Oncogenic intelligence

From c-*fos* to v-*fos*

from Inder M. Verma

THE discovery of kinship between retroviral oncogenes (v-*onc*) and their cellular homologues or proto-oncogenes (c-*onc*) has caused much of the recent excitement in cancer research. The precise mode of acquisition of cellular sequences by retroviruses remains obscure, but clearly it is an exceedingly rare event. To date nearly 20 unique v-*onc* genes have been isolated and characterized extensively. One such oncogene, *fos*, has been identified as the transforming gene of FBJ murine osteosarcoma virus (FBJ-MuSV) which was isolated from a spontaneous tumour in a CF1 mouse[1,2].

FBJ-MuSV proviral DNA contains 4,026 nucleotides which include two long terminal repeats (LTRs) of 617 nucleotides each, 1,639 nucleotides of acquired cellular sequence (v-*fos*) and a portion of the *env* gene encoding the viral envelope protein[3] (see Fig. 1). The acquired sequences encode a v-*fos* protein of 381 amino acids, with a calculated molecular weight of 41,601. In cells transformed by FBJ-MuSV, a phosphoprotein of apparent molecular weight 55,000 (on SDS-PAGE) has been identified as the transforming protein[4]. The discrepancy in size is probably due to both phosphorylation and the unusual amino acid composition of the *fos* protein (10 per cent proline) which enables it to be extensively folded.

Using v-*fos*-specific sequences, c-*fos* genes have been isolated from mouse and human cells and their complete nucleotide sequences determined[3,5]. The predicted mouse and human c-*fos* proteins differ in only 24 of their 380 amino acids. The sequences in c-*fos* that are homologous to v-*fos* are interrupted by four regions of non-homology, three of which represent *bona fide* introns. The fourth, 104-nucleotide, region, which is present in both mouse and human c-*fos* genes, is not an intron but part of the c-*fos* coding sequence; nevertheless it has evidently been deleted during the genesis of the v-*fos* gene with a consequent shift in the reading frame. The result is that all but 5 of the first 332 amino acids of the c-*fos* and v-*fos* proteins (380 and 381 amino acids, respectively, in total) are identical but, because of the out-of-frame deletion, their C-termini are quite different (Fig. 1*a*).

FBJ-MuSV presumably arose by recombination between c-*fos* sequences and FBJ murine leukaemia virus (FBJ-MuLV), probably through a 5-nucleotide sequence they share at a position corresponding to the 5′ end of v-*fos* and 10 out of 11 nucleotides they share at the 3′ end (Fig. 1*b*). Sequences involved in recombination at the 5′ end lie in the untranslated region of FBJ-MuLV and immediately downstream from the predicted 5′ end of c-*fos* mRNA. At the 3′ end, they involve the p15E region of the FBJ-MuLV *env* gene and the 3′-untranslated region of the c-*fos* gene. The 104-base pair sequence in the c-*fos* gene that is missing in the v-*fos* sequence is bounded by a 5-nucleotide inverted repeat which could have been looped out in the formation of FBJ-MuSV.

Despite their differences at the C-terminus, the v-*fos* and c-*fos* gene products are both located in the nucleus[6]. Furthermore, the altered C-terminus of the v-*fos* protein does not appear to be what determines its ability to transform fibroblasts *in vitro*, since the c-*fos* gene can be activated to transform fibroblasts without altering the coding region. Two manipulations are required to activate c-*fos* genes: a transcriptional enhancer element (contained in the LTRs) has to be linked to the gene and an interaction between the C-terminal coding and downstream non-coding sequences, which seems to inhibit c-*fos* expression at the level of translation or RNA maturation[7], has to be disrupted.

Expression of the c-*fos* gene is developmentally regulated. During prenatal development, it is expressed at high levels only in the extra-embryonal tissues (amnion, chorion and placenta)[8,9]. The c-*fos* protein has been found in the nucleus of normal mouse amnion cells[6] in concentrations that are equivalent to those of v-*fos* protein in cells transformed by FBJ-MuSV. Here, then, is the enigma: although v-*fos* and c-*fos* proteins have different C-termini, they have the same subcellular location and both can transform fibroblasts *in vitro;* yet amnion cells expressing high levels of c-*fos* protein in their nucleus are not morphologically transformed. I submit that normal cellular *fos* protein can induce transformation when it is expressed in an inappropriate cell. □

Inder M. Verma is at the Molecular Biology and Virology Laboratory, The Salk Institute, San Diego, California 92138.

