Leucemia linfatica cronica: I WILL SURVIVE!

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B-cell chronic lymphocytic leukemia (CLL)

- B- cell leukemia characterized by peripheral accumulation of CD5$^+$ B cells
- Late-onset, variable clinical course
- Disease aggressiveness related to prognostic markers: mutational status *IGHV*, CD38, ZAP-70, chromosomal aberrations (del 11q, 13q, 17p; trisomy 12)
- Enhanced BCR signaling in aggressive disease presentation
- Neoplastic B cells accumulate primarily because of extended lifespan

Intrinsic and extrinsic factors regulate the lifespan of B cells
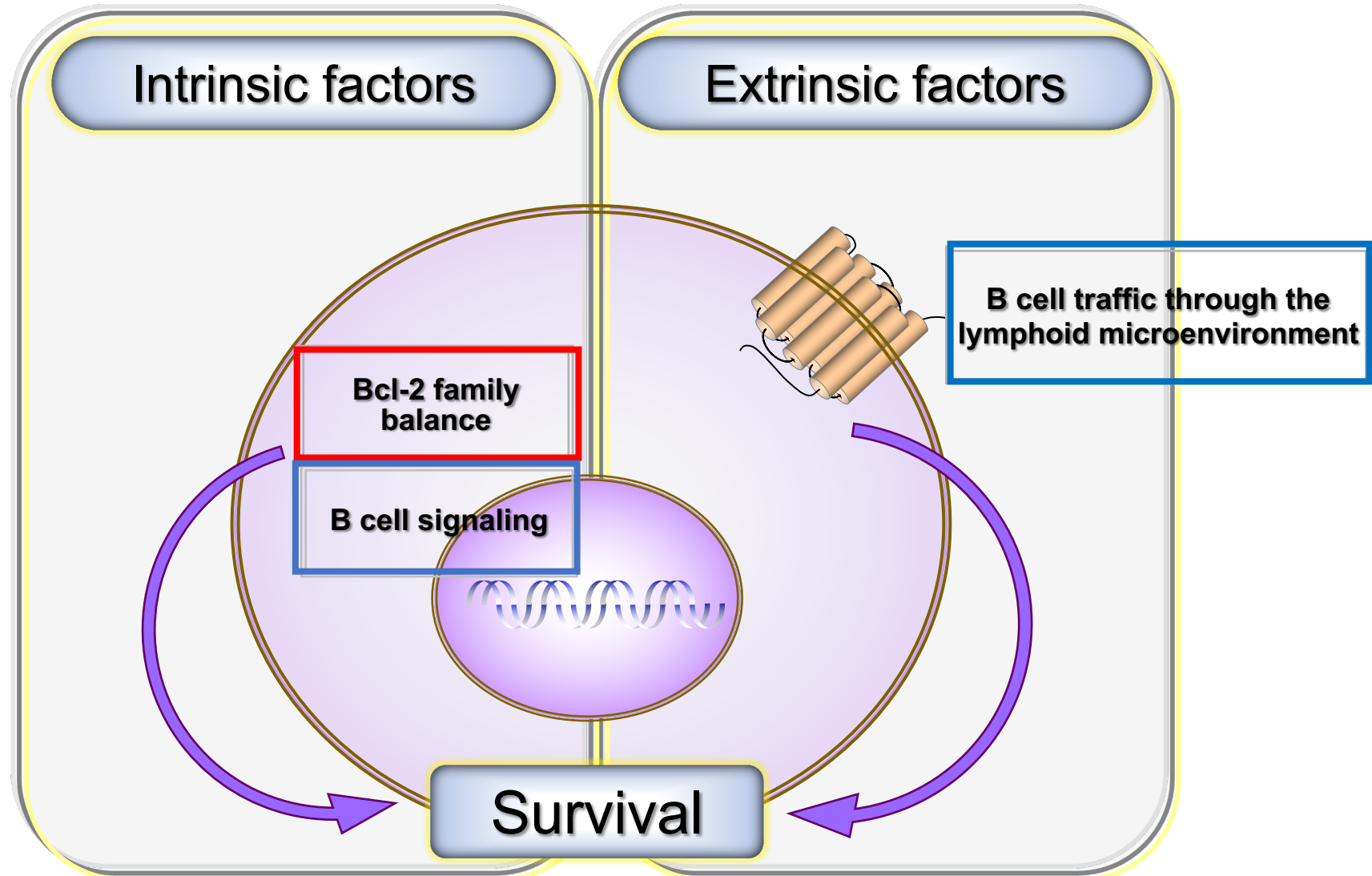
Intrinsic defects in CLL: apoptosis
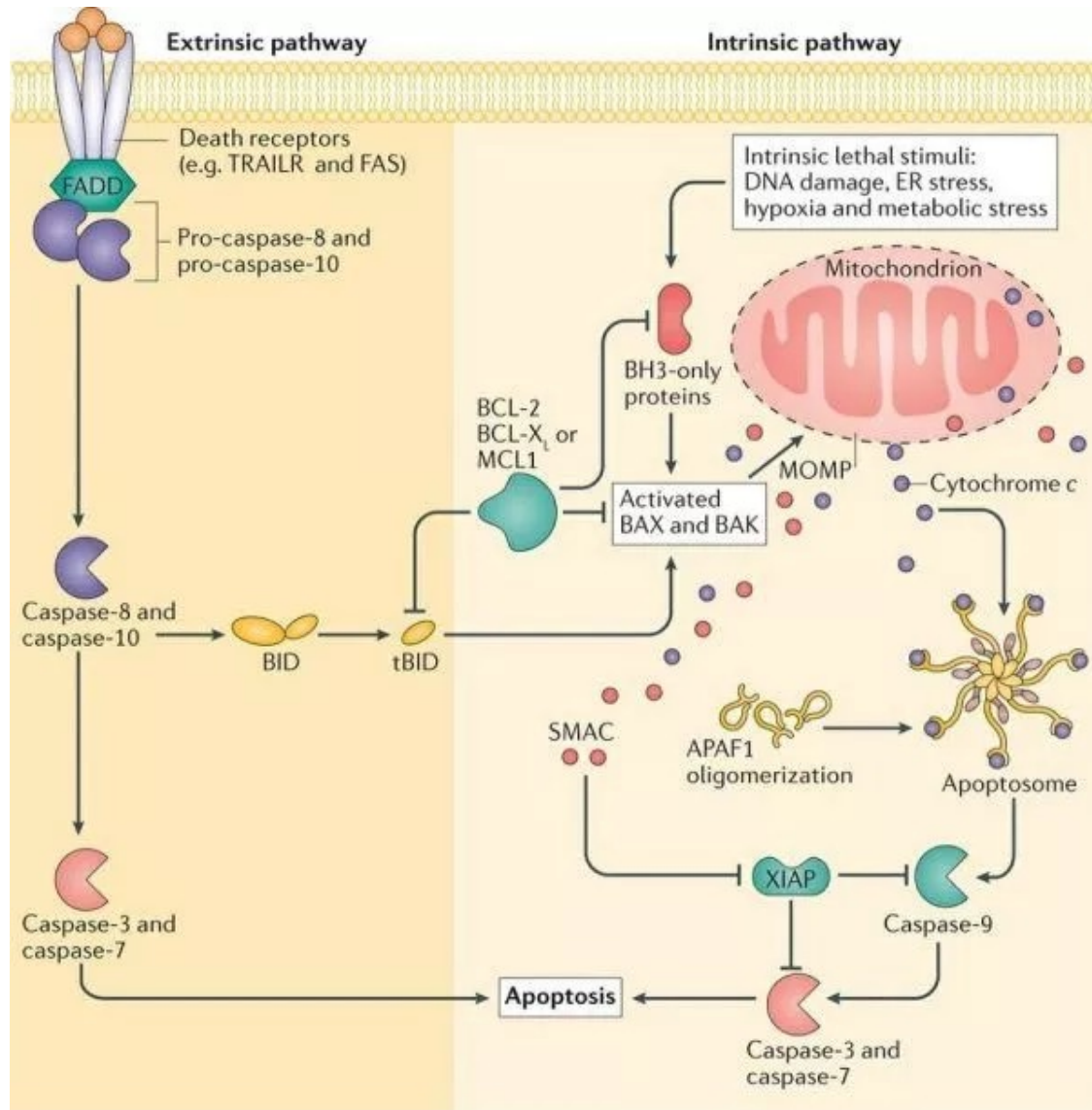
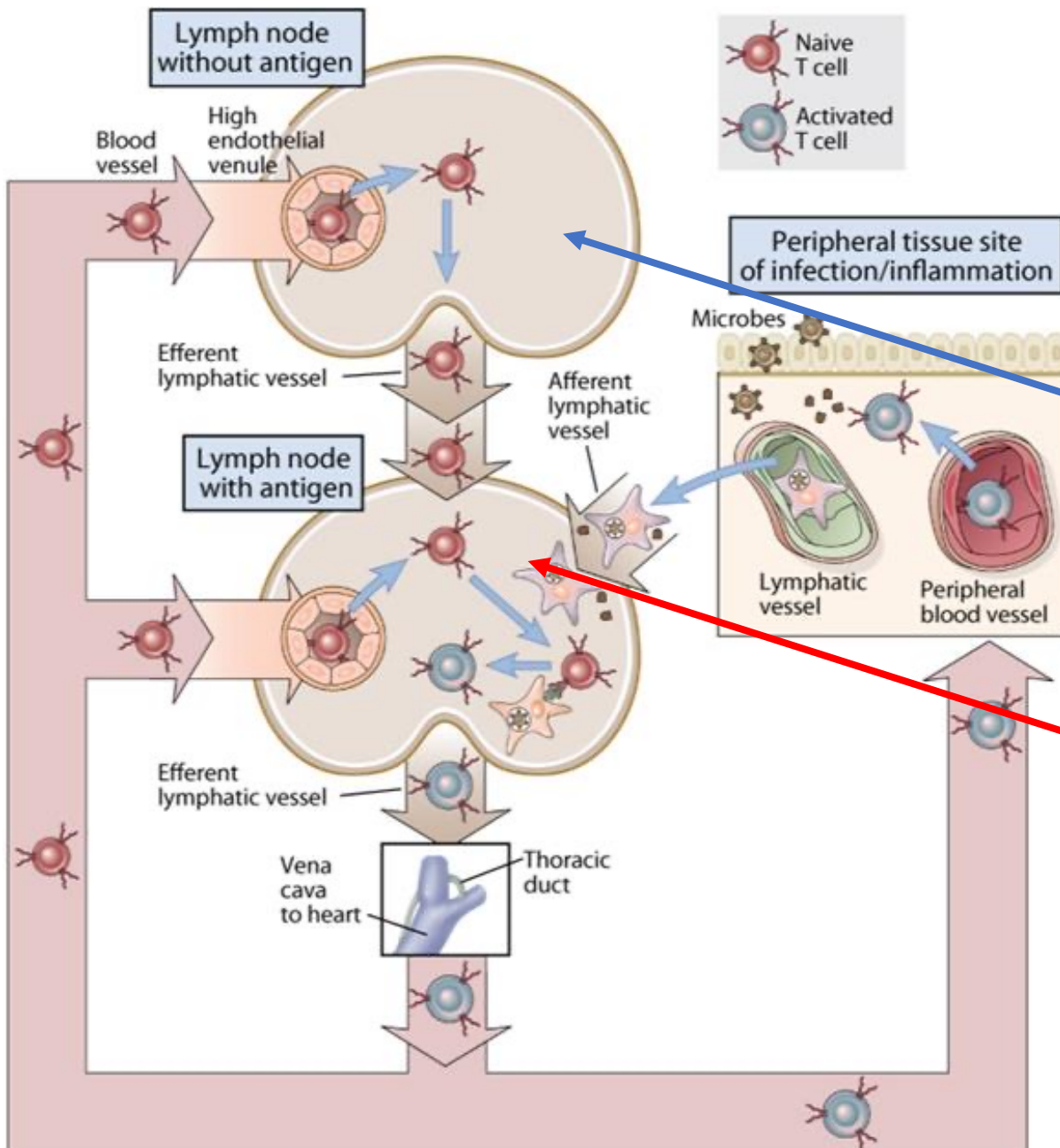# Intrinsic defects in CLL: survival signaling
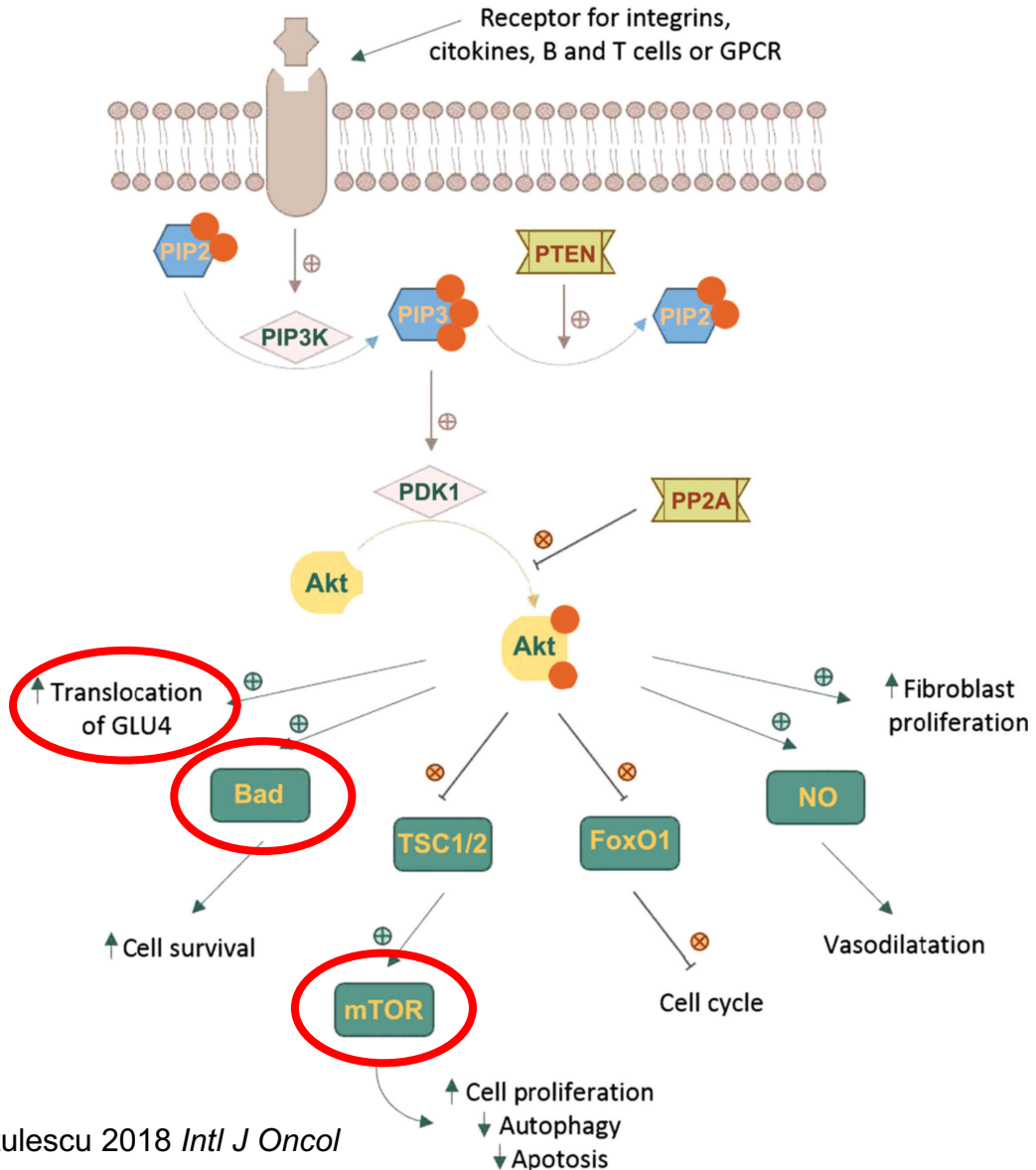
CLL

