There is, however, an unresolved question related to the v-*src* ability to immortalize transformed cells. This is of importance because chicken cells, similarly as human cells, are not generally prone to produce immortalized cell lines. As a cytoplasmic oncogene, v-*src* by itself is lacking the immortalization activity exerted by nuclear oncogenes like SV40 large T antigen or adenoviral E1A.

It has been well documented that cell longevity and immortalization depends upon the degree of the telomerase activity, which ensures expansion of the telomere sequence, thus compensating telomere shortening at every cell division. It was estimated that about 85% of human solid tumours display such an activation (for review see Urquidi et al., 2000). So far, the telomerase activity has not been studied in chicken v-*src*-transformed cells. However, it was shown that v-*src* activates the protooncogene c-*myc* through a so far not elucidated signalling pathway, most probably independent of *ras* (Sovová et al., 1993; Barone and Courtneidge, 1995). This may play an important role in preventing cell senescence, because the c-*myc* product interacts with the telomerase gene promoter and activates its transcription (Greenberg et al, 1999; Wu et al., 1999). Further experiments are needed in order to verify this possibility even for chicken cells.

There is only one molecular study touching the immortalization of a v-*src*-transformed cell line (Ulrich et al., 1992) that indicates that this process is correlated with a loss of *p53*. While attempting to passage v-*src* tumours to syngeneic chickens *in vivo*, Plachý (2000) obtained successful results only in about one out of five tumours despite using large amounts of minced tissue. However, when tumours became transplantable, the amount of cells required for passaging dropped to low numbers (around 100). We should certainly learn what additional genetic changes are needed for chicken tumour cell immortalization. But, is this a prerequisite for v-*src* primary tumour formation? It seems not to be the case, because palpable v-*src*-induced tumours appear about one week after inoculation and they grow progressively during the next three weeks, killing most of the animals. It was estimated that a cell reaches the first stage of senescence after about 30 to 50 cell divisions (Hayflick, 1965; Beug and Graf, 1977), which corresponds to about 10^{12} cells. Even taking into account the death of some cells, we are still above 10^{10} cells, which constitutes a large tumour.

An additional problem in interpreting v-*src* oncogenesis stems from the fact that v-*src*-induced tumours are largely monoclonal. This might be taken as an argument that a second change is required for tumour growth. The same is true for another well-defined oncogene *myc* activated by its translocation to immunoglobulin loci, which triggers Burkitt's lymphoma (Klein and Klein, 1985). Not only such lymphomas, but also immunoglobulin heavy-chain enhancer-driven c-*myc* in transgenic mice produce monoclonal lymphomas with high frequency (Adams et al., 1985). Besides inferring the second hit, there is also the possibility that the target cells lack some factor(s) or substrate(s) required for accomplishing tumorigenicity. This may look as a highly speculative view, but it was proposed for v-*src* inability to transform human in contrast to rodent fibroblasts (Hjelle et al., 1988). Essentially, we are in this case dealing with a problem of cell nonpermissiveness, which has been well established in the case of retrovirus infection (Svoboda, 1998). Similarly, a proper tuning of signal pathways might also influence the proneness of a target cell to oncogenicity. While discussing v-*src* oncogenicity, it should be noted that there are additional blank spots. Among them is efficient vascularization of tumours, which should occur by some unknown pathway, triggered probably by v-*src*.

This short review was devoted to v-*src*, but some new findings related to other oncogenes should be at least shortly commented. A new impetus was provided by the development of conditional transgenesis, in which oncogenes were placed under the control of additional elements allowing the oncogene to switch off. In such a way oncogenes like *ras* and *myc* could have been down-regulated at different time intervals after triggering their oncogenic activity *in vivo*. Both *ras* and *myc* switching off at the stage when they produced melanoma or lymphoma, respectively, led to rapid tumour regression accompanied by apoptosis (for review see Chin and DePinho, 2000). However, in a small fraction of animals the tumour process was renewed in the absence of a functioning oncogene. Such "escapees" should have therefore arisen by other, so far unknown, probably genetic changes. Thus, a picture emerges confirming that oncogenes act as dominant genes involved not only in tumour induction but also in tumour maintenance. Despite that this has not been extended to v-*src* so far, there is ample evidence from the past that this oncogene follows a similar path. Among such data belongs the discovery of RSV-transformed mammalian cell reversion (Macpherson, 1965), which was later shown to be accompanied by provirus methylation; this correlates with v-*src* transcriptional silence (Searle et al, 1984). Hejnar et al. (1994) have shown that reversion occurs with high frequency also in the v-*src*-induced hamster tumour line H-19. When transcriptionally silent methylated proviruses were stripped of methylcytosine in the course of molecular cloning, they became again oncogenic, as shown by their inoculation in chickens. This is in agreement with the postulation of v-*src* requirement not only for tumour induction, but also for the maintenance of oncogenic properties. However, reversion is not absolute in this case, either. In spite of the fact that 10 H-19 cells were sufficient to produce tumours, the revertants retained a residual oncogenicity, but more than 10^6 cells were needed for efficient tumour production. Thus, the H-19 cells, through long-term *in vivo* and *in vitro* growth, acquired additional change(s), probably related to cell immortalization which, disregarding v-*src* expression, ensured a low degree of malignancy.

