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Review Article

Chemical Kinship of DNA and Protein

Heinz Kohler*

Department of Microbiology and Immunology, University of Kentucky, USA

***Corresponding author:** Heinz Kohler, Department of Microbiology and Immunology, University of Kentucky, Lexington KY 40537, USA

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Abstract

The Molecular Recognition Theory [MRT] of Blalock can predict amino acid sequence regions that have mutual attraction in peptides and proteins. Using this concept an antibody affinity domain was discovered leading to novel approaches in the immunotherapy of human diseases. MRT has also led the foundation for a binary code based interpretation of the genetic code. Reading the binary code in DNA database has predicted protein-protein contacts described by three-dimensional models.

Keywords: Molecular recognition theory; DNA; Homophilic antibodies; protein

The Molecular Recognition Theory

In 19894 Blalock and Smith [1] recognized an interesting relationship between the genetic code and the amino acids encoded. Codons for hydrophilic and hydrophobic amino acids on one strand are complementary to codons for hydrophobic and hydrophilic amino acids on the other strand, respectively. The segregation of codons into a group that encodes hydrophilic amino acids and a group that encodes hydrophobic is based on the chemical nature of the second base in the triplet codon. Purin nucleotides in the second codon position encod hydrophilic amino acids and pyrimidine encode hydrophobic amino acids. Bost et al. [2] reasoned that this pattern can result in the binding of peptides that are encoded by complementary RNA strands. This hypothesis was confirmed by testing the binding of ACTH to a peptide encoded by the complementary RNA strand coding for ACTH. The specificity of this interaction was demonstrated with antibodies to the peptide encoded by the complementary RNA for ACTH recognizing the adrenal cell ACTH receptor. The finding that the code controls not only the transcribed amino acid but also peptides encoded by both complementary DNA strands bind to each other indicates the existence of another code, a two-dimensional genetic code, that predicts how proteins interact (a proteomic code) (for review see [3]). Blalock uses the hydropathic complementarity to propose a "Molecular Recognition also Theory" (MTR) [4]. A list of the usage of this chemical codon relation has been compiled by Heal at al [5].

While most of the reports on using the Molecular Recognition Theory (MRT) provide proof of principle MRT was also used to develop a new therapeutic concepts. Kang et al. [6] identified the sequence region in the T15 antibody that causes self-binding. Subsequently, Zhao et al. [7,8] used photo-affinity conjugation to crosslink the T15 peptide to antibodies thereby converting antibodies into homophilic antibodies with enhanced potency. Kohler et al. [9] used industry standard methods(recombinant technology) to generate a fusion protein homophilic antibody demonstrating the therapeutic utility of homophilic antibodies. Recently, the discovery of the homophilic domain let Kohler and Bryan [10] to use the homophilic peptide to inhibit the dimerization of the B-cell receptor in malignant B-cell tumors. This measure blocked the growth signal pathway and suppressed tumor growth. Galin et al. [11] used MRT to develop a vaccine against Myasthenia Gravis.

The hidden binary code

Inspection of the triplet codes for amino acids shows that their hydrophobicity is determined by the nucleotide base in the second position of the triplet. The codon assignment to the second base has been selected during the evolution of the genetic code [12]. This reasoning let Kohler et al. [13] to propose the existence of an ancient binary code that determines the physical-chemical characteristic of encoded amino acids. Nucleotides in the single letter primordial code using purine and pyrimidine nucleotides are chemical compounds that have different hydrophilicities and stereo-chemical shapes. Accordingly, code evolution started with a single letter code language encoding a reduced set of amino acids. Such a primordial code allows reading the code in two directions that would support genetic replication mechanism without or with RNA enzymatic processes (ribozymes). Because of the distinctly different physical-chemical properties of the nucleotides it can be envisioned that DNA or RNA nucleotides can pair with amino acids of complementary structures and hydrophilicity providing an effective and simple method of genetic replication.

The ancient binary code controlling the hydropathy of amino acids is still present in the second base of the triplet. As proposed [14], the hidden binary code could be used to detect protein regions that are involved in protein contacts, thereby becoming a search concept in proteomics. Finkel and Kohler [15] analyzed the frequency of amino-acids that were recruited early and late into the genetic code. The four oldest amino acids have a balanced representation in a binary code, in the sense that two have a purine and two have a pyrimidine in the second position. A balanced representation of the two nucleotides would be needed to encode for amino acids in a primordial organic world. In the absence of enzymatic gene replication and with chemical complementarities of nucleotides the oldest amino acids would suffice for a nucleotide encoded protein based life form. This conclusion supports the hypothesis that the current quaternary triplet genetic code is derived from an earlier quaternary doublet code, which in turn comes from a binary singlet code.

The hidden binary code predicts protein-protein contacts

Proteins in functional pathways contain domains that enable selective contacts with other proteins. Because of this vital requirement these sites tend to be evolutionary highly conserved. Finkel and

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Kohler [16] have used the hidden binary code to discover the highly conserved sequence regions in pairs of interacting proteins. Instead of using the entire DNA strand the binary code reduced search removes the first and third base position of the triplet that reflect the redundancy of the present genetic code. It uses the primordial binary code extracted from the DNA database. Determining the degree of evolutionary conservation takes second base nucleotide transversions as significant but transitions as insignificant in the primordial binary code because only transversions change the hydrophilic character of the encoded amino acid.

Furthermore these authors filter out amino acids that are hydrophobic and unlikely to be on the surface of interacting proteins. Only the evolutionary variability of surface-exposed regions are used in the contact prediction. It has been argued that these surface regions are highly conserved as protein interacting sites since they are part of signal pathways. Mutating the contact of one of the protein partners would interrupt or weaken the signal transfer. To restore the signal flow a compensatory mutation would be need on the complementing site. To adapt to environmental changes it would be evolutionary less taxing to select mutations in the functional or substrate specificity of effector proteins in the pathway. The method described by Finkel and Kohler [16] is based on this proposition and correctly predicts several known binding sites for the BRCA2 protein with PABL2 and RAD51 as well as the binding sites of the MDM2-P53complex.

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