A MIM depicting intramolecular domains, their modifications and molecular interactions:

Activation of src by EGFR

Src has the following domains:

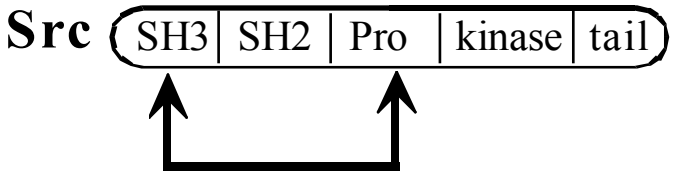
SH3: binds to proline-rich domains

SH2: binds to phosphotyrosine motifs

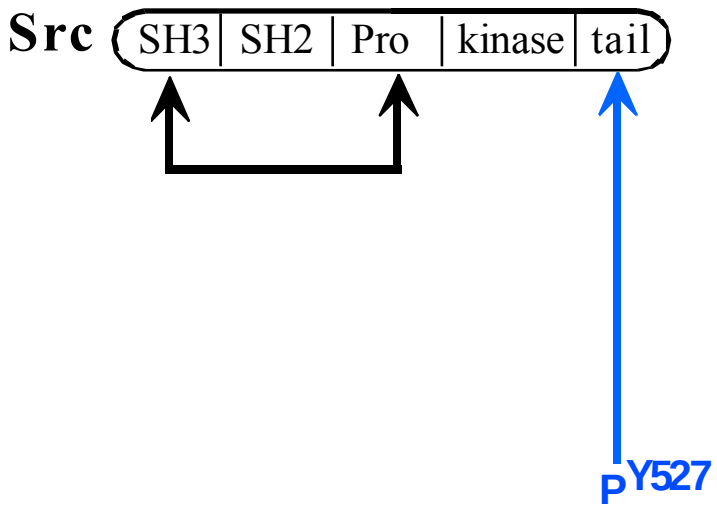
Pro: proline-rich domain

kinase: tyrosine kinase domain

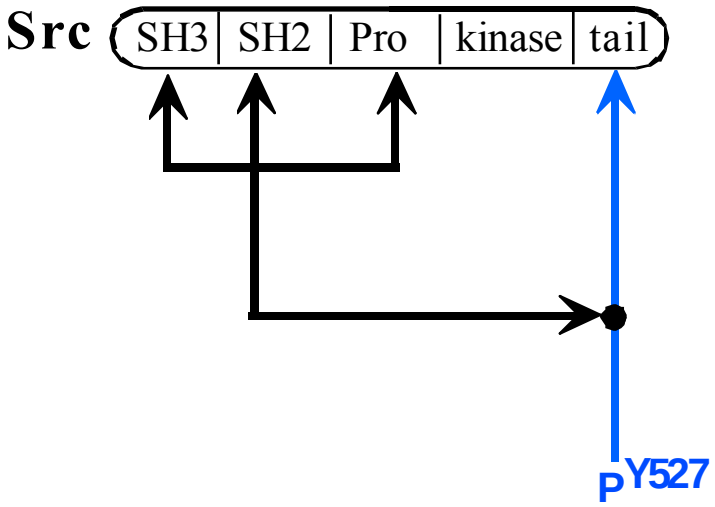
The SH3 domain binds the Pro domain.



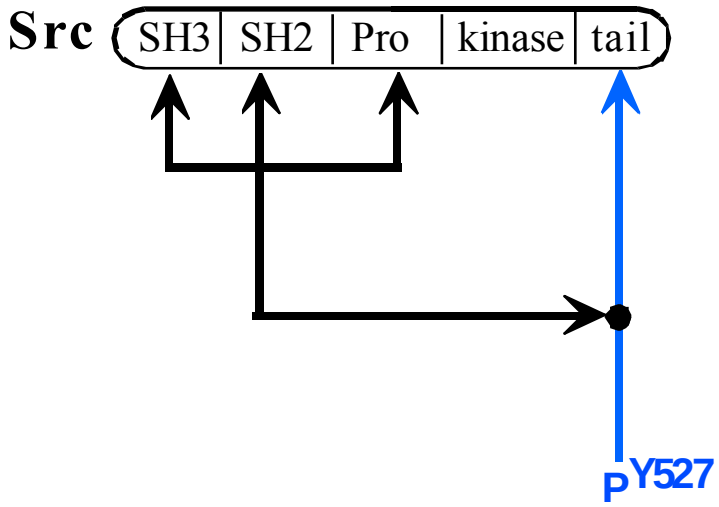
The Src tail region can be phosphorylated at Tyr 527.



