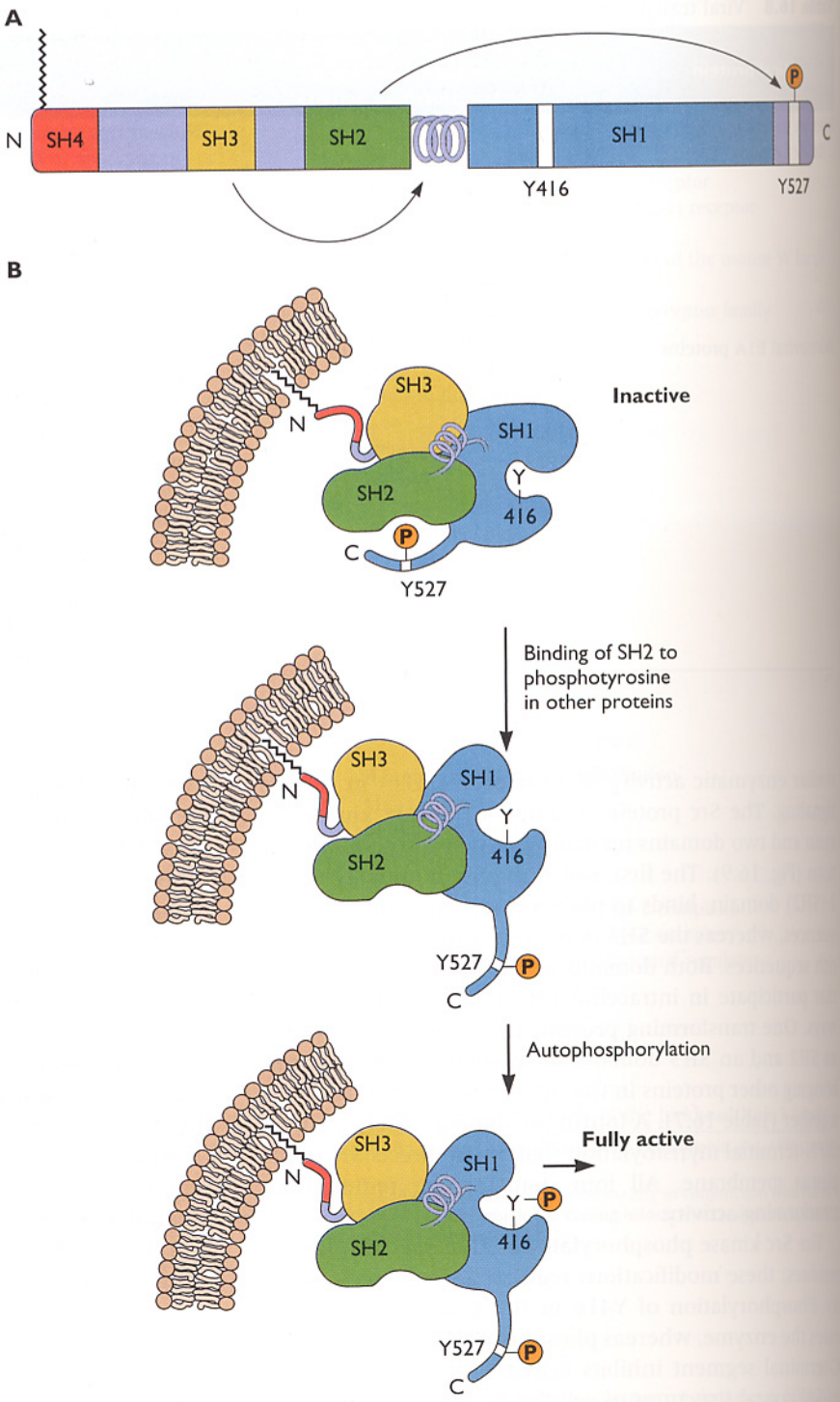

Figure 16.9 Organization and regulation of the c-Src tyrosine kinase. (A) The functional domains of the protein. The SH4 domain contains the site for addition of the myristate chain that serves to anchor the protein to the cell membrane. The SH2 and SH3 domains mediate protein-protein interactions by binding to phosphotyrosine-containing and proline-rich sequences, respectively. Arrows represent intramolecular interactions observed in the repressed-state crystal structures of Src. (B) The interactions and their reversal. When Y527 is phosphorylated, the C-terminal region of c-Src in which this residue lies is bound to the SH2 domain. This interaction brings a helix located between the SH3 and SH1 domains into contact with the SH3 domain, as illustrated at the top. Such intramolecular associations maintain the kinase domain (SH1) in an inactive conformation. A conformational change that activates the kinase can be induced as shown, as well as by binding of the SH3 domain to proline-rich sequences in other proteins and probably by dephosphorylation of Y527 (see Fig. 16.15). Once released from the autoinhibited state in this way, Y416 in the kinase domain is autophosphorylated, a modification that stabilizes the active conformation of the SH1 domain. The v-Src protein is not subject to such autoinhibition because the sequence encoding the C-terminal regulatory region of c-Src was deleted during transduction of the cellular gene.