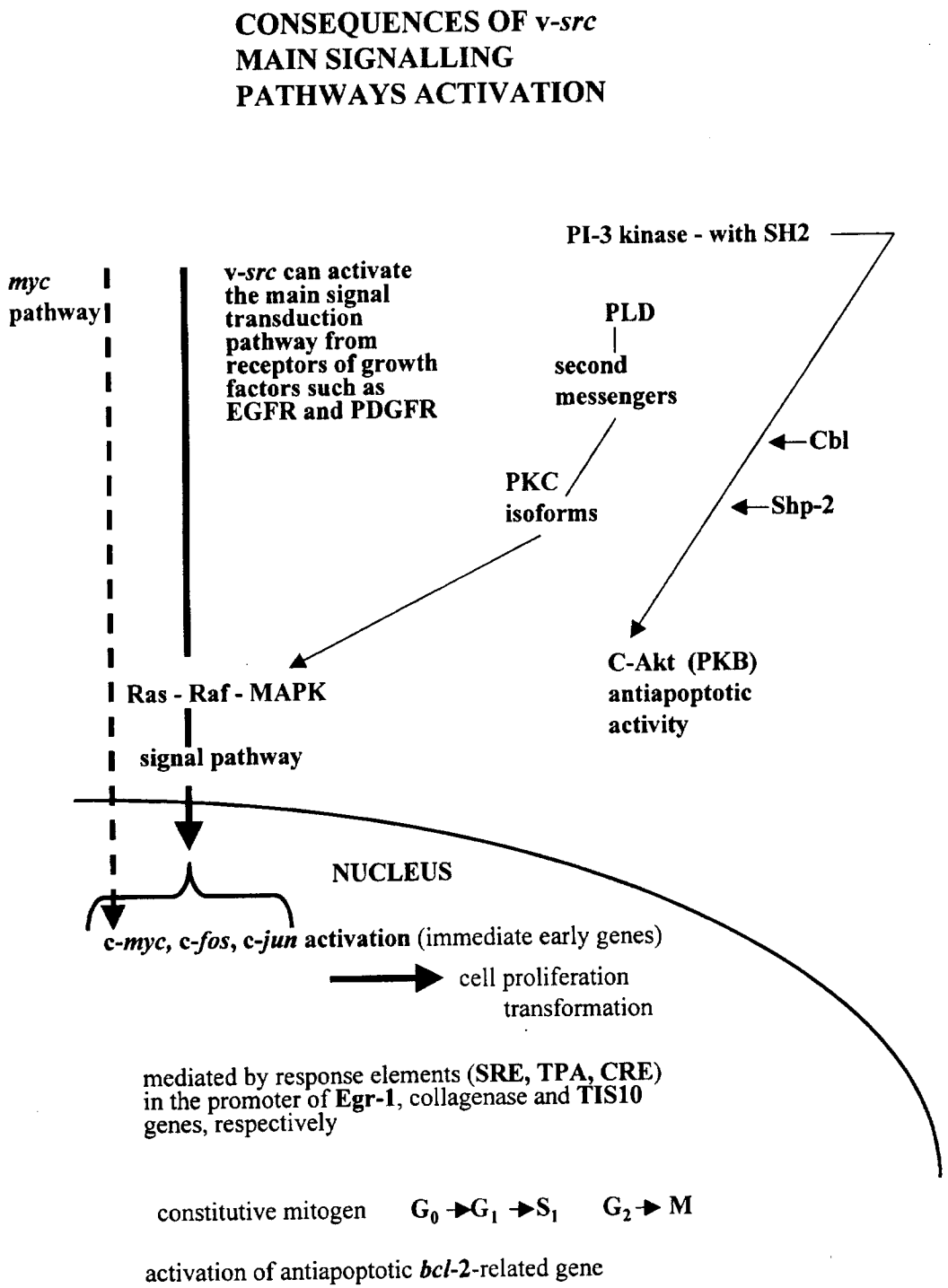

Fig. 1. Illustration of some principal signalling pathways that can be activated by v-*src*. The main signalling pathway is schematically drawn as a solid arrow. For further information about the role of Src in signal transduction and the molecular events influencing its tyrosine phosphorylation activity, see Abram and Courtneidge (2000), and Hakak et al. (2000). Nuclear protooncogene activation and the elements involved in it are summarized according to Curto et al. (1997). SRE – serum response element, TPA – 12-O-tetradecanoylphorbol-13-acetate response element, CRE – cAMP response element. The protooncogene *myc*-activating pathway (see text) is illustrated as a dashed vertical arrow. On the right side, the pathway resulting in phosphoinositide-3-OH kinase (PI-3 kinase) (through its SH-2 domain) and protooncogene Akt (PKB) activation is given. For this pathway, the adapter protein Cbl and protein-tyrosine phosphatase (Shp-2) are required (Hakak et al., 2000). The oncogene v-*src* also activates especially phospholipase D (PLD) (Jiang et al., 1995), and second messengers then trigger the protein kinase activity of some PKC isoforms (Zang et al., 1995), which could reinforce the main signalling pathway leading to cell proliferation and also contribute to cell transformation. The Src involvement in other cell signalling events, especially those mediated by focal adhesion kinase (FAK), are not included.