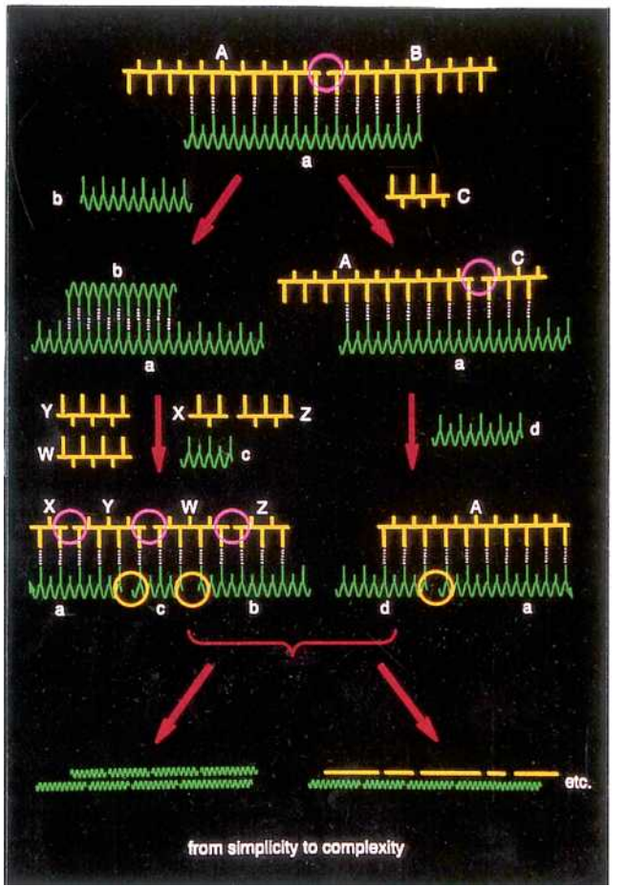
β-sheet, leading to a stable complex. That the oligonucleotide and peptide backbones are compatible has recently been demonstrated by a stable pairing between an RNA strand and a so-called peptide nucleic acid (PNA) strand [23]. In PNAs, the phosphodiester backbone is replaced by a polyamide, resulting in a spacing between bases which is similar to the one found between the side-chains of amino acids in peptides. Moreover, due to the location of the amide groups, both in the backbone and in the side-chains of a PNA, the flexibility of its backbone is comparable to the one of a peptide [23].

A Possible Interaction Mode in Proteins

Although no experimental structural data is yet available, it is presumed that the pairing mode described in our model may contribute to interactions between the bases of single-stranded nucleic acids and the side-chains of proteins. Specific pairings between bases and amino acids (Figure 1) may be important for several biological processes. Some proteins may form stable complexes with RNA for processing and translational regulations. A recent observation by Perutz et al. [24] points out that several conserved RD nuclear RNA-binding proteins in human and mouse have a binding motif with clusters of alternating Arg-Asp (RD) [25]. They proposed that this RD motif may adapt a β-sheet conformation and interact with RNA. During protein-dependent RNA processing, the RNA needs to be folded in a particularly stable conformation in order to guarantee correct splicing. Specific pairing between selected segments of single-stranded RNA and β-stranded motifs, as described by our model, may enable precise splicing. The observations and the proposal by Perutz et al. suggest that a segment of the U1 70K protein with Arg-Asp in a β-sheet structure may bind with RNA in a group of small nuclear ribonucleoproteins U1 70K (snRNP U1) of human, *Xenopus*, and *Drosophila* [26-28]. It is known that snRNP U1 70K participates in protein-dependent RNA splicing. The proposal by Perutz et al. reinforces our hypothesis. In addition, such specific pairing may also be employed in protein translational regulation because several clusters of charged residues such as Lys and Glu in a proposed β-sheet structure are found in ribosomal proteins [29]. Conversely, sequence motifs with alternating Ala-Gln [30] and the like, for example, can form nonspecific hydrogen bond pairings with a variety of base sequences [see Figure 1(c-j)]. This pairing may be important in a nondiscriminating dynamic chromatin organization, and in the stabilization of the unwound and separated strands of double-helical DNA in replication, transcription and recombination. Furthermore, it may be also possible to construct a triplex between two β-stranded peptides and a single-stranded nucleic acid, where the second peptide strand forms Hoogsteen-type hydrogen bonding with bases via N6/O6 as well as N7 positions of purines. We wish only to focus on Watson-Crick-type complementary pairing in this communication, and a detailed analysis involving other types of pairing will be emphasized in a separate communication.