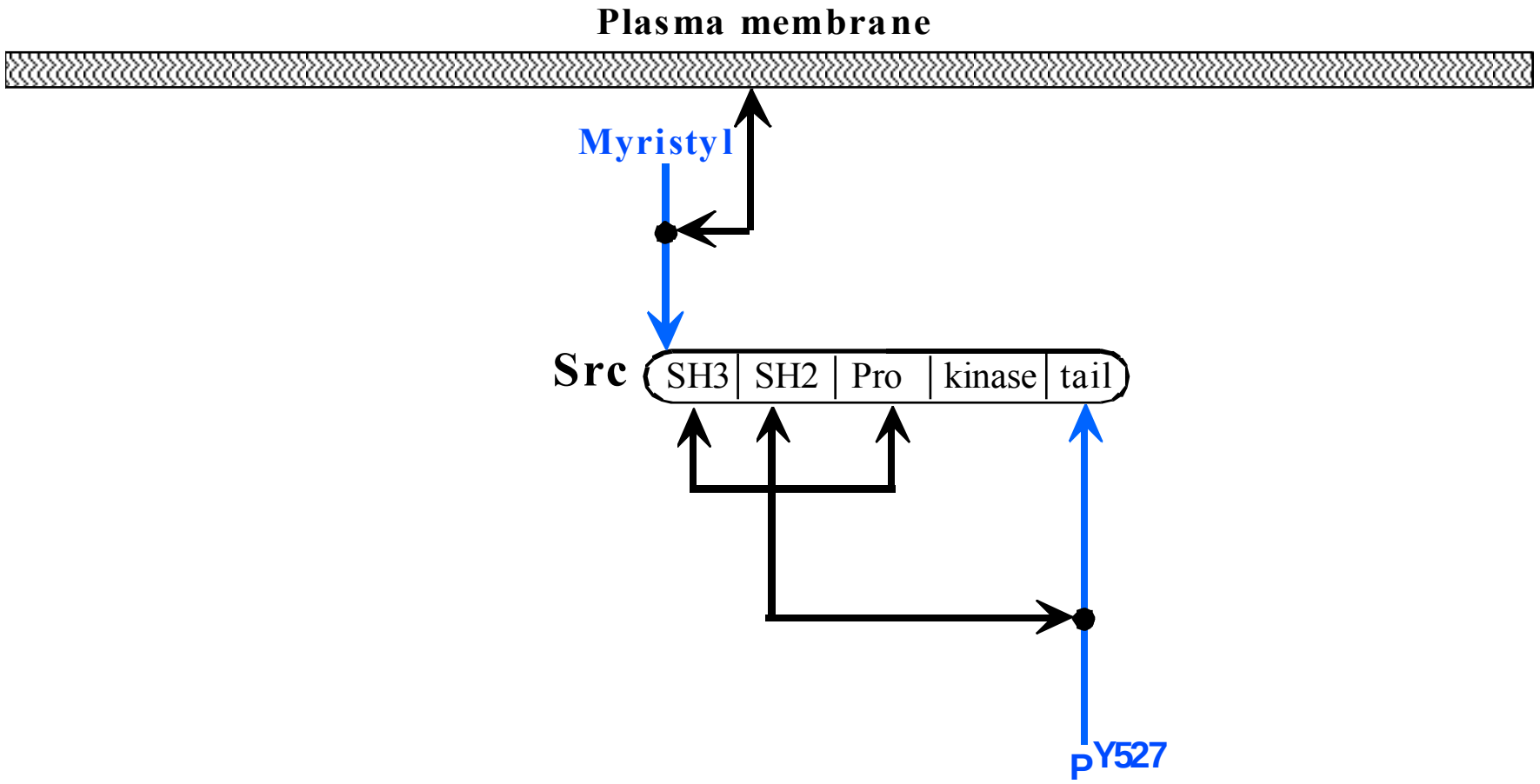
The SH2 domain binds to the tyrosine-phosphorylated tail.



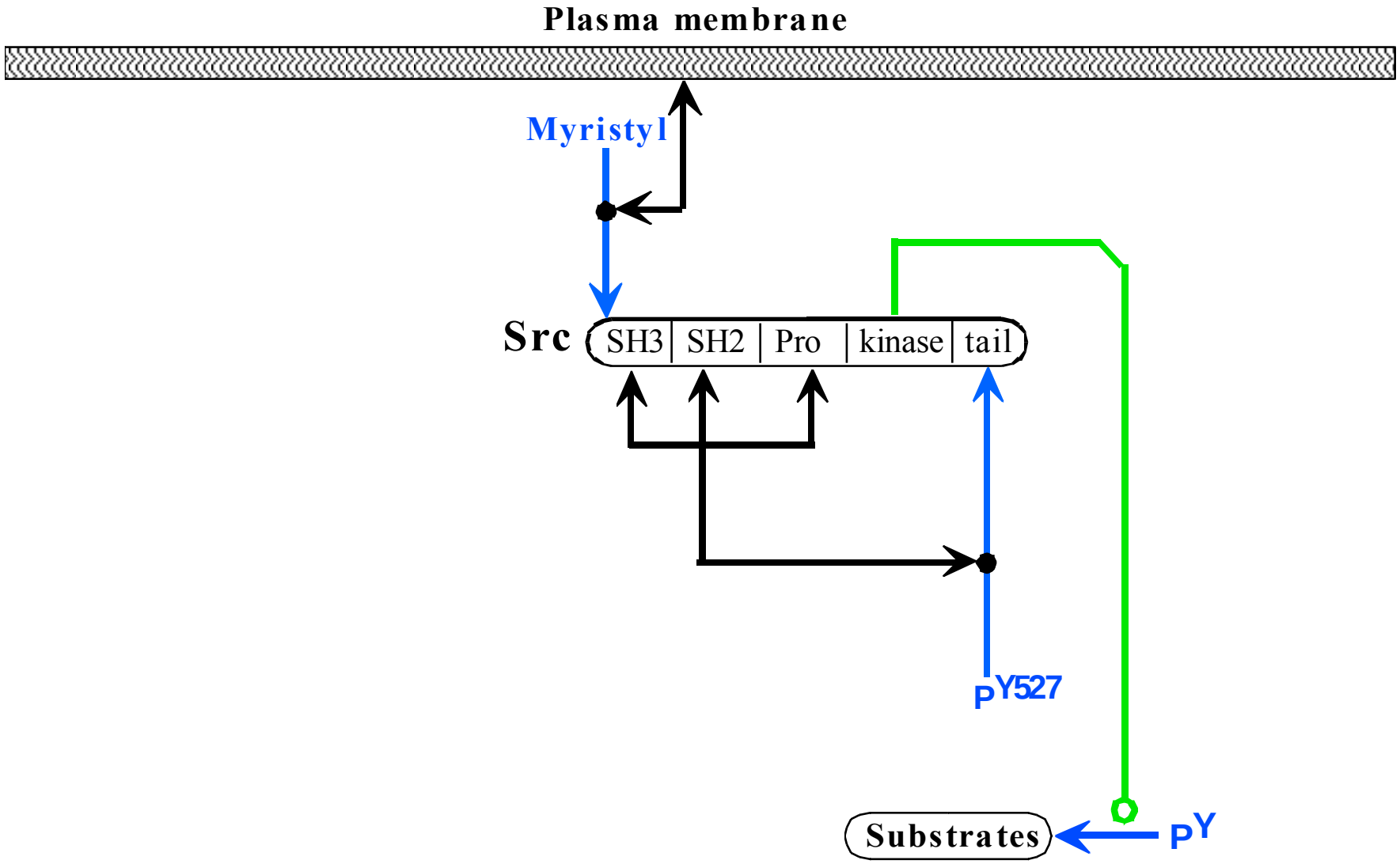
The 2 intra-molecular bonds form cooperatively, and fold the Src molecule, hiding the kinase domain and keeping Src in an inactive configuration.



