Tertiary structure of the mRNA coding for J-chain might be involved in differentiation of mature B-lymphocytes to $(IgM)_5$- secretory cells

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Abstract Mature B lymphocytes differentiate to cells that excrete pentamer immunoglobulin M not before they synthesize intracellularly J-chain protein. It is suggested that a tertiary structure of J-mRNA may be involved in regulating its translation and thereby, in differentiation. Indirect evidence consistent with existence of such a structure is described, and ways to confirm this notion are discussed.

Introduction

DNA is the major genetic information store in all living organisms. The limited scope of the universal, degenerate, non- overlapping triplet codex[1] has constantly been extended to include recognition sequences for RNA polymerase and repressors,[2,3] for restriction/modification enzymes,[4,5] for site- specific recombination involved in prophage integration, *etc.*[6] [For a comprehensive dictionary, see ref.7.] Several roles of RNA secondary structures in controlling basic biological processes have been discovered during the last decade:[8] mRNA stability[9] and splicing,[10] ribosomal assembly,[11] initiation,[12] attenuation[13] and elongation[14] of transcription, amino acids-accepting functions of tRNA,[15] protein secretion[16] and initiation or elongation of DNA replication,[17-19] are several established examples.

Here, it is postulated that translation of mRNA coding for J-chain (J-mRNA)[20] can be blocked due to a tight structure formed by folding the J-mRNA upon itself around the AUG (start) codon.

The biological system

B-type lymphocytes make immunoglobulin M (IgM) which is bound to the cell membrane as a receptor. The proper antigen elicits a response of increased production of IgM and its assembly to the pentameric form $(IgM)_5$, which is then excreted from the cell. This differentiation process, which converts mature B lymphocytes into secretory cells, requires

an additional polypeptide,[20] the J-chain (for joining). The mechanism of pentamerization involves disulphide binding of two monomers through J-chain,[21] dimer IgM then serves as a nucleus for successive disulphide bindings of three additional monomers.[22]

Murine J-chain includes 137 amino acids but is synthesized in the lymphocytes as a precursor, containing additional hydrophobic amino acids at its N-terminus.[23] The amino acid sequence of the mature polypeptide is highly homologous to that of human J-chain,[24] supporting the notion that it is crucial for the immune response of vertebrates.[20] A special regulatory mechanism is thus likely to have been evolved in B lymphocytes over the expression of J-chain.

Recent studies of J-gene organization[25] reveal that the J-chain encoding cDNA (J-cDNA) prepared from murine J-mRNA (MJ-mRNA) includes a short stretch of 26 base pairs (bp) as an inverted copy of the original MJ-mRNA around its ATG codon (Figure 1). This artefact could have arisen during J-cDNA synthesis copied from MJ-mRNA, presumed to be found in a complex tertiary structure.

The postulated structure of J-mRNA

The existence of an inverted copy (Figure 1) attracts attention to 67 bp (bases) surrounding the ATG (AUG) codon of J-gene (or its message), flanked by two sets of five thymine (uracil) residues (Figure 2).[23,25] In the search for complementary inverted sequences, several possible stem-and-loop conventional structures were found in this region of MJ-mRNA, the most stable of which thermodynamically is depicted in Figure 2. This structure involves pairings of about two-thirds (44) of its composing bases and stores -25.3 kcal/mol (Table 1).[26] Two further facts that support existence of this structure, or a similar variant of it, are location of the AUG codon, and the most probable mechanism of formation of the artefact (see below).