⬆ protein and lipid biosynthesis

⬇ apoptosis

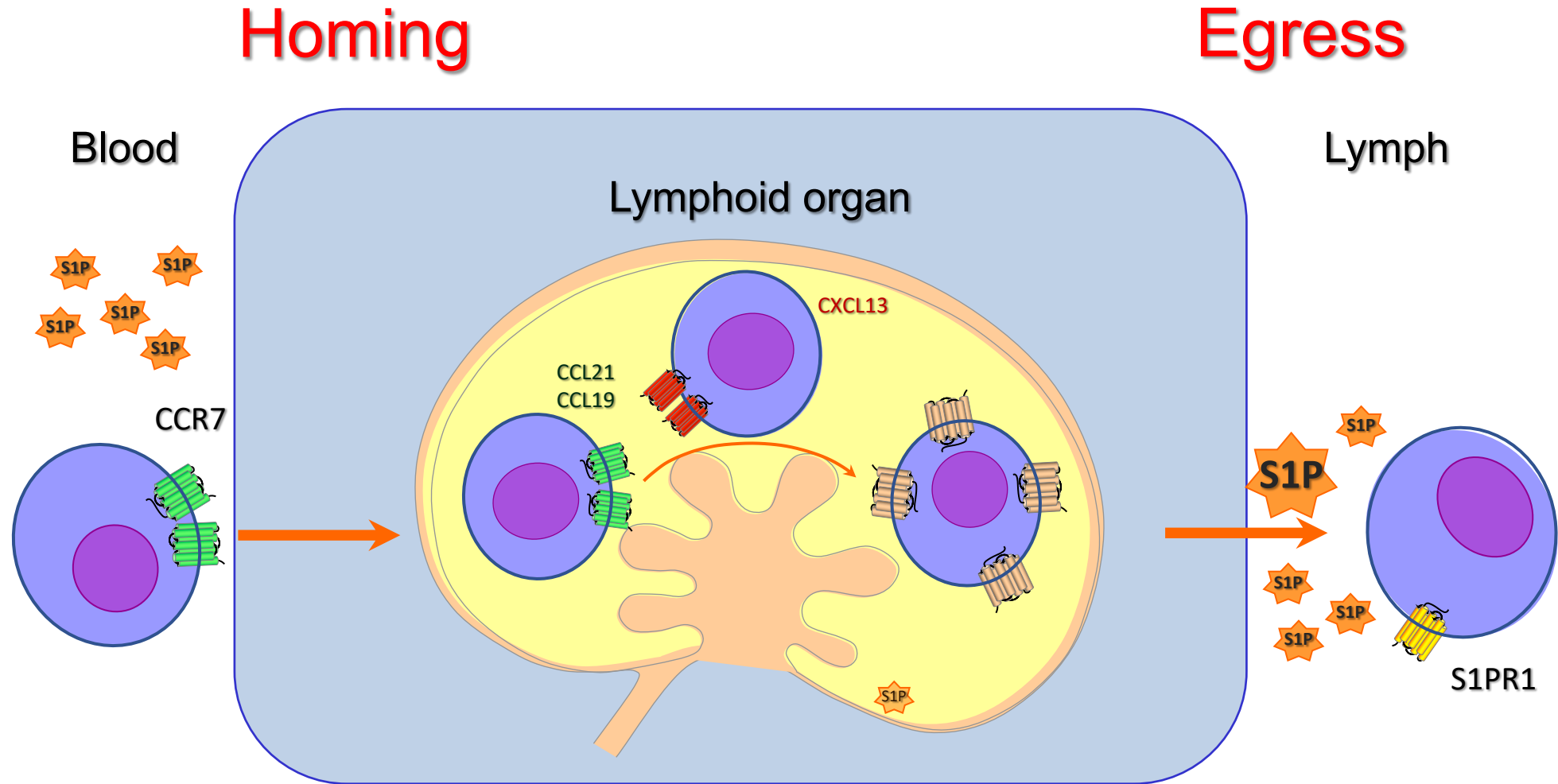Survival signals are delivered by the BCR and chemokine receptors **in the lymphoid microenvironment**

