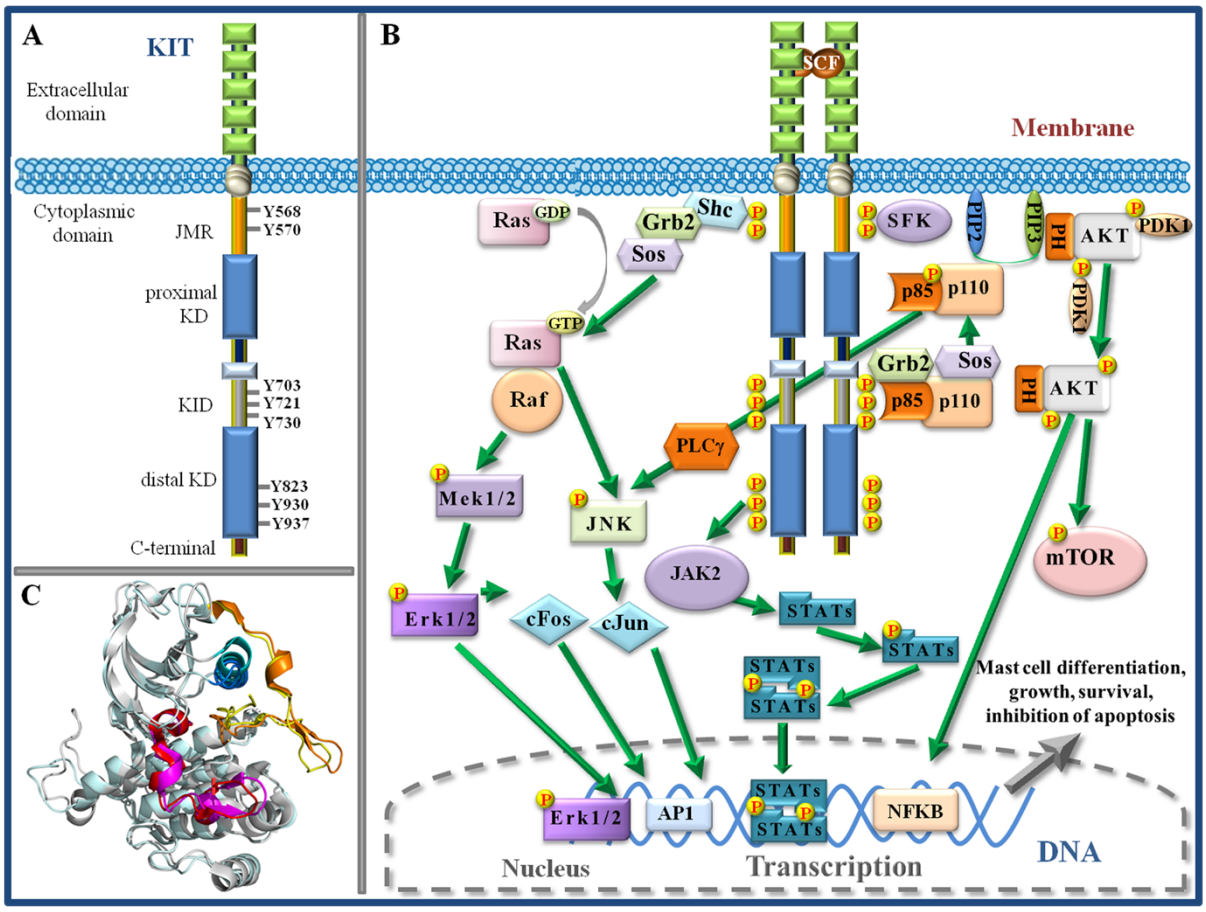
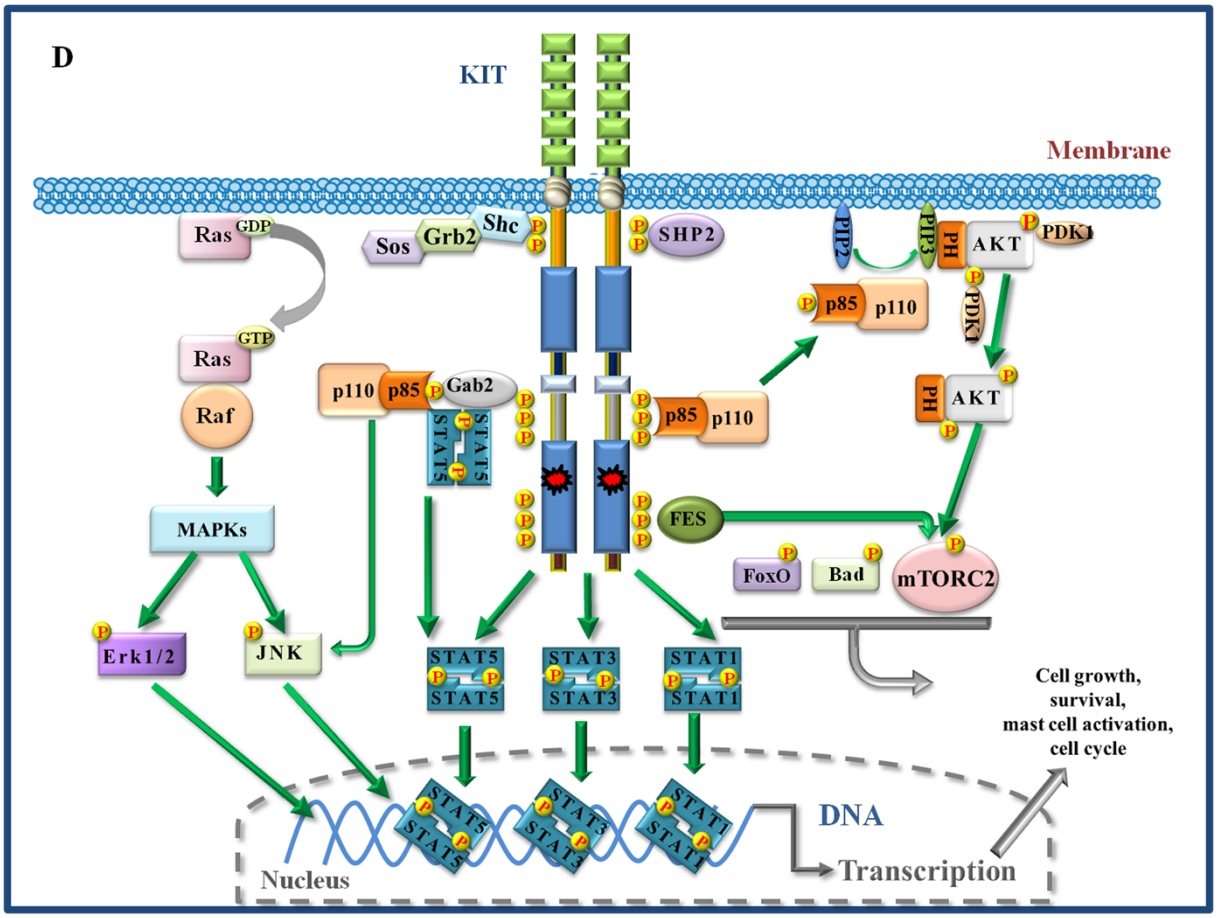
Supplementary Information