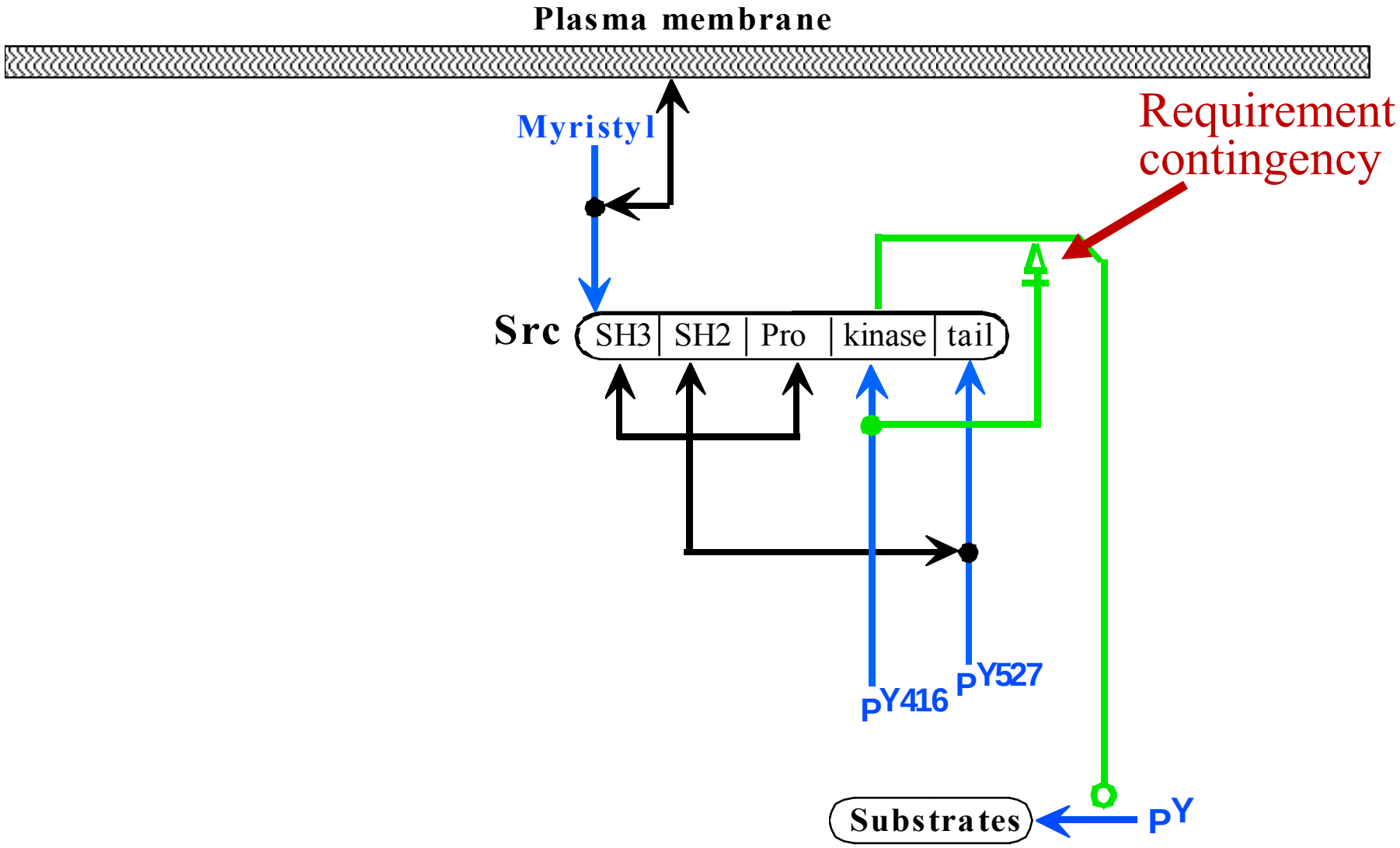
Src binds to plasma membrane through a myristyl group.