FIGURE 5



From simplicity to complexity. A possible pathway for generating complex biological molecules. A proposed physical basis of bio-molecular evolution is schematically illustrated. Oligopeptides are in yellow, whereby the horizontal lines represent the backbones and the vertical lines represent amino acid side chains. The long vertical lines correspond to those amino acids which form pairs with the bases of the nucleic acids and the short lines on the opposite side represent the amino acids which stabilize the β-stranded conformation of the oligopeptide. Oligonucleotides are in green, whereby long vertical lines represent purines and short ones represent pyrimidines. The circles between adjacent molecules (violet for oligopeptides and orange for oligonucleotides) point out the gaps which may be closed by self-condensation or by an auto-catalytic ligation. The pairings may be heterologous between oligopeptides and oligonucleotides and homogeneous between oligonucleotides. Iterative pairings and separations of such species may eventually generate an immense biological molecular complexity.

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A Simple and Versatile Coding System in Prebiotic Molecular Evolution

Heterologous duplexes between nucleic acids and peptides constitute a very simple coding system for reciprocal information transfer between oligonucleotides and oligopeptides with possible relevance for prebiotic molecular evolution. The nonspecificity of certain pairings is a prerequisite for molecular diversification, selection, and evolution. During the early stages of molecular evolution, error tolerance is extremely important, it is "the primary requirement for a model molecular population taking its first faltering steps toward life" [31]. In our model, the nature of the pairing combinations between amino acids and nucleotides would determine the relative numbers of specific and nonspecific prebiotic information transfers. Such a reversible communication between oligopeptides and oligonucleotides could eventually have set forth the molecular diversity and complexity now encountered. Kauffman also proposed that "mixed polymer systems which are autocatalytic are not unthinkable" [32]. It is known from laboratory studies that peptides with a tendency to form β-sheets are selected to a greater extent due to their self association under certain conditions [33]. On the other hand, mono- and short oligo-ribonucleotides can polymerize into longer RNA molecules [34]. We postulate that in the presence of both β-sheet-forming peptides and single-stranded RNA, reciprocal information transfer may have been facilitated under certain prebiotic conditions. Since our proposed complementary pairing is reciprocal, iterative pairings, ligations/condensations, and separations may produce an immense amount of complex biological molecular information.

From Simplicity to Complexity

We have proposed a simple and versatile heterologous pairing mode between two molecules that are key elements for molecular information transfers. The initial pairings may be simple but allow degeneracy and overlaps (Figure 5). The gaps representing the molecular bond formation may be closed when the ends of molecules are in close proximity. This will likely result in offsprings that are slightly different from the initial molecules. Nevertheless, iterative pairings between overlapping fragments, both in a homologous fashion between nucleic acids and in a heterologous fashion between nucleic acids and oligopeptides may eventually generate an enormous molecular complexity. These molecules in turn may have evolved into the diverse molecules we now encounter. It is interesting to point out that all biological molecules are made from the same sets of simple building blocks, such as nucleic acids and amino acids, etc., and the same simple genetic code is common among all organisms.

Experimental Predictions

Based on our proposed model, several specific predictions can be made. All of these can be tested experimentally. (i) The proposed interaction mode between single-stranded nucleic acids and β-stranded peptides may be observed in the binding motifs of certain nucleic acid binding proteins. (ii) Heterologous double-stranded molecules consisting of oligopeptides and oligonucleotides may have a measurable melting curve upon thermal denaturation in solution. (iii) The structures of the heterologous duplexes may be measurably different from those of either the single-stranded oligonucleotide or the oligopeptide alone, or of homogeneous pairs thereof. These structural differences could be detected by circular dichroism (CD), UV, Raman and NMR spectroscopy. (iv) Short oligopeptides may be condensed at a higher rate in the presence of complementary oligonucleotides than in the absence of such templates. Likewise, (v) short oligonucleotides may be ligated at a higher rate in the presence of complementary oligopeptides than in the absence of the peptide template. These different rates may reflect the effectiveness of direct reciprocal information transfer. We hope that our hypothesis will stimulate such experiments in the near future.

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