Retroviral protease-like sequence in the yeast transposon Ty1

RECENTLY, Mellor *et al.*¹ determined the nucleotide sequence of the 5'-terminal portion of the yeast transposon Ty1 and identified two open reading frames, ORF1 and ORF2, which are in the same relative positions as the *gag* and *pol* coding sequences in retroviruses. In addition, they showed that Ty1 produces a fusion protein by a specific frameshifting process similar to that used by retroviruses. We have shown that retroviruses, cauliflower mosaic virus (CaMV), *Drosophila copia*-like element 17.6 and Syrian hamster intracisternal A-type particle (IAP) contain sequences homologous to the *gag*-specific protease p15 of Rous sarcoma virus (RSV) in the same relative positions^{2,3}. Furthermore, these p15-related sequences contain a highly conserved stretch of amino acids which shows a close similarity with sequences around the active-site amino acids Asp-Thr-Gly of the acid protease family, suggesting that they possess a similar activity to that of acid proteases².

A computer-assisted search for homology has revealed the presence of the

Fig. 1 Maps of homology between protease regions of reverse transcriptase-containing viruses and transposons: *a*, Ty1; *b*, CaMV; *c*, 17.6; *d*, M-MuLV; *e*, RSV; *f*, IAP; *g*, HTLV-I (human adult T-cell leukaemia virus). Homologous segments are linked by slanted lines. No open reading frames are assigned between *gag* and *pol* in HTLV-I. Data were taken from ref. 2 for *b-e* and *g*, and from ref. 3 for *f*. AS, the region showing a close sequence similarity with active-site amino acids of the acid protease family.

Table 1 Amino-acid sequence comparison between p15-related proteases and pepsin-related acid proteases

Viral protease	
Ty1 ORF2	GHLL-DSGASRTLIRS
CaMV ORF5	LHCFV-DTGASLCIA-S
17.6 ORF2	LKCL1-DTGSTVNMT-S
M-MuLV <i>pol</i>	VTFLV-DTGAQHSVL-T
RSV <i>gag</i> p15	ITALL-DSGADITII-S
IAP ORF3	FEGIM-DSGADKSI-S
HTLV (<i>gag-pol</i>)	IEALL-DTGADMTVL-P
Acid protease (C-terminal)	
Pepsinogen (human)	* COAIV-DTGTSLLTG-P
(porcine)	COAIV-DTGTSLLTG-P
Prochymosin (bovine)	COAIL-DTGTSKLVG-P
Penicillopepsin	FSGIA-DTGTTLLLL-B
Renin (mouse)	CEVWV-DTGSSFTSA-P
(human)	CLALV-DTGASYISG-S
Acid protease (N-terminal)	
Pepsinogen (human)	DFTVVFDTGSSNLWV-P
(bovine)	DFTVIFDTGSSNLWV-P
(porcine)	DFTVIFDTGSSNLWV-P
Prochymosin (bovine)	EFTVLFDTGSSDFWV-P
Penicillopepsin	TLNLFDTGSSADLWV-F
Renin (mouse)	TFKVMFDTGSSANLWV-P
(human)	TFKVMFDTGSSNVWV-P

As pepsin-related proteases consist of two topologically similar domains and two active-site aspartic acids, the amino-acid sequences around the two active sites were aligned between the N- and C-terminal halves. Bold type indicates amino acids that are identical or chemically similar among 18 sequences (90%) out of 20 at each position. Gaps (-) were inserted to increase sequence similarity. * Active sites of acid protease family. For sequence data, see refs 2 and 3.

p15-related sequence in the ORF2 of Ty1 (Fig. 1, Table 1). Thus, the N-terminal portion of the ORF2 product may have an activity similar to that of acid proteases. Such a widespread occurrence of the protease sequence suggests that it is vital for these viruses and transposons. Mellor *et al.* suggested that the fusion protein is processed proteolytically¹; the ORF2-coded protease may be involved in this processing. The relative positions of the conserved segments are almost the same among Ty1, CaMV, 17.6 and Moloney murine leukaemia virus (M-MuLV) (Fig. 1), suggesting that the observed homologies are the result of divergence, not convergence. This also supports the notion that the ORF2 corresponds to *pol* in retroviruses¹, and thus the reverse transcriptase coding sequence, which is highly homologous among reverse transcriptase-containing viruses and transposons²⁻⁵, probably lies in a region immediately downstream from the protease region.

HIROYUKI TOH*
MASAO ONO†
KAORU SAIGO‡
TAKASHI MIYATA*

* Department of Biology,
Faculty of Science,
Kyushu University, and
‡ Department of Biochemistry,
Kyushu University School
of Medicine,
Fukuoka 812, Japan

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† Department of Molecular Biology,
School of Medicine,
Kitasato University,
Sagamihara-shi,
Kanagawa 228, Japan

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MELLOR ET AL. REPLY—We thank Toh *et al.* for their interest in our paper¹ and for pointing out the homology with acid proteases at the beginning of ORF2 in Ty1-15. We would like to add that in pulse-chase experiments the protein, p1(Ty1-15), encoded by ORF1 in Ty1-15 seems to be processed, presumably by proteolytic cleavage. Furthermore, we have recently identified a candidate for the 'natural' product of ORF1/ORF2 fusion. This protein, p3(Ty1-15), has a relative molecular mass of 190,000 and can be seen only in short pulse-labelling experiments. Like p1(Ty1-15), therefore, it also appears to be proteolytically cleaved. We have observed four possible cleavage products and their relationships with p1(Ty1-15) and p3(Ty1-15) are presently being established. The 'processing' of p1(Ty1-15) is dependent on the expression of ORF2, a result that is consistent with the processing protease being encoded within this region and therefore in agreement with the