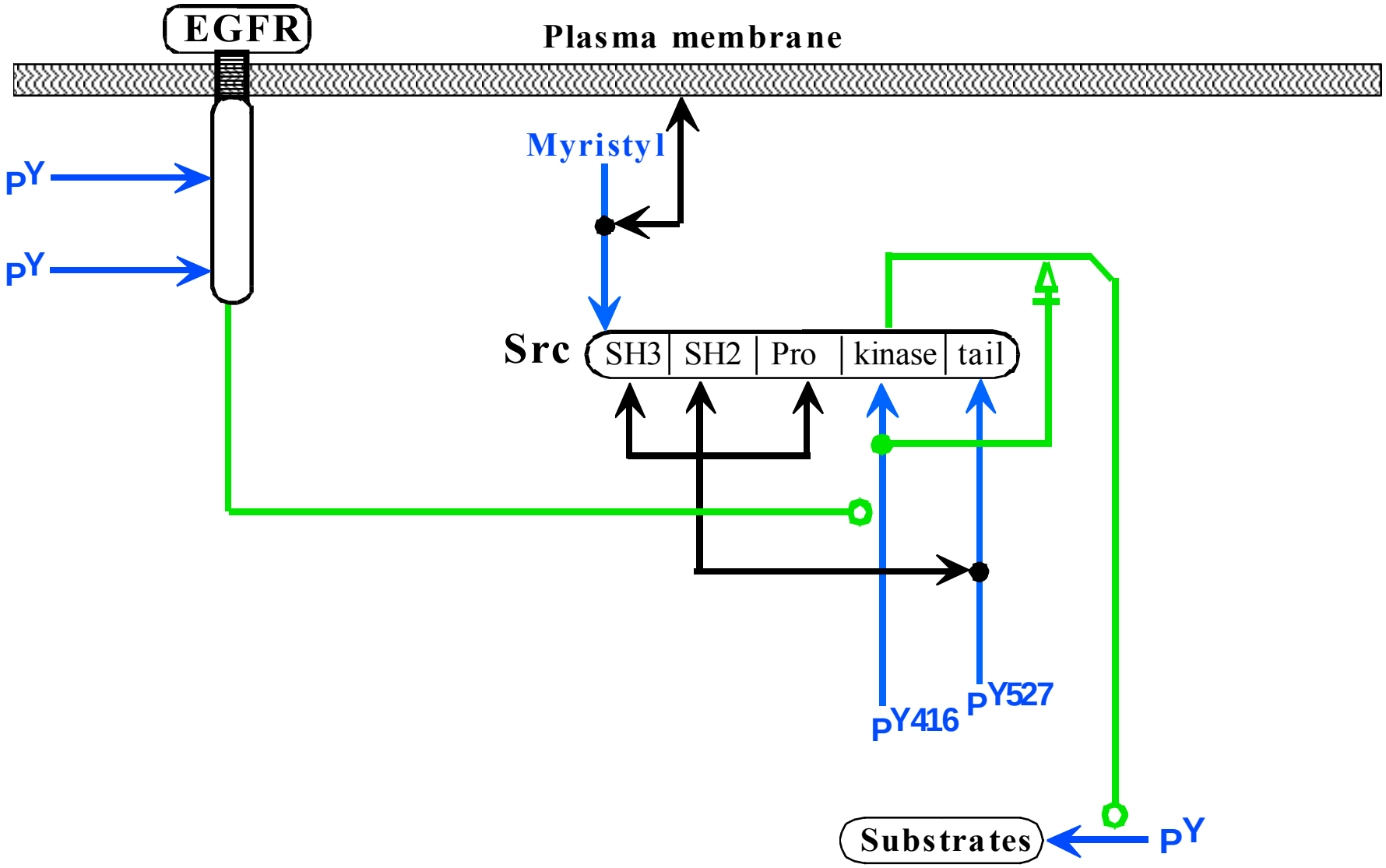
Src's tyrosine kinase domain could phosphorylate various substrates



