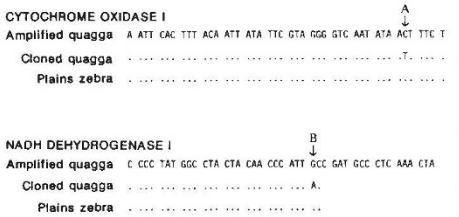
will completely block the enzyme. Thus, damaged DNA molecules in the amplification reaction can be expected either not to be replicated at all or to be at a replicative disadvantage, so that intact molecules will amplify preferentially during PCR. This is in sharp contrast to molecular cloning, where bacterial repair and recombination systems will 'salvage' damaged and altered molecules, and thus will introduce a high number of cloning artefacts. In line with this expectation, we find that only short pieces of DNA can be amplified from old or ancient DNA, as all longer templates presumably have been altered so as to be refractory to amplification by PCR.

It should be noted that the high error rate of *Taq* polymerase will be detected if the amplification products are cloned and individual clones are sequenced, whereas all random misincorporations by the enzyme are averaged out when the amplification products are sequenced directly[2]. Only if the amplification is started from an extremely low number (<10) of template



Mitochondrial DNA sequences from a 140-year-old quagga skin determined by direct sequencing of PCR products and from cloned DNA. The corresponding sequences from the plains zebra are shown below. A and B denote the positions of the two cloning artifacts.

molecules, can a particular damaged site be expected to show up in the direct sequencing. To our knowledge, no errors introduced by the *Taq* polymerase have been detected in the now numerous DNA sequences determined by direct sequencing of PCR products in this and other laboratories (H.A. Erlich, U. Gyllensten and T.J. White, personal communication). Thus, the polymerase chain reaction appears not to be a major source of errors but rather offers the possibility of avoiding cloning artefacts.

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Transforming and membrane proteins

SIR—Two recent reports[1,2] reveal a striking sequence homology between phospholipase C and the non-catalytic region of the non-receptor class (*src* class) of tyrosine kinases. Particularly intriguing is the finding of Mayers[2] that a novel oncogene *crk*, which shows common domains with PLC, lacks the tyrosine kinase domain possessed by other members of the *src* group, and yet shows transforming capacity. A hypothesis accruing from these observations is that PLC and the noncatalytic regions of the non-receptor tyrosine kinases share: (1) a similar activity (lipase?) which in oncogene transformed cells might become overexpressed; or (2) interaction with the same or similar cellular components (inhibitor of tyrosine kinase activity) which could be competed out by *crk*.

In recent work (V.-M.W. *et al.*, submitted) we found that α-spectrin has a significant sequence similarity with the non-catalytic domain of *src* and *yes* oncogenes. The homologous domain is in the middle of the α-spectrin molecule and forms a deviant stretch (DI) in a sequence which mostly encodes 106-amino-acid motifs. The homologous domain in c-*src* exactly coincides with the region A (nomenclature from ref. 1) which shows the sequence similarity with PLC. We have not identified any B or C regions in α-spectrin, nor have we observed any sequence homology between α-spectrin and PLC other than that corresponding to A like region in these two molecules. The homology in region A in α-spectrin, PLC, v-*src* and v-*crk* is depicted in the figure.

```
spectrin
D1      (940)  TGKELVLALYDYQEKSPREVTMKKGDILTLLNSTNKDWWKVE-VNDRQ-GFVPAAYVKKLDPAQSASR
                *    +*****   +  ++  ***+ * ++* *  ***    +   * *++* **   *  *
v-src    (81)  GGVTTFVALYDYESWTETDLSFKKGERLQIVNNTEGDWWLAHSLTTGQTGYIPSNYVAPSDSIQAEEW
                *    **+*+    + ** ****+ * *    *  ** *    *  * ** **
v-crk   (368)  EEVEYVRALFDFKGNDDGDLPFKKGDILKIRDKPEEQWWNAE-DMDGKRGMIPVPYVEKCRPSSASVS
                     *+*****+*   + +* * *  *+   +* *  **  +    *    *  ***      *
PLC     (791)  TFKCAVKALFDYKAQREDELTFTKSAIIQNVEKQEGGWWRGD-YGGKKQLWFPSNYVEEMVSPAALEP
```

Alignment of similar domains in the chicken α-spectrin, v-*src*, v-*crk* and phospholipase C. Identical residues are marked with stars and conserved substitutions with crosses. Numbers, the first amino-acid residues included in the alignment.

The function of the DI region in spectrin, in the middle of which the homology occurs, is unknown. We do not think it has any major enzyme function, such as lipase, as such an activity would probably have been observed previously. Rather, we think that DI and its homologous regions in, for example, *src* proteins and PLC, represent interaction sites with a common cellular component. One candidate for such a component is calpactin I (also termed lipocortin II or p36), the major substrate of *src* proteins which is also known to bind to spectrin. Whether p36 also interacts with PLC and whether it serves only as an anchorage point or has more subtle or varying effects on the interacting proteins remains to be elucidated. Of course we cannot exclude that G-proteins or even a new class of regulatory proteins would regulate the function of tyrosine kinases and PLC as suggested by Katan and Parker[4].

Cytoskeletal changes have been recognized as one of the earliest changes seen in *src*-induced transformation[3]. Recently, Warren *et al.*[5] have demonstrated that elevated expression of *src* protein induces a dramatic change in cell shape and especially in membrane plasticity of an epithelial cell line (MDCK-cells) without having a mitogenic effect. These findings, together with the observation on the sequence similarity between *src*, PLC and spectrin, will undoubtedly bring plasma membrane and its underlying spectrin-based membrane skeleton more into focus in studies of oncogene-induced transformation.

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Scientific Correspondence

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