Lymphocytes recirculate continually to secondary lymphoid organs in search of cognate antigen
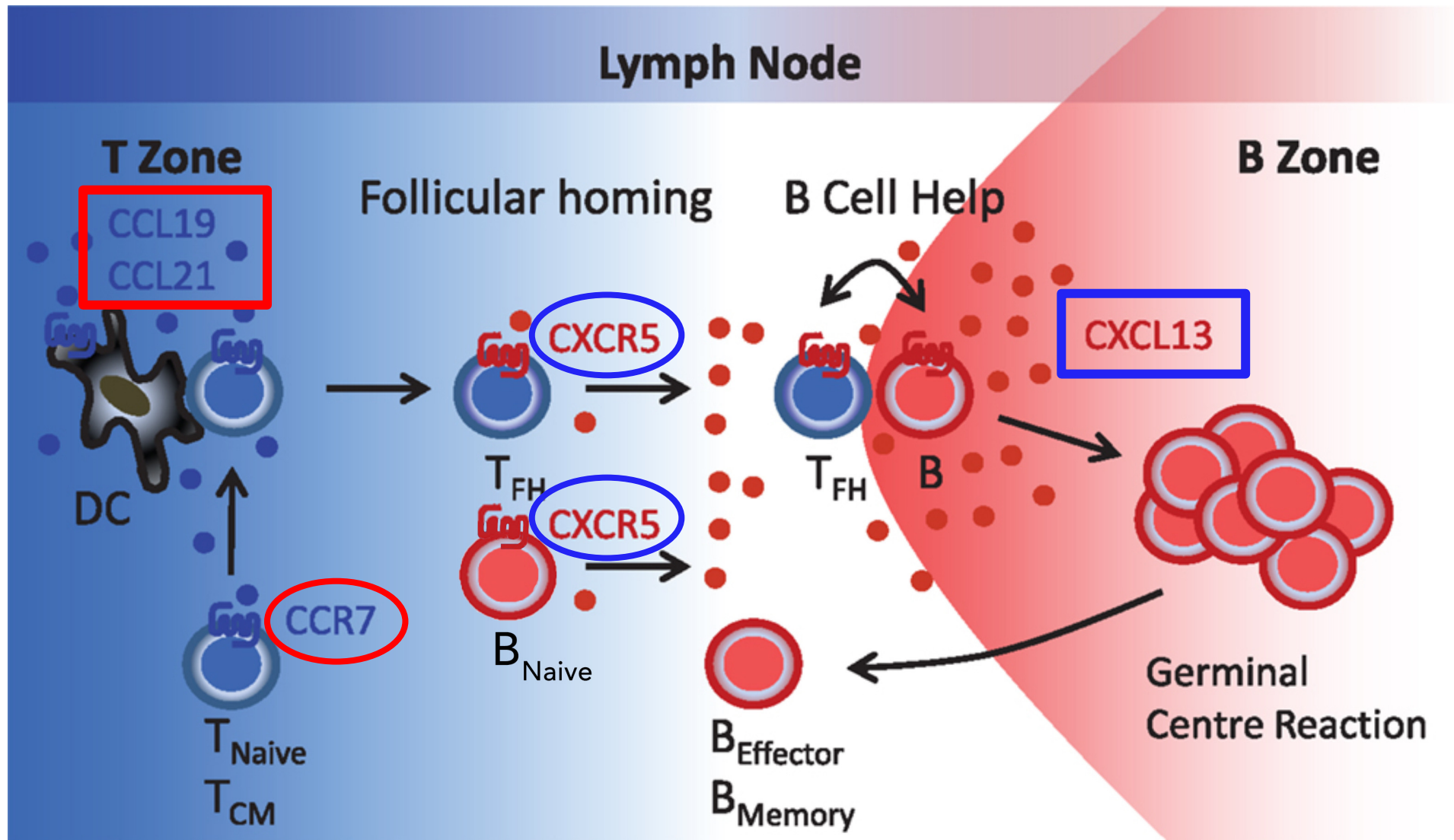
Survival signals
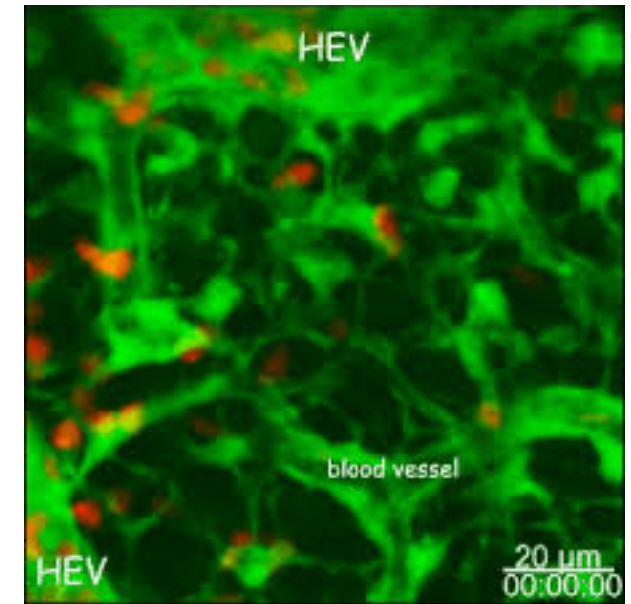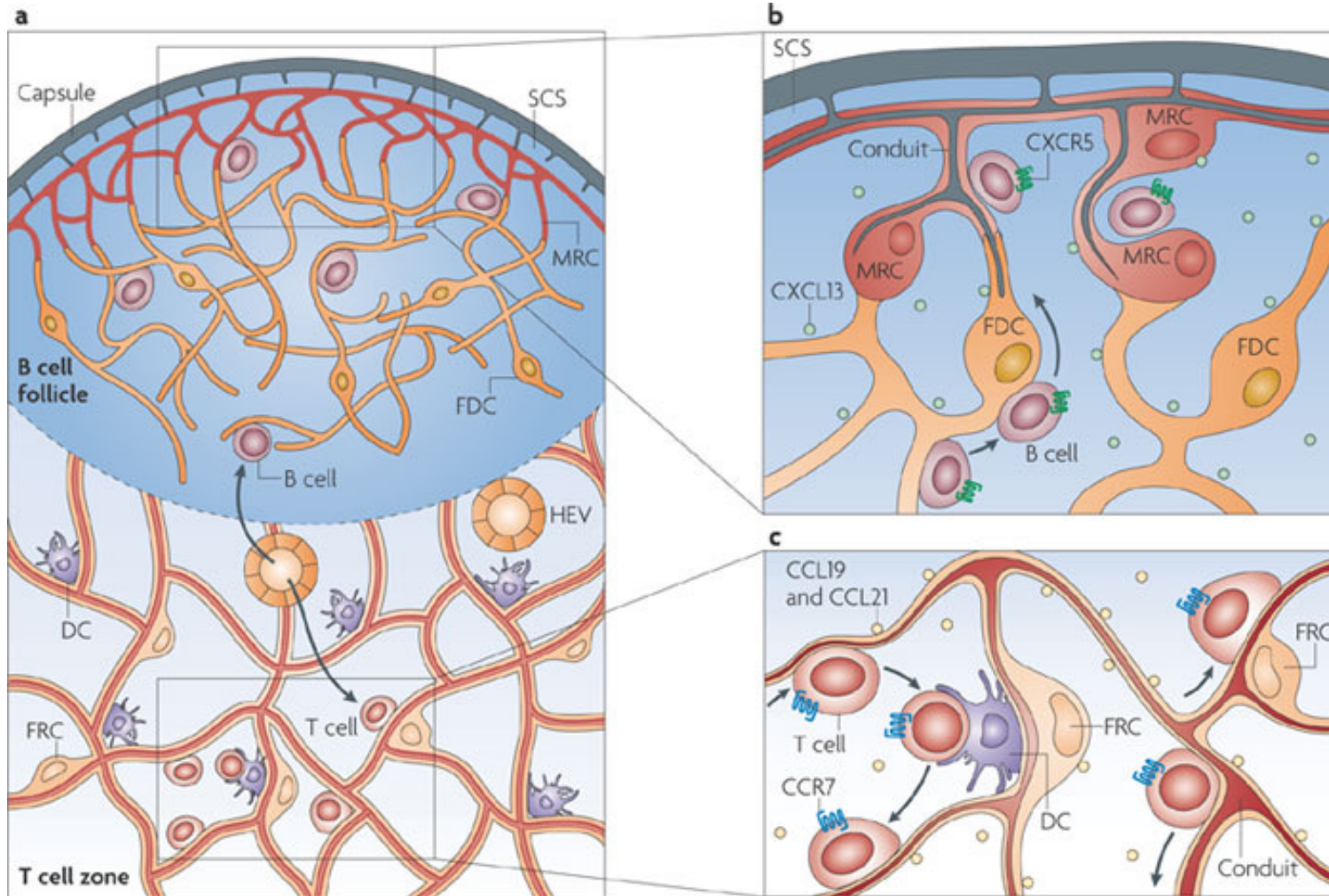
Proliferation & differentiation signals