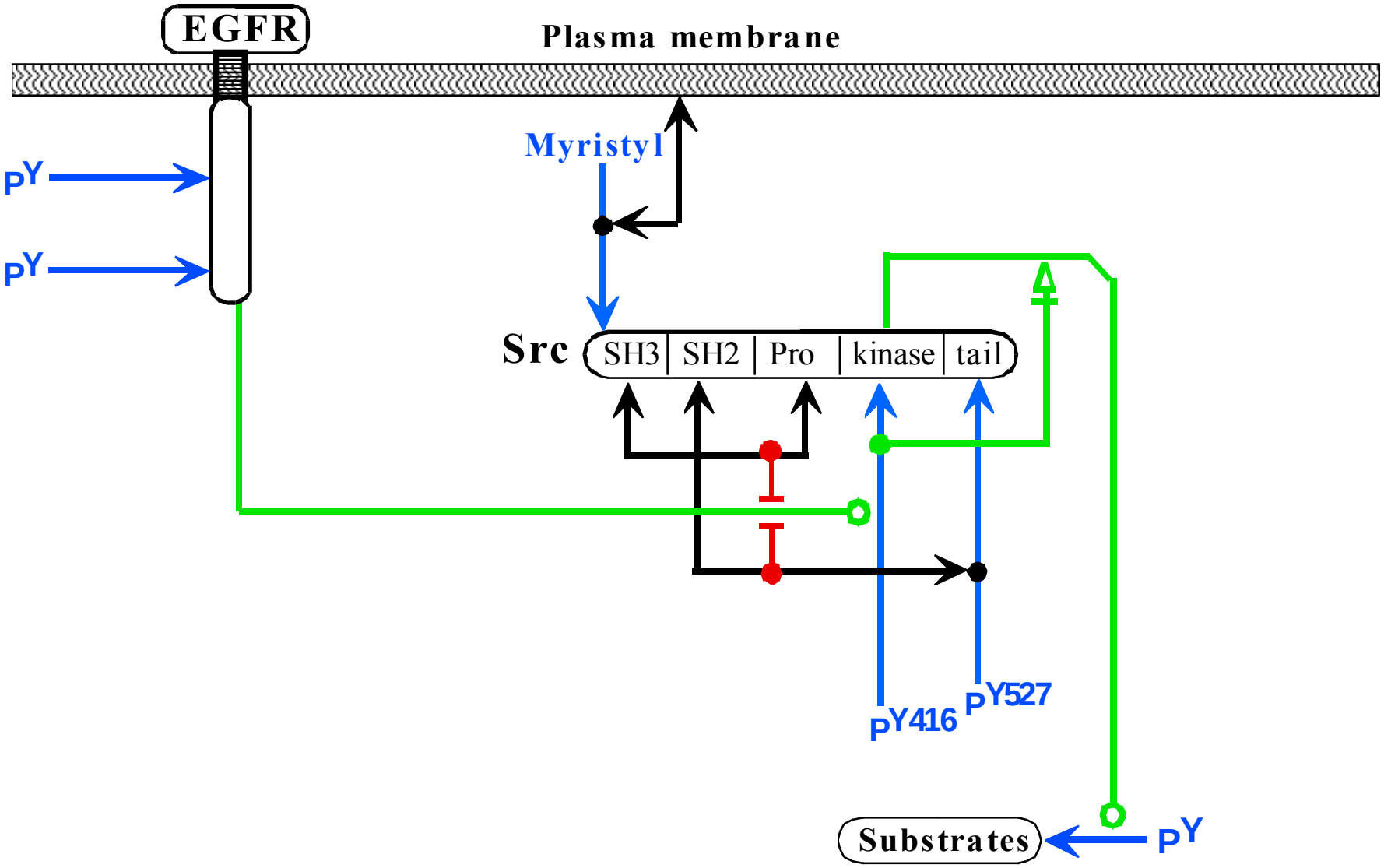
Phosphorylation of Tyr416 is required for the kinase to be active.



Activated (phosphorylated) EGFR could phosphorylate Tyr416

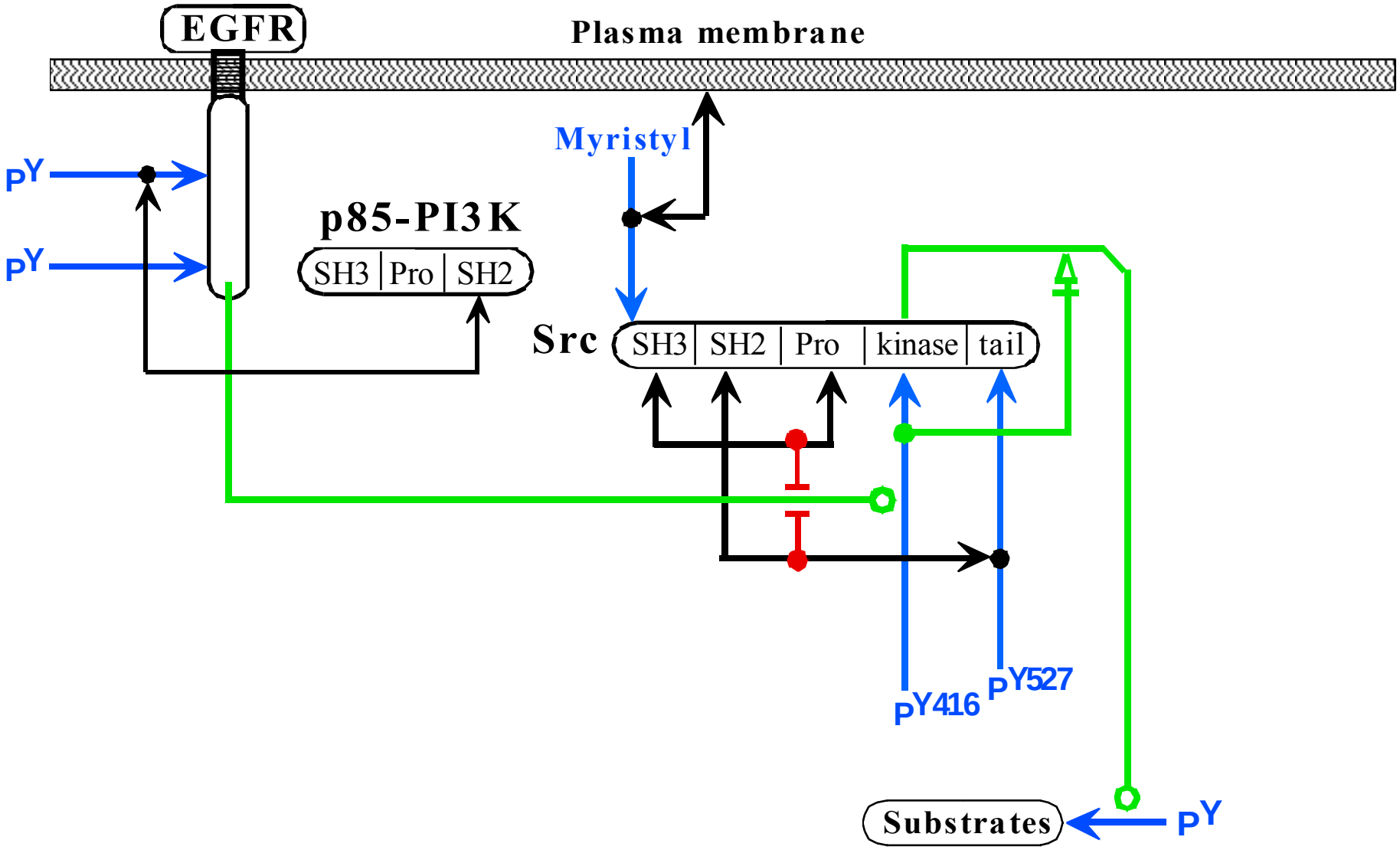


However, access to Tyr416 is blocked by the intra-molecular folding.