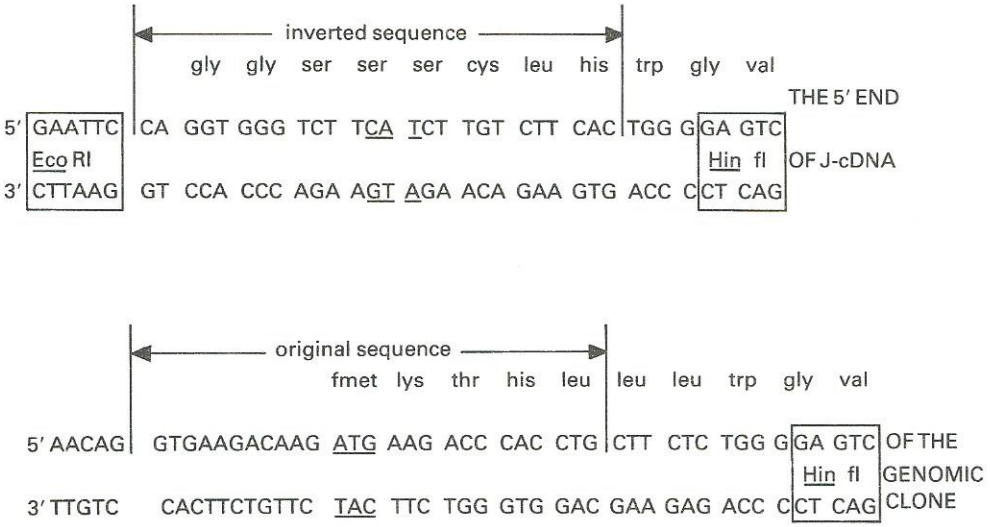

Figure 1 *Murine J-cDNA in which the complementary inversion occurred. Recognition sequences of relevant restriction enzymes are framed. ATG, its inverted sequence (GTA) and their complementary sequences (TAC and CAT, respectively) are all underlined.*

Table 1 *Detailed calculation of free energy stored in the J-mRNA of Figure 2.*

Bases involved[a]	Local structure[b]	Local DG^c (kcal/mol)
1 - 5, 63 - 67	$Stem_5$	-13.3
6 - 8	$I(GA)_3$	+1.75
9 - 13, 34 - 38	$Stem_5$	- 7.5
14 - 15, 56 - 57	$Stem_2$	2.1
16 - 17, 54 - 55	$I(GC)_4$	1.6
18 - 20, 51 - 54	$Stem_3$	- 4.2
21, 50	$I(GG)_2$	0.1
	$Stem_7$	-14.4
22 - 30, 43 - 49 {		
	$2.B_1$	+ 5.6
31 - 33	$I(GA)_3$	+ 1.75
39 - 42	$I(GG)_4$	+ 1.6
58 - 62	$I(AA)_5$	+ 3.8

		-25.3 = **S***DG*

[a] Consecutive numbers refer to order of nucleotide residues, as in Figure 2.

[b] Notations are taken from Figure 3 of ref. 26. Subscripts refer to the number of bases involved in the particular local structure.

[c] Free energy for each local structure (second column), calculated according to Salser.[26]

Translational control

Gene expression may be regulated at the level of transcription or downstream the flow of genetic information. The control of translation-initiation is thought to be exerted by modulation of ribosomal binding efficiency (ref.8 and references cited therein). Several recent publications[27-30] suggest that enclosing the AUG codon of mRNA in a stem-and-loop structure withholds ribosomal progress along the message thus inhibiting translation of the polypeptide chain. The first AUG codon of MJ-mRNA is buried deep in the proposed structure (Figure 2), which could well be a regulatory feature with implications for B cell development.

Origin of the inversion

The inverted copy in J-cDNA[25] could be either real or a cloning artefact. It would be highly hypothetical and too demanding to invoke a structural difference between J-gene of an expressing cell and of a non-expressing cell (the 5'-end of the gene must be flipped for expression to occur). This was not found.[25] Moreover, primer extension studies[25] eliminate this explanation.