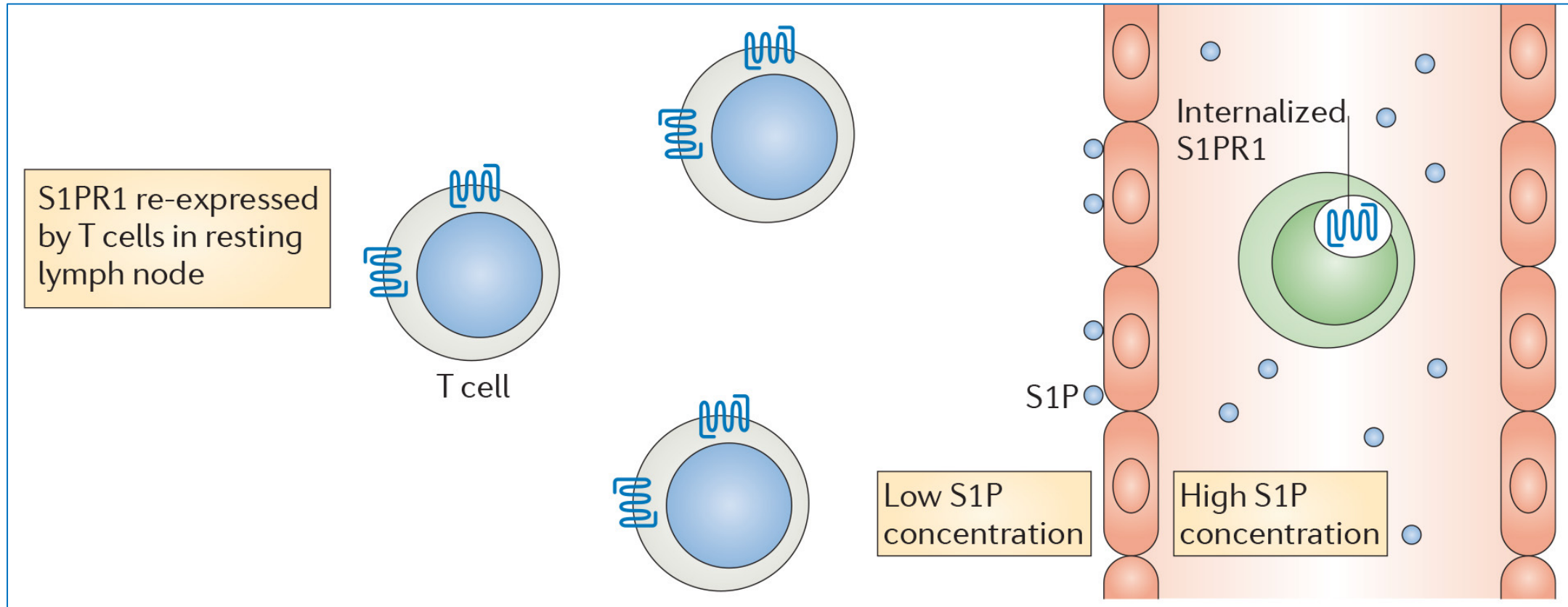Lymphocyte traffic is orchestrated by opposing chemotactic cues

Chemokines attract T and B cells to secondary lymphoid organs and regulate their localization therein
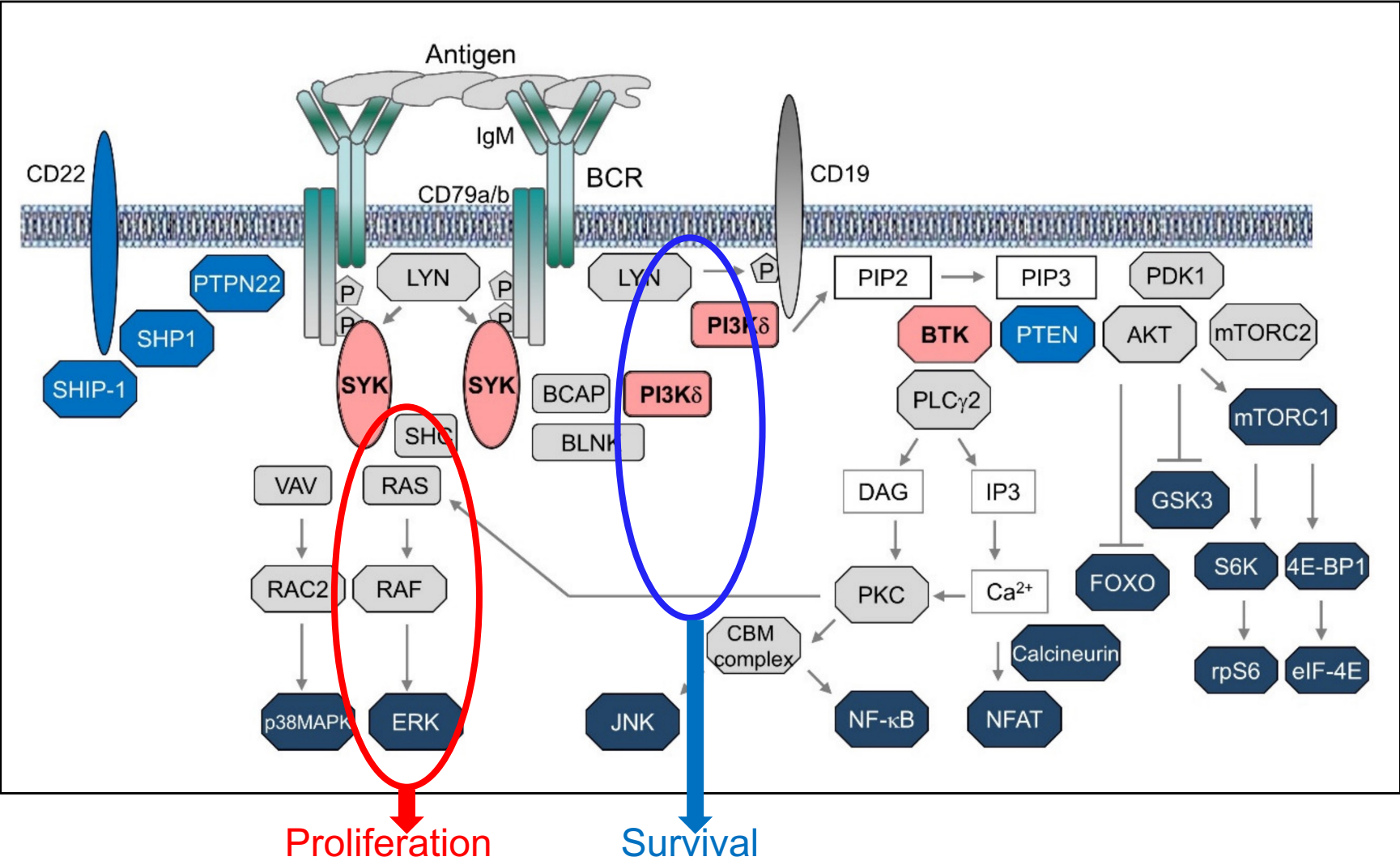
# In lymphoid tissues lymphocytes move along paths set by stromal cell networks