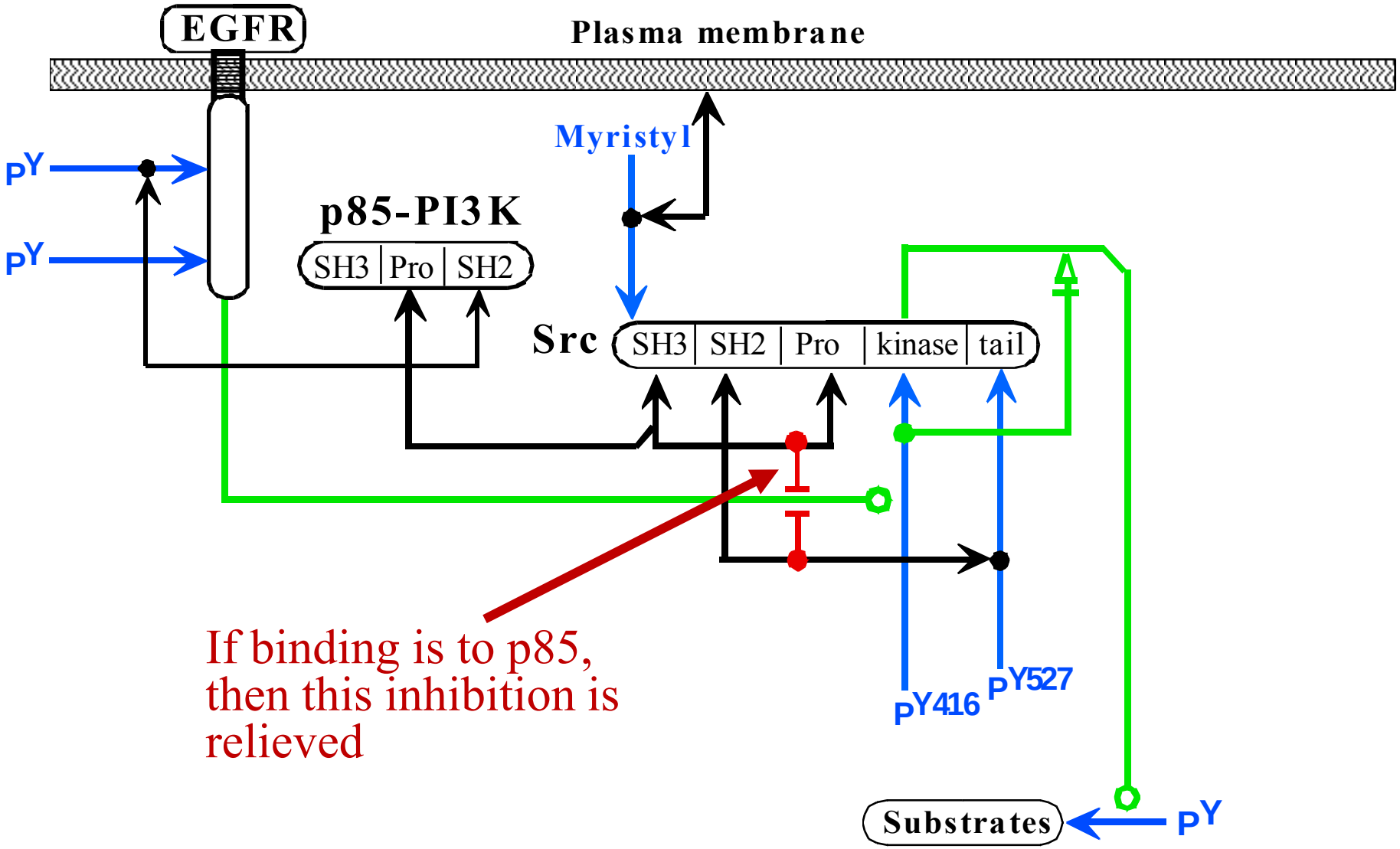


SRC activation:

