Volume 174, number 2 FEBS 1759 September 1984

Hypothesis

Homologies between a brain-specific identifier (ID) sequence and regions of Harvey murine sarcoma virus and Rous sarcoma virus genomes

Putative role of identifier sequences in the tissue specificity of malignant transformation by RNA tumor viruses

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Received 28 June 1984

As a step toward understanding of the tissue specificity of cellular transformation by RNA tumor viruses we looked for the presence of a putative brain specific regulatory (identifier) sequence (C82B) in the genome of various oncornaviruses. The genomes of Harvey murine sarcoma virus and Rous sarcoma virus contain sequences flanking the viral oncogenes with >80% and >60% homology to C82B, respectively. We suggest that identifier sequences acquired by oncoviruses may determine the potential target cells of malignant transformation after virus penetration.

Nucleic acid homology *RNA tumor virus* *Identifier sequence* *Cell transformation* *Tissue specificity*

1. INTRODUCTION

Harvey murine sarcoma virus (Ha-MuSV), a replication defective retrovirus, was isolated during the course of routine passage of Moloney murine leukemia virus (Mo-MuLV) in rats [1,2]. Besides Mo-MuLV related sequences the genome of Ha-MuSV contains a rat-derived sequence responsible for transformation of fibroblasts [3]. This region encodes a 21-kDa phosphoprotein (p21has), the putative 'transforming protein' of Ha-MuSV [4]. The nucleotide sequence of the gene coding for p21has (v-has) has been determined [5], and two control regions of a potential RNA polymerase III promoter have been localized upstream from the potential translational initiation codons of v-has. However, the physiological significance of these sequences in determining transcripts within the Ha-MuSV genome in vivo has not yet been assessed. Here we demonstrate that the same region shows a greater than 80% homology to a brain specific identifier (ID) sequence (C82B) potentially involved in the regulation of tissue-specific gene expression [6]. We also show that the intercistronic region (6863–7037 nucleotides) of Rous sarcoma virus (RSV) – a retrovirus capable of inducing neurogenic tumors in many species including rats – contains a sequence with a less stringent homology to C82B as well.

We hypothesize that the homology between identifier sequences and flanking sequences of viral *onc* genes may play a role in determining the tissue specificity of transformation by retroviruses.

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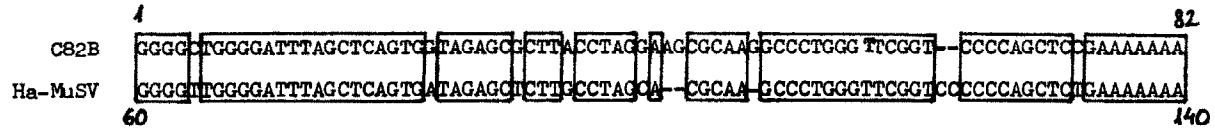

Fig.1. Sequence homologies (boxed areas) between a common 82-nucleotide sequence unique to brain RNA (C82B, nucleotides 1116–1197 of clone p1B224 in [6]) and the 5′-flanking region of the v-has gene of Ha-MuSV [5]. The sequences were aligned for maximum homology. The figures above and below letters refer to the positions of nucleotide residues. Percent homology was calculated as follows:

$$\% \text{ homology} = \frac{\text{No. of identical residues}}{\text{No. of aligned residues} + \text{No. of gaps}} \times 100$$

The putative RNA polymerase control regions in the Ha-MuSV genome are between positions 52–63 and 112–123.

2. RESULTS AND DISCUSSION

As a step toward understanding the tissue specificity of transformation by RNA tumor viruses we looked for the presence of sequences homologous to a putative brain specific regulatory sequence [6] in the genome of various oncornaviruses. A computer-aided inspection of the primary structures of C82B and the 5′-half of the Ha-MuSV genome revealed that 80% of the sequence of C82B is homologous to a region localized upstream from the v-has gene (fig.1).

To look for the possible origin of the ID-like sequence in the Ha-MuSV genome, we compared C82B and its inverse complement with the nucleotide sequence of the cellular *has* gene (c-has). Unfortunately, the rat c-has primary structure is not available. The published human c-has sequences [7,8] – including their introns and flanking 5′ and 3′-regions – do not contain the ID-like sequence, in spite of the presence of short homologous nucleotide stretches. C82B is also absent from the flanking regions of *YP2* gene, coding for a protein homologous to p21has in yeast [9]. We suggest that the Ha-MuSV genome arose by multiple recombination events between the Mo-MuLV genome, an ID-like sequence and other rat-derived sequences.

The intercistronic region of Rous sarcoma virus (Prague C strain) (nucleotides 6863–7037) is a 175-nucleotide region between the *env* and v-src genes [10]. Comparison of this sequence with C82B is shown in fig.2. The degree of homology is >60% between positions 4–63 of C82B and nucleotides 6948–6994 of the intercistronic region. Furthermore, an oligo (A) stretch (position 7018–7023) is localized following a region of non-homology downstream from the homologous sequences.

The C82B-homologous region of the RSV genome is part of a direct repeat flanking the v-src gene. Nucleotides 6897–6989 of the intercistronic region are directly repeated – with 82% homology – on the 3′-side of the v-src gene (nucleotides 8791–8890) [10].

The homology of nucleotides 8852–8890 of the 3′ direct repeat with C82B is 47.5%. This is comparable with the degree of homology found between small nuclear RNAs U1 and U4 [11].

Sutcliffe et al. [12] proposed that transcription of ID sequences located in the introns of brain genes by RNA polymerase III activates these genes for RNA polymerase II transcription. The presence of a putative RNA polymerase III promotor and an ID-like sequence in the vicinity of v-has suggests that a similar mechanism may participate in the

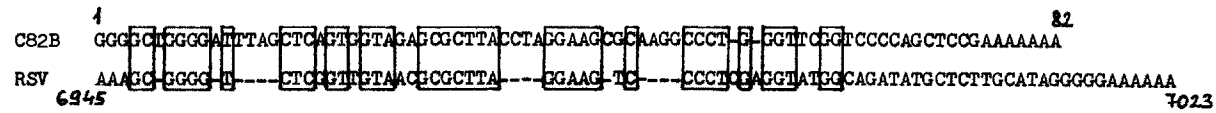

Fig.2. Sequence homologies (boxed areas) between a common 82-nucleotide sequence unique to brain RNA (C82B, nucleotides 1116–1197 of clone p1B224 in [6]) and sequences of the intercistronic region (nucleotides 6863–7037) of the Rous sarcoma virus [10]. The figures above and below letters refer to the positions of nucleotide residues.

regulation of the expression of this viral oncogene. Furthermore, we suggest that Ha-MuSV is capable of transforming neuroblasts and/or neurogenic tissues. The intercistronic region of RSV – a retrovirus with well documented capabilities of inducing neurogenic tumors and transforming retinoblasts [13,14] – also shows a less stringent but significant homology to C82B. This region might contribute to the tissue specificity of cell transformation by RSV. We suggest that ID sequences and/or tissue-specific enhancers acquired by oncoviruses may determine the potential target cells of malignant transformation after virus penetration.

Note: After completion of this manuscript we learned that the homology between C82B and Ha-MuSV was also noticed but not discussed from the point of view of tissue-specific transformation by Milner et al. [15].

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