Lymphocyte egress from secondary lymphoid organs is guided by sphingosine-1-phosphate

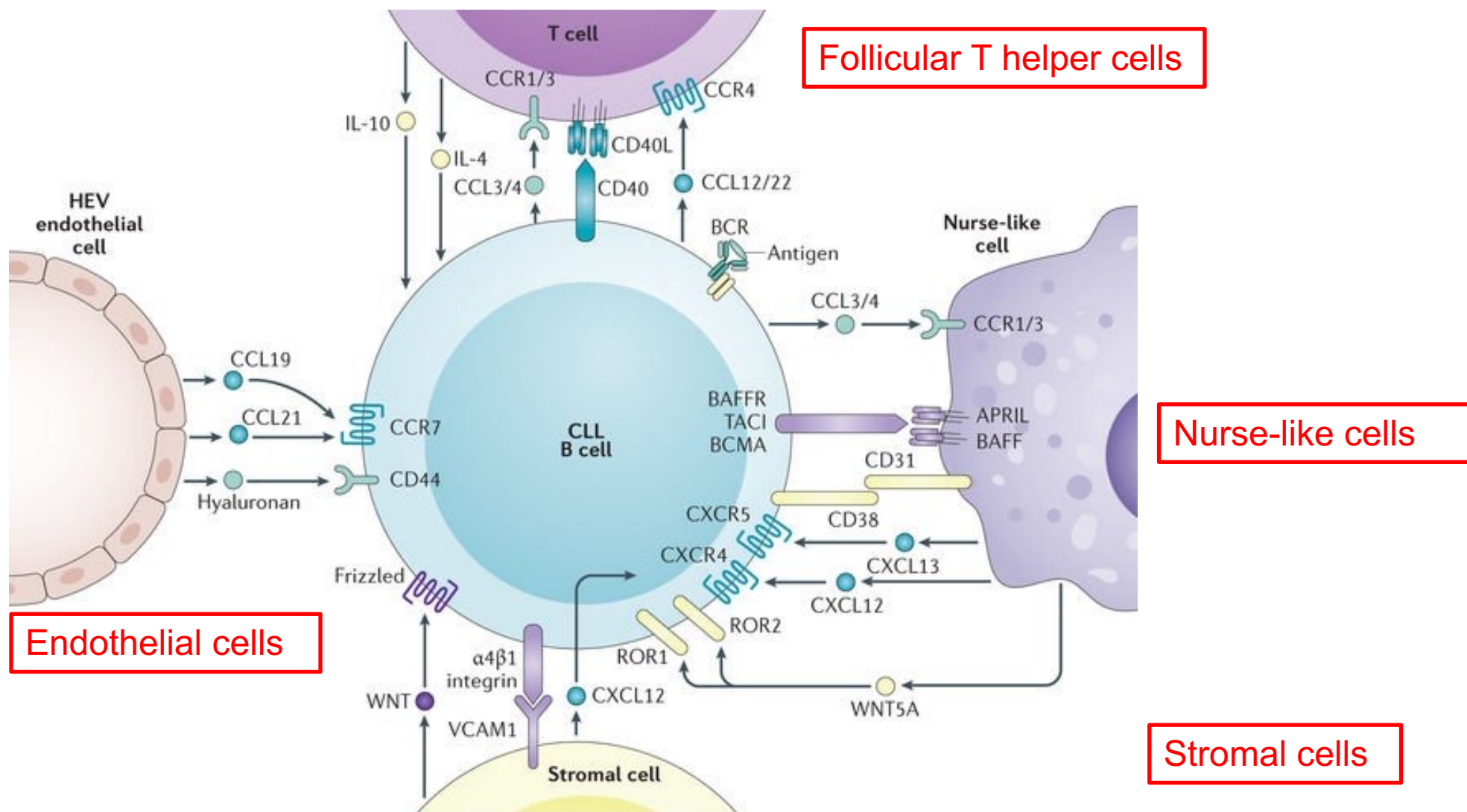
Spiegel & Milstein 2011 *Nat Rev Immunol*