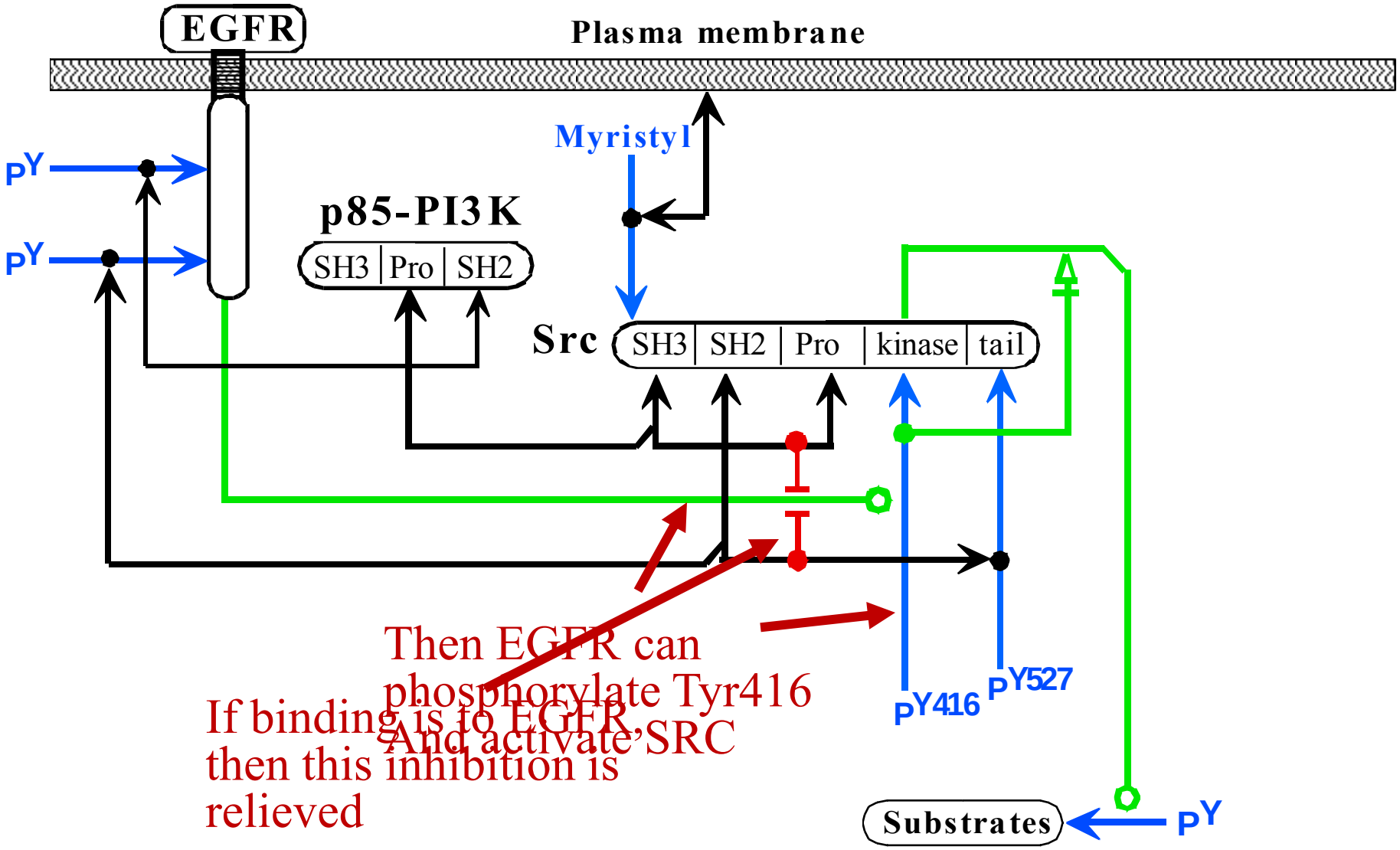
Through one of its phosphotyrosines, activated EGFR recruits p85.