We are thus left with the simpler interpretation, that the inversion is a cloning artefact, which can readily be explained by the structure postulated here (Figure 2), or a similar

variant of it. Several routes can be imagined which may bring about this inversion, but there is no evidence to prefer any particular one. Nevertheless, the simplest way, which is schematically illustrated in Figure 3, seems that it was facilitated by the presence of our postulated structure (Figure 2) in the double- stranding reaction mixture during cloning.[23,25]

Implications and Speculations, Predictions and Tests

The scheme just described (Figure 3) may be instructive towards a better understanding of the action mechanism of reverse transcriptase or of DNA polymerase, and may perhaps be exploited for constructing anti-sense RNA species.[31] It is a potential pitfall though, in which cDNA cloners could easily fall, as we have (Figure 1),[23] by obtaining the wrong sequence of nucleotides (and thus of the translated amino acids) at the 5'-end (N-terminus) of the gene or its message (and of the encoded protein).

Several cases of cDNAs have already been reported to have similar artefacts at their 5'-end[32-34] and several mechanisms for their generation similar to the one proposed here have been considered.[33-36] The *in vitro* manipulations involved in cDNA preparation are liable to generate such artefacts. It should therefore not be surprising if more of these are discovered when more comparisons of cDNAs with their homologous genes are

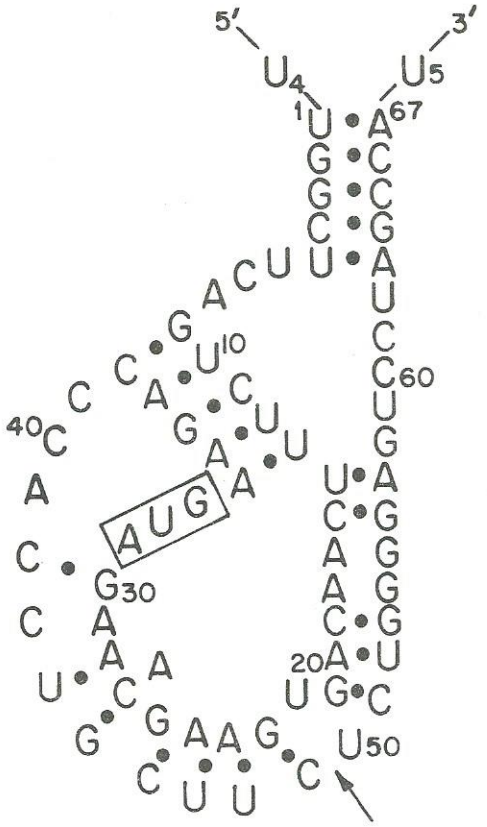

Figure 2 *Two-dimensional schematic representation of the postulated J-mRNA structure. Nucleotide residues are numbered consecutively, starting from the last of the five 5' flanking uracils. Dots represent anti-parallel, conventional base pairings. Translational start codon (AUG) is framed. Arrow, as in Figure 3.*