B cells acquire proliferation and survival signals during their transit in the lymphoid stroma: BCR signaling
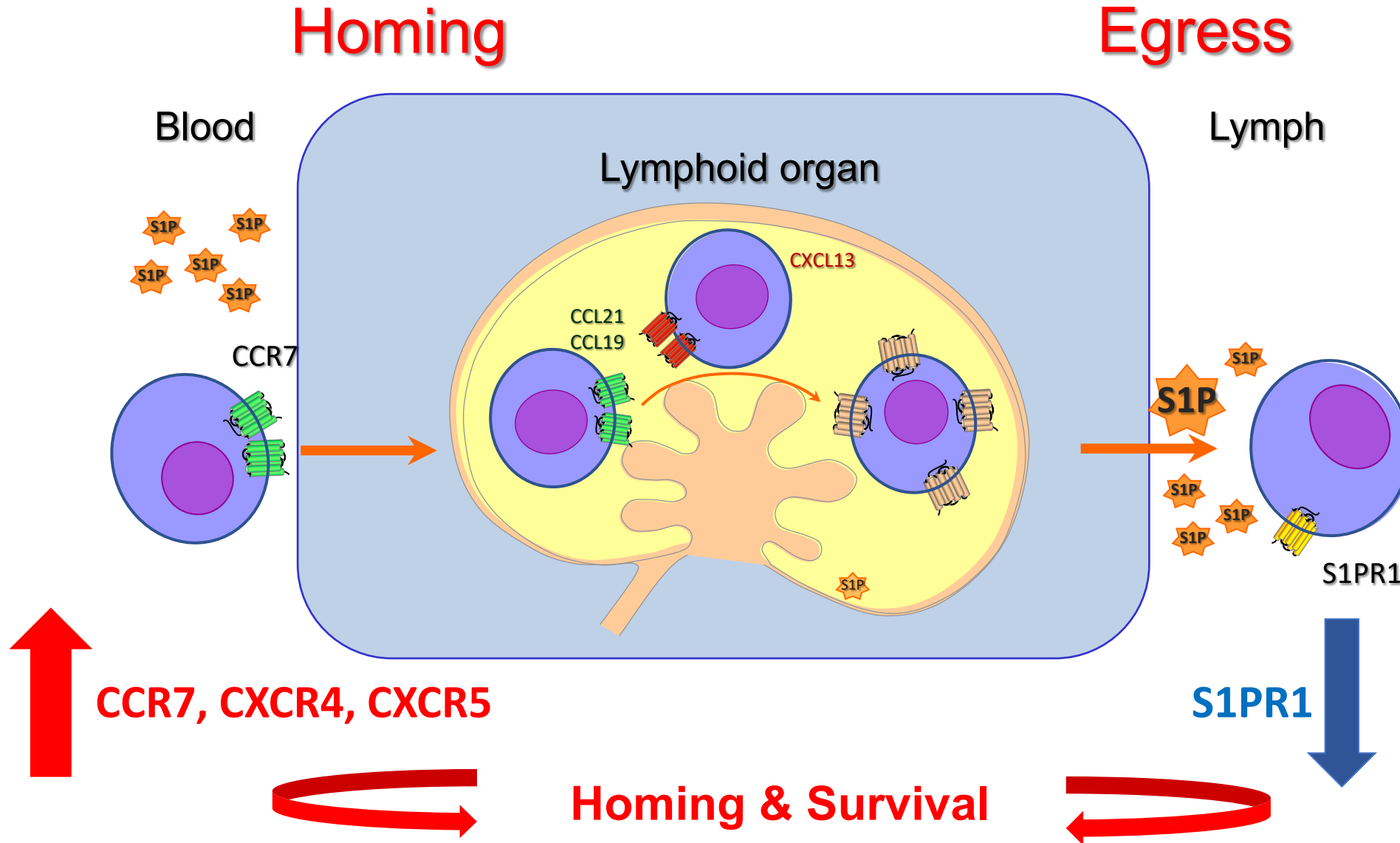
B cells acquire proliferation and survival signals during their transit in the lymphoid stroma: chemokine receptor signaling
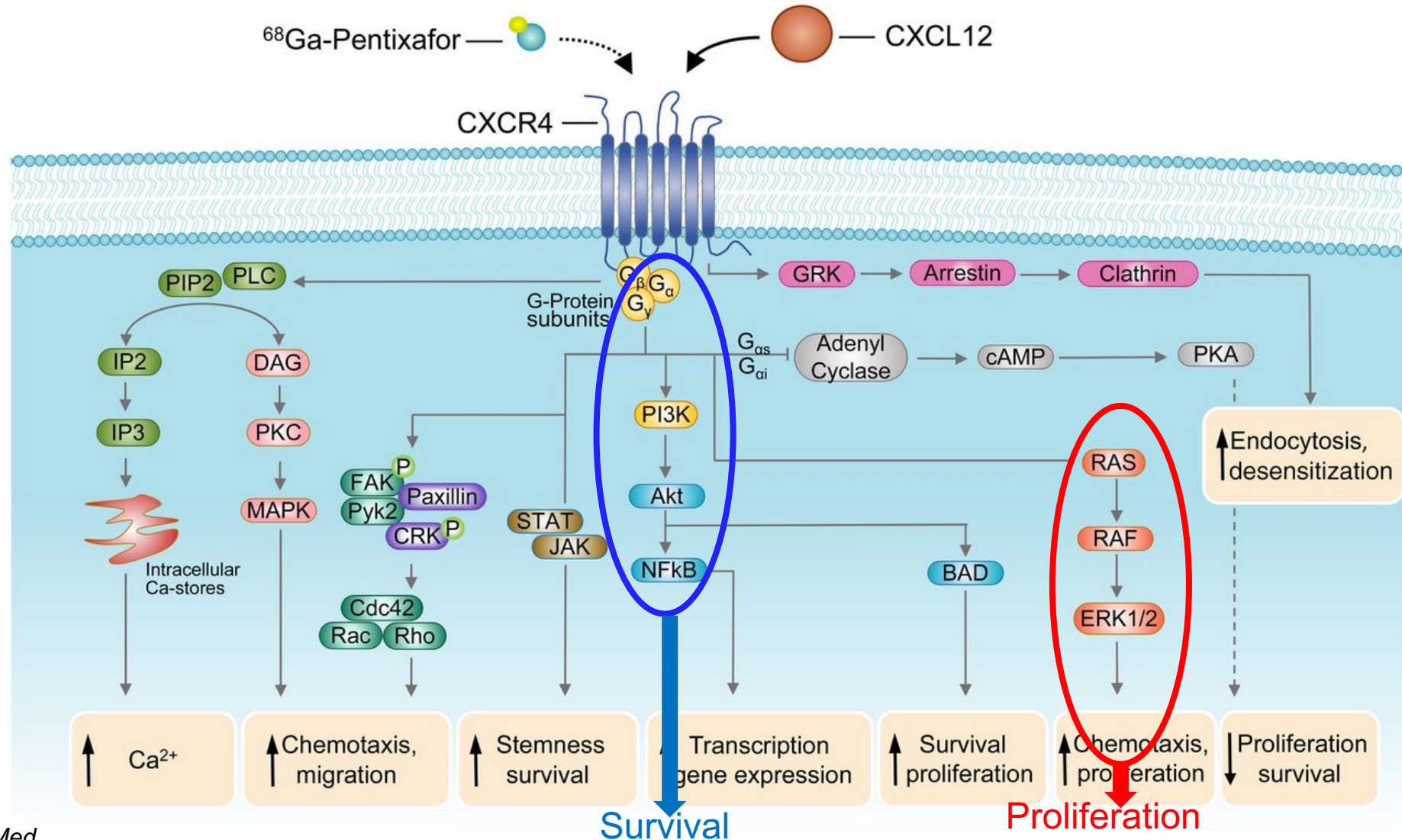
# CLL cells exploit the recirculation process to acquire survival cues from the lymphoid microenvironment

Follicular T helper cells

Nurse-like cells

Endothelial cells

Stromal cells

Nature Reviews | Disease Primers

Abnormalities in homing and egress receptor expression in CLL