Table 16.7 Functional classes of oncogenes transduced by retrovirus[a]

Transduced oncogene	Viral oncoprotein[b]	Function of cellular homolog
Growth factor		
sis	$p28^{env\text{-}sis}$	Platelet-derived growth factor (Pdgf)
Tyrosine kinase growth factor receptors		
erbB	$gp65^{erbB}$	Epithelial growth factor (Egf) receptor
fms	$gp180^{gag\text{-}fms}$	Colony-stimulating factor 1 (Csf-1) receptor
sea	$gp160^{env\text{-}sea}$	Receptor; ligand unknown
kit	$gp80^{gag\text{-}kit}$	Hematopoietic receptor; product of the mouse W locus
ros	$p68^{gag\text{-}ros}$	Receptor, ligand unknown
mpl	$p31^{env\text{-}mpl}$	Member of the hematopoietin receptor family
eyk	$gp37^{eyk}$	Receptor, ligand unknown
Hormone receptor		
erbA	$p75^{gag\text{-}erbA}$	Thyroid hormone receptor
G proteins		
H-*ras*	$p21^{ras}$	GTPase
K-*ras*	$p21^{ras}$	GTPase
Adapter protein		
crk	$p47^{gag\text{-}crk}$	Signal transduction
Nonreceptor tyrosine kinases		
src	$pp60^{src}$	Signal transduction
abl	$p460^{gag\text{-}abl}$	Signal transduction
fps[c]	$p130^{gag\text{-}fps}$, $p105^{gag\text{-}fps}$	Signal transduction
fes[c]	$p85^{gag\text{-}fes}$	Signal transduction
fgr	$p70^{gag\text{-}actin\text{-}fgr}$	Signal transduction
yes	$p90^{gag\text{-}yes}$, $p80^{gag\text{-}yes}$	Signal transduction
Serine/threonine kinases		
mos	$p37^{env\text{-}mos}$	Required for germ cell maturation
raf[d]	$p75^{gag\text{-}raf}$	Signal transduction
mil[d]	$p100^{gag\text{-}mil}$	Signal transduction
akt	$p86^{gag\text{-}akt}$	Signal transduction
Nuclear proteins		
jun	$p65^{gag\text{-}jun}$	Transcriptional regulator (Ap-1 complex)
fos	$p55^{fos}$	Transcriptional regulator (Ap-1 complex)
myc	$p100^{gag\text{-}myc}$, $p90^{gag\text{-}myc}$, $p200^{gag\text{-}pol\text{-}myc}$, $p59^{gag\text{-}myc}$	Unknown; possibly transcriptional regulator
myb	$p45^{myb}$, $p135^{gag\text{-}myb\text{-}ets}$	Transcriptional regulator
ets	$p135^{gag\text{-}myb\text{-}ets}$	Transcriptional regulator
rel	$p64^{rel}$	Transcriptional regulator
maf	$p100^{gag\text{-}maf}$	Transcriptional regulator
ski	$p110^{gag\text{-}ski\text{-}pol}$	Transcriptional regulator
qin	$p90^{gag\text{-}qin}$	Transcriptional regulator of the forkhead/Hnk-3 family

[a]Adapted from J. Nevins and P. Vogt, p. 301–343, in B. N. Fields et al. (ed.), *Fields Virology*, 3rd ed. (Lippincott-Raven Publishers, Philadelphia, Pa., 1996), with permission.

[b]Designations for viral proteins: p, protein; gp, glycoprotein, pp, phosphoprotein. The last is not applied consistently but is used mainly in conjunction with the *src* product. The numbers give the estimated molecular mass in kilodaltons, and the superscript lists the genes from which the coding information is derived in the 5′ → 3′ direction. The listing of more than one protein for an oncogene signifies its inclusion in independent virus isolates.

[c]*fps* and *fes* are the same oncogene derived from the avian and feline genomes, respectively.

[d]*raf* and *mil* are the same oncogene derived from the murine and avian genomes, respectively.