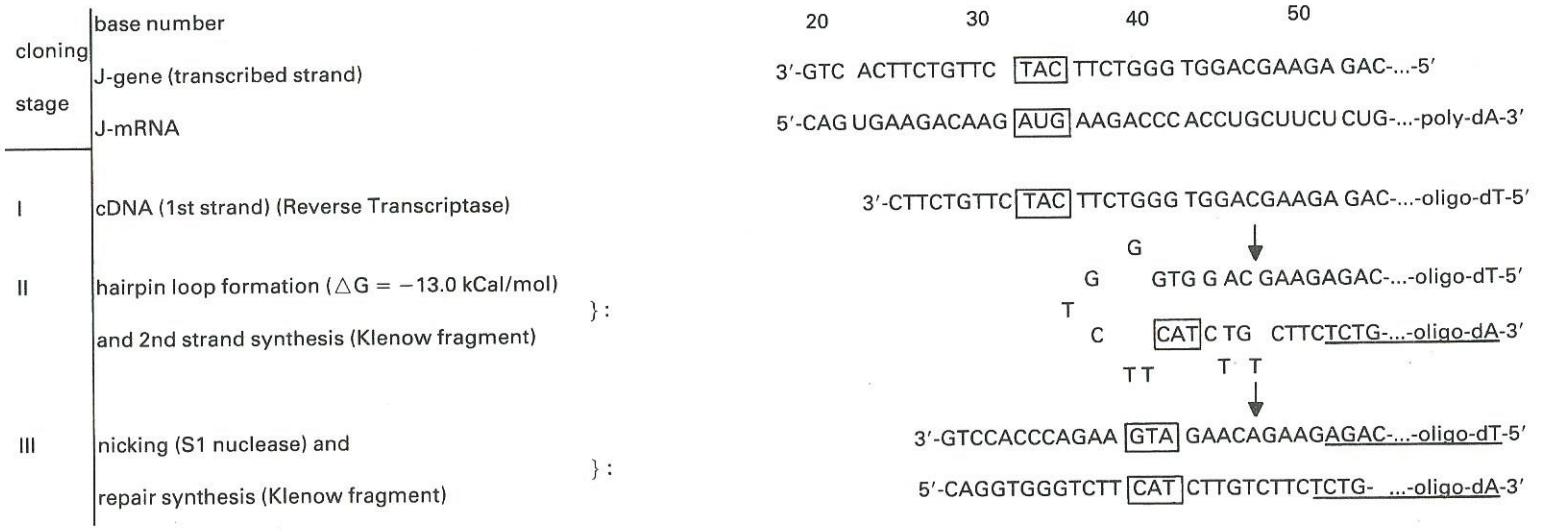

Figure 3 *Possible interpretation for artefact formation of inverted copy in cDNA during the cloning procedure.*[23] *Underlined segment was presumably produced during second-strand synthesis (stage II). Arrow points to the site of presumed nicking by S_1- endonuclease. AUG, its inverted DNA sequence (GTA) and their complementary DNA sequences (TAC and CAT, respectively) are all framed. Other symbols, as in Figure 2.*

performed. A general scheme for correcting such artefacts in cDNAs exploiting their homologous genomic fragments would be useful.[37]

The large proportion of nucleotides (66%) composing the proposed structure (Figure 2), the high negative free energy stored in it (Table 1) and its resemblance to the secondary structure of 5S rRNA,[38-40] are all strong indications that it exists at least in the artificial conditions prevailing during cloning. Whether or not it is a natural constituent of B lymphocytes is yet to be determined, but its postulated participation as a control element in J-gene expression is a mere speculation at the moment. In this line, the compact nature of this structure raises another possibility, that it has a high affinity to a regulatory protein which stabilizes it still further upon binding. If so, it should be easy to isolate such a protein by affinity binding to one of the MJ-cDNA strands or to MJ-mRNA itself, then characterize it and its postulated interaction with the MJ-mRNA.

Several variants may exist that resemble the structure depicted in Figure 2, with similar apparent stabilities. For example, the three cytosine residues (numbered 40, 42, 43) can perhaps be paired with the three guanosine residues (55, 56, 58). This would eliminate two G-C pairings (those of 15 with 56 and 30 with 42), but may impose a still higher negative free energy on the system, and make it more compact.

A totally different structure can be devised (Figure 4) if parallel base pairings are allowed. Thus, on top of the two stem's skeleton (Table 1), two other stems can be added, one in which bases 22-26 are paired in parallel with bases 46-50 and another of 6-8 with 57-59. Here, the proportion of participating bases (36/67 = 54%) is lower, and the energy stored is probably lower too. Nevertheless, stabilizing proteins are able to bring loose bare structures to a much higher negative free energy state, and it is impossible to predict *a*