Scheme S1. **Structural organization and possible signaling pathways of receptors tyrosine kinases (RTKs) (*e.g.*, KIT)**. (**A**) RTKs of type III comprise an extracellular ligand binding domain, a single transmembrane helix, a juxtamembrane region (JMR), a conserved kinase domains (proximal and distal) linked by a hinge and a carboxy-terminal tail (C-terminal). Phorphorylation sites are shown. (**B**) Activation of KIT induced by binding of SCF-ligand leads to dimerization, phosphorylation of specific tyrosine residues, and recruitment of several proteins at the intracellular portion of the receptors. Several proteins (*e.g.*, the cytokine receptor-associated Janus kinase, JAK2) bind directly to the receptor, whereas Ras/Raf pathways and AKT pathway need several specific adaptor molecules. JAK2 converts the latent monomeric form of the STAT molecules to the activated dimeric form through tyrosine phosphorylation. The dimers bind to specific DNA response elements and are able to induce transcription. All possible pathways result in nuclear activation of genes regulating cell growth, survival and mast cell activation. (**C**) Superimposed crystallographic structures of the cytoplasmic region of KIT and CSF-1R receptors in the inactive form show several differences. The proteins are presented as cartoon, CSF-1R is in light blue and KIT is in light grey. The key structural fragments of receptors in the inactive and the active conformations are highlighted in color. The JMR is in yellow and in orange ; the A-loop is in red and magenta; the Cα-helix is in cyan and blue, in KIT and CSF-1R respectively. (**D**) The constitutively activated receptor KIT stabilized by oncogenic point mutation (red spots with black contour), prompts alternative signaling routes, either through FES or by direct interaction with STAT5. These pathways result in nuclear activation of genes related with cell growth, survival and mast cell activation. Scheme was adapted from M. Arock's personal communication.


A
KIT
Extracellular domain
Cytoplasmic domain
JMR
Y568
Y570
proximal KD
KID
Y703
Y721
Y730
distal KD
Y823
Y930
Y937
C-terminal
B
SCF
Membrane
Ras
GDP
GTP
Grb2
Shc
Sos
SFK
PIP2
PIP3
PH
AKT
PDK1
p85
p110
Raf
PLCγ
Mek1/2
JNK
JAK2
STATs
Erk1/2
cFos
cJun
mTOR
Mast cell differentiation, growth, survival, inhibition of apoptosis
AP1
NFKB
Nucleus
Transcription
DNA
C


D
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Membrane
Ras
GDP
GTP
Sos
Grb2
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PIP3
PH
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p110
Gab2
STAT5
STAT3
STAT1
Raf
MAPKs
Erk1/2
JNK
FES
FoxO
Bad
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Cell growth, survival, mast cell activation, cell cycle
Nucleus
DNA
Transcription