Viral Mimics of Cellular Signaling Molecules

The Transduced Cellular Genes of Acutely Transforming Retroviruses

The v-*src* paradigm. The protein product of v-*src* was the first retroviral transforming protein to be identified, when serum from rabbits bearing tumors induced by Rous sarcoma virus was shown to immunoprecipitate a 60-kDa phosphoprotein ($pp60^{v\text{-}src}$) (Table 16.7). The v-Src protein was soon found to possess protein tyrosine kinase activity, a property that provided the first clue that specific phosphorylation of cellular proteins is critical to oncogenesis. The discovery of this protein tyrosine kinase led to the identification of a large number of other proteins with

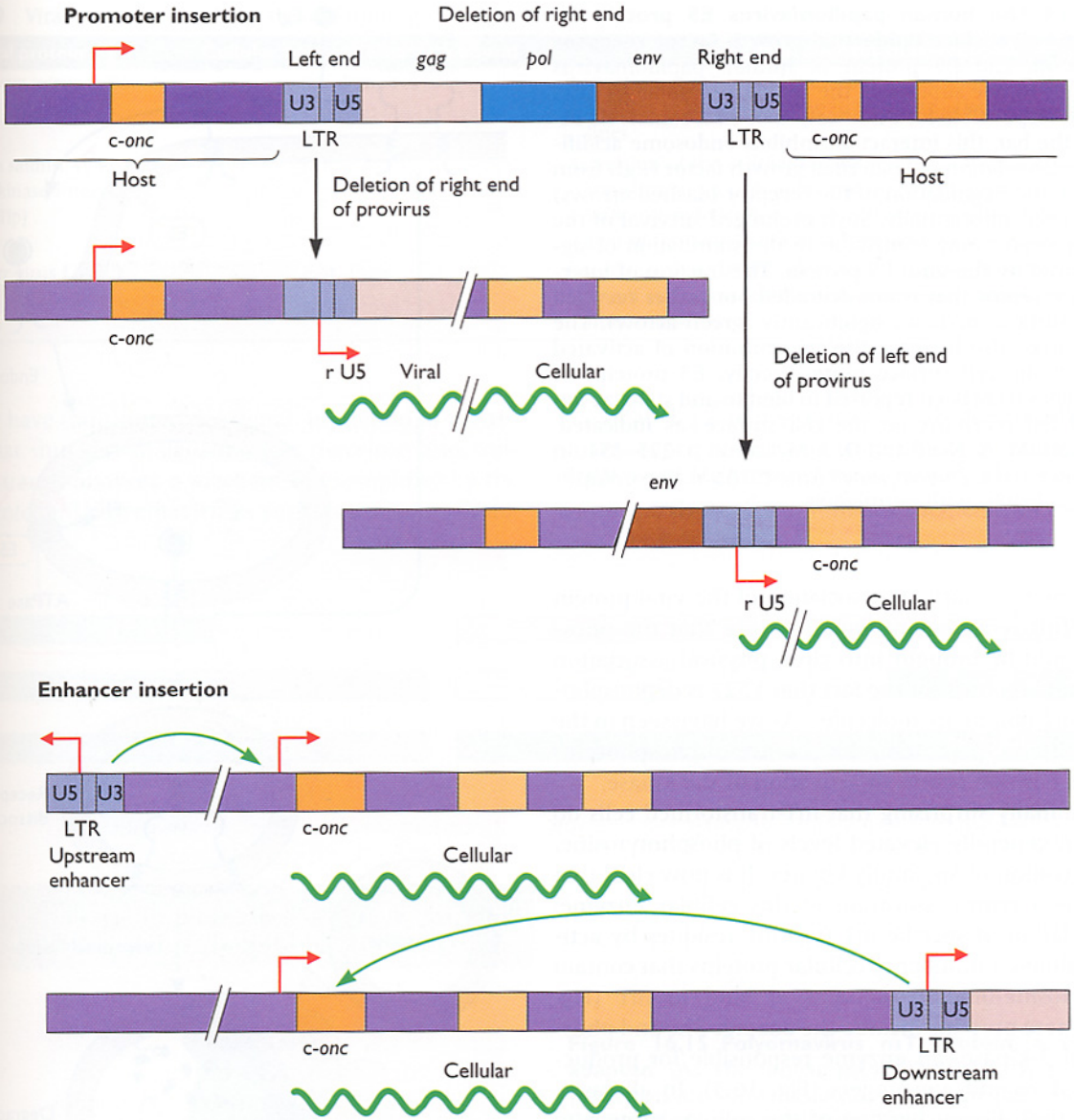

Figure 16.13 Mechanisms for insertional activation by nontransducing oncogenic retroviruses.