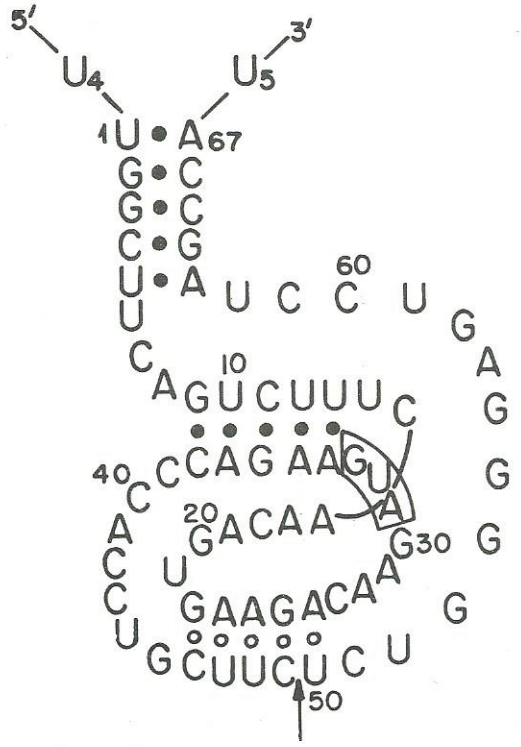

Figure 4 *A hypothetical folding involving parallel base pairings. Open circles represent postulated parallel base pairings. Other symbols, as in Figure 2.*

priori which is the one that exists and persists.

Parallel pairings of two separate bases along a tRNA molecule have been demonstrated,[15,41] but the ability of a stretch of consecutive bases to pair naturally in parallel has never been directly shown, to the best of our knowledge. "Curling hair loop formation" by parallel base pairings of complementary reiteration was only lately proposed as forming bioactive structures,[42,43] although other types of pairings than the conventional Watson- Crick have been shown to exist for over 20 years now[44-46] with no apparent direct steric effects on the geometry of the base pairs. If such parallel pairings are demonstrated, the number of options for any single-stranded RNA to form secondary structures will dramatically increase, thus significantly complicating algorithms for discovering them.[47]

The high degree of J-chain conservation among vertebrates[20,23] may become an aid in determining the actual MJ-mRNA structure, because sections essential for its construction and function are expected to be even more conserved than others. Thus, for instance, an important pairing is substantiated when a change in a nucleotide at a crucial location is always associated with another change at the complementary nucleotide to allow a similar pairing, as are the cases in tRNAs.[15,41] Our clone (MJ-cDNA) of murine J-cDNA[23] is expected to ease "fishing" homologous J-mRNAs of other vertebrates and comparing their sequences, to reveal such crucial regions. Human J-chain has indeed been recently sequenced,[48] but insufficient data upstream ATG does not allow the desired comparison to be made at this stage. To this end, gene structure analysis is necessary, as performed on the murine homologue.[25]

The limitations of drawing three-dimensional structures in two dimensions are obvious, particularly in the example shown in Figure 4. A real feasibility test can be performed with space- filling models, which should fortunately eliminate certain possibilities thus leaving the experimentalists with a smaller number to deal with. A straightforward procedure to verify a structure is to identify fragments remaining following activation of selected enzymes specific for certain nucleic acid sequences.[49-52] Previous cross-linking with psoralen + near ultraviolet irradiation, for example,[14,53] is helpful. Such sections can also be deciphered from infrared spectra[43] as well as from nuclear magnetic resonance spectra[54] [for a review, see ref.11]. Electron microscopy has also been successfully utilized to visualize secondary structures.[55] New, sophisticated techniques for RNA structure analysis are now being frequently invented.[56] Footprinting, for example, is of great help when a high-affinity binding protein is isolated.[57]

The necessary condition for any further investigation, of having at hand the correct encoding sequence of interest, is now fulfilled for murine J-mRNA by using both MJ-cDNA and the genomic clone.[37] The procedure employed, which can serve as an example for correcting similar artefact-bearing cDNAs, exploited the *Hin*fI site immediately downstream the complementary inverted region to replace the artefact by the homologous genomic fragment (Figure 1). Such construction depends upon finding an appropriate restriction enzyme recognition site and on not having introns in the region. In our case, the procedure resulted in a full-length J-chain coding-information (Jci) which includes a 122 bp region upstream of ATG. This sequence is expected to contain the control elements for translation-initiation and some of the transcription signals.[24,25] It could therefore be useful for studies of B cell differentiation by transfecting various cell lines blocked at certain developmental stages.[24,58]