1. Finkel, M. P., Biskis, B. O. & Jinkins, P. B. *Science* **151**, 698 (1966).
2. Curran, T. *et al. J. Virol.* **44**, 674 (1982).
3. Van Beveren, C. *et al. Cell* **32**, 1241 (1983).
4. Curran, T. & Teich, N. M. *J. Virol.* **42**, 114 (1982).
5. van Straaten, F. *et al. Proc. natn. Acad. Sci. U.S.A.* **80**, 3183 (1983).
6. Curran, T. *et al. Cell* **36**, 259 (1984).
7. Miller, A.D., Curran, T. & Verma, I.M. *Cell* **36**, 51 (1984).
8. Müller, R. *et al. Nature* **299**, 640 (1982).
9. Müller, R., Verma, I. M. & Adamson, E. A. *EMBO J.* **2**, 679 (1983).

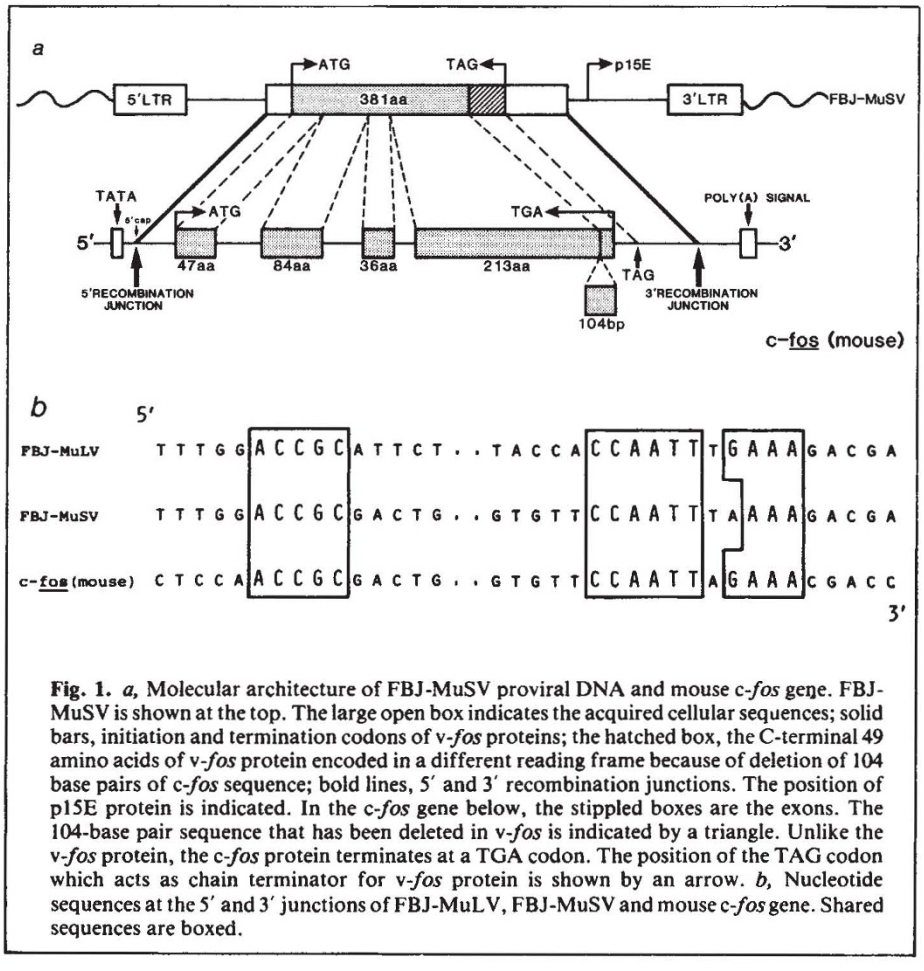

Fig. 1. *a,* Molecular architecture of FBJ-MuSV proviral DNA and mouse c-*fos* gene. FBJ-MuSV is shown at the top. The large open box indicates the acquired cellular sequences; solid bars, initiation and termination codons of v-*fos* proteins; the hatched box, the C-terminal 49 amino acids of v-*fos* protein encoded in a different reading frame because of deletion of 104 base pairs of c-*fos* sequence; bold lines, 5′ and 3′ recombination junctions. The position of p15E protein is indicated. In the c-*fos* gene below, the stippled boxes are the exons. The 104-base pair sequence that has been deleted in v-*fos* is indicated by a triangle. Unlike the v-*fos* protein, the c-*fos* protein terminates at a TGA codon. The position of the TAG codon which acts as chain terminator for v-*fos* protein is shown by an arrow. *b,* Nucleotide sequences at the 5′ and 3′ junctions of FBJ-MuLV, FBJ-MuSV and mouse c-*fos* gene. Shared sequences are boxed.