Pro domain of p85 competes with Pro of Src for binding to SH3 of Src

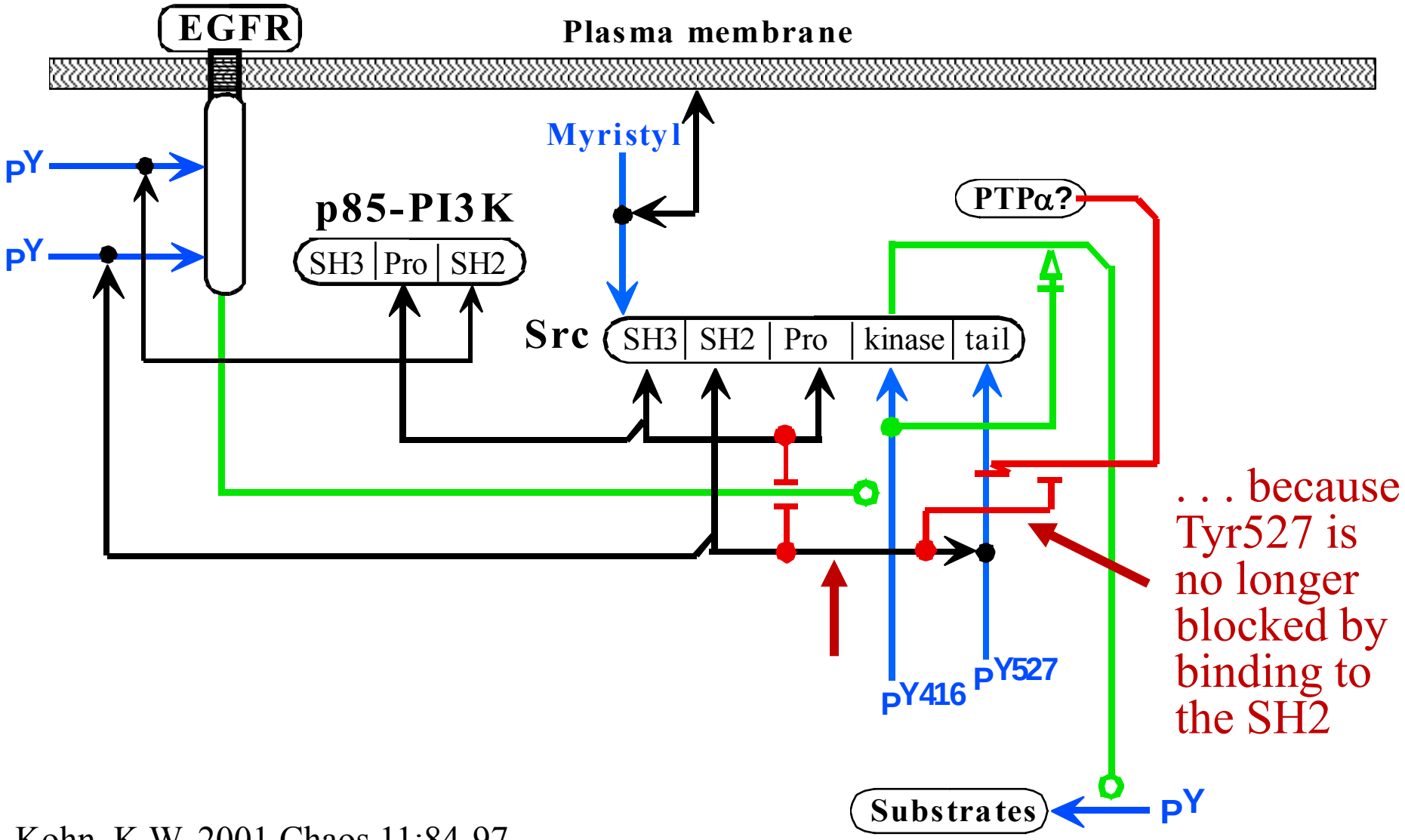


Phosphotyrosine of EGFR competes with P-Tyr527 of Src for binding to SH2 of Src



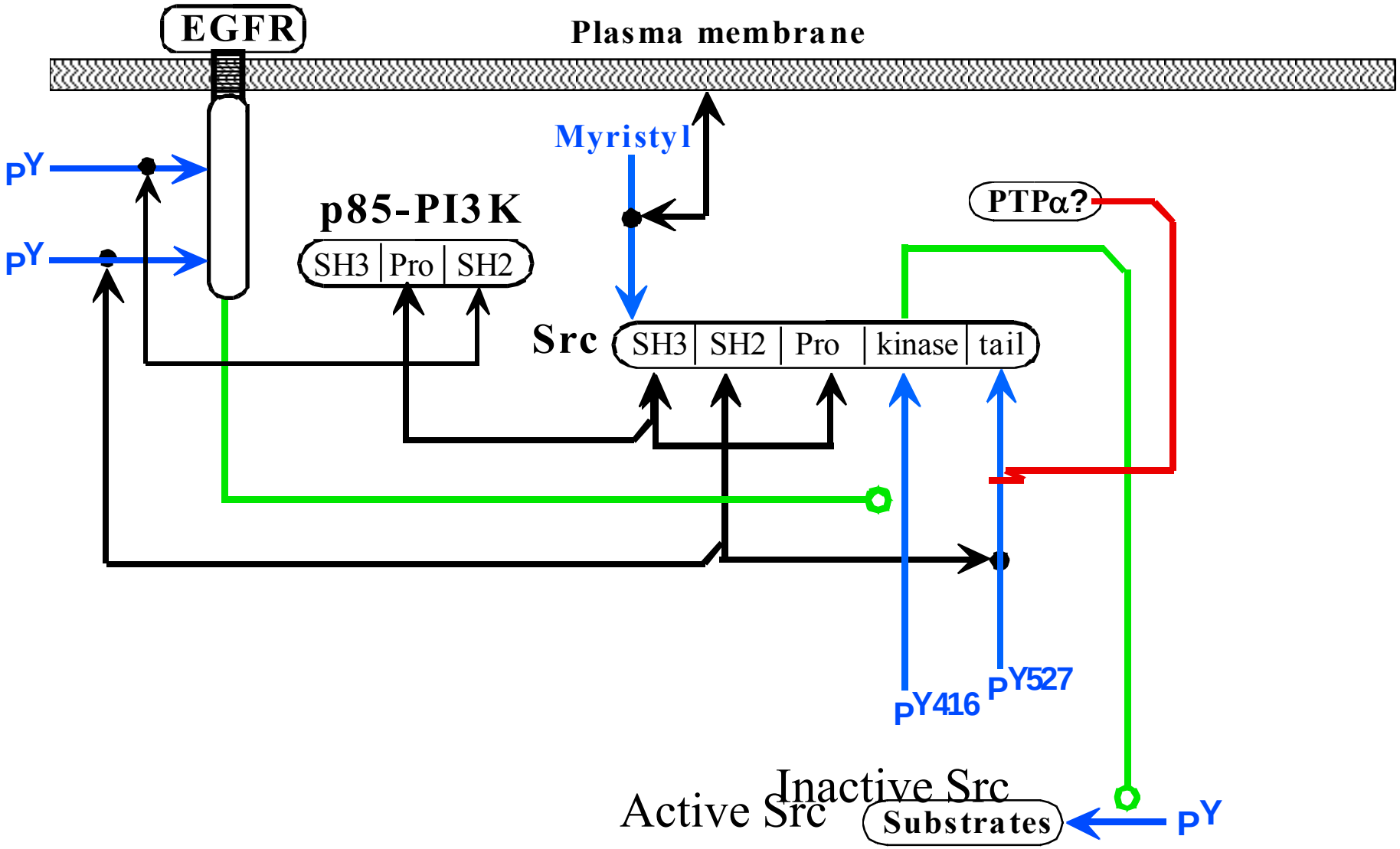
With Tyr527 gone, Src cannot refold and remains active even if it dissociates from the EGFR:p85 complex.
Thus multiple Src's can be activated by a single active EGFR -- *i.e.*, an amplification step.

Then a phosphatase can remove Tyr527 . . .



Kohn, K.W. 2001 Chaos 11:84-97

A dynamic animated map of Src activation by EGFR
(press the arrow keys to follow the interactions)



Summary of src activation
(no need to press any key)