The existence of both clones [MJ-cDNA and Jci],[37] would make it possible to demonstrate modulation of gene expression by anti- sense RNA, where the transcription product of the original clone, MJ-cDNA,[23] can serve as the anti-sense RNA. Introduction of both clones to non-secreting B lymphocyte cell lines deficient in J-chain production[24,58] and regulation of their expression by separate control elements[59] will allow *in vivo* studies

of Ig polymers assembly, and perhaps clarify possible involvement of J-chain in B cell differentiation. The failure to change the ratio $\mathbf{m}_m/\mathbf{m}_s$ in BCL_1 cells by induction of J-mRNA[60] does not preclude this possibility in other lines with lesions in different stages of development.

Concluding remarks

The use of bacterial vectors[61,62] to express efficiently Jci will overcome the difficulties in recovering sufficient amounts of murine J-chain and of its encoding mRNA for biochemical and biophysical investigations, and circumvent the problems associated with isolating them from the Ig polymers[63] and from excreting lymphocytes,[64] respectively.

Descriptions of structure-function relationships in murine J-chain and in its encoding mRNA are conceivable using mutant forms, to be obtained by site-directed *in vitro* mutagenesis.[65,66]

A present frontier in molecular and cellular biology is the assembly of complex molecular structures from their subunit components to display activities in heterologous systems. Pentamerization of IgM in bacteria may be considered as a simple model system because the pentamer contains three polypeptides only, one of which is J-chain. The cDNAs for both immunoglobin heavy (**m**) and light (**k**) chains have already been cloned together in a single *Escherichia coli* cell and the expression products were assembled *in vivo*, albeit at a low efficiency.[67]

The potential of a polynucleotide to store biological information and to deliver meaningful signals other than by the conventional genetic code has gained a strong hold among biochemists during the last decade, as reviewed here [and see ref.7]. We believe that the signals yet to be discovered are much more abundant than already found, and that the compact structure of J-mRNA proposed here is likely to be such.

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Laser fibre-ring interferometric gyroscopes and Einstein's second postulate

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With the recent successful commercialization of the laser-ring gyroscope[1,2] in such aircraft as the B-237, -257 and -267, the long-puzzling results of the Sagnac experiment[3] are confirmed by being put to practical usage, as indeed are the similar data of the Michelson-Gale[4] experiment.

Furthermore, the rotation-sensitive fibre-ring interferometer[5] has now demonstrated, and in an irrefutable manner, that a terrestrially localized Maxwellian field exists which, carried through space with the Earth's physical body during its orbital motions, transmits electromagnetic radiation relative to coordinates that are geocentric.

Accordingly, this interesting development in applied optics now assures us that each observer operates within a locally autonomous and totally dependable field which uniformly transmits its disturbances at velocity c relative to the coordinates of that field. And in thus explaining the null datum of that long historic series of experiments of Michelson-Morley type,[6] the annoying paradoxes of Einstein's Special Theory vanish. For without $(c \pm v)$-velocities, the "ring laser gyro" would not function.

But this means in turn that a restatement of Einstein's Second Postulate is in order: namely that the velocity c in electrodynamics is always a constant relative to any observer. This now must be modified to state that the velocity c in electrodynamics is always a constant *relative to the coordinates of the field transmitting the signal*, and only relative to the observer when he himself is at rest within the signal- transmitting field.

In a more universal context, the postulate should read: *Within the domain of any given electromagnetic field, the velocity* c *is a constant relative to the coordinates of that domain.*

Since a *magnetosphere* is now known to surround numerous celestial and planetary bodies, including the Earth, representing both the measure and the configuration of the Maxwellian field generated and maintained by the central physical body, it logically follows that this is the "domain" in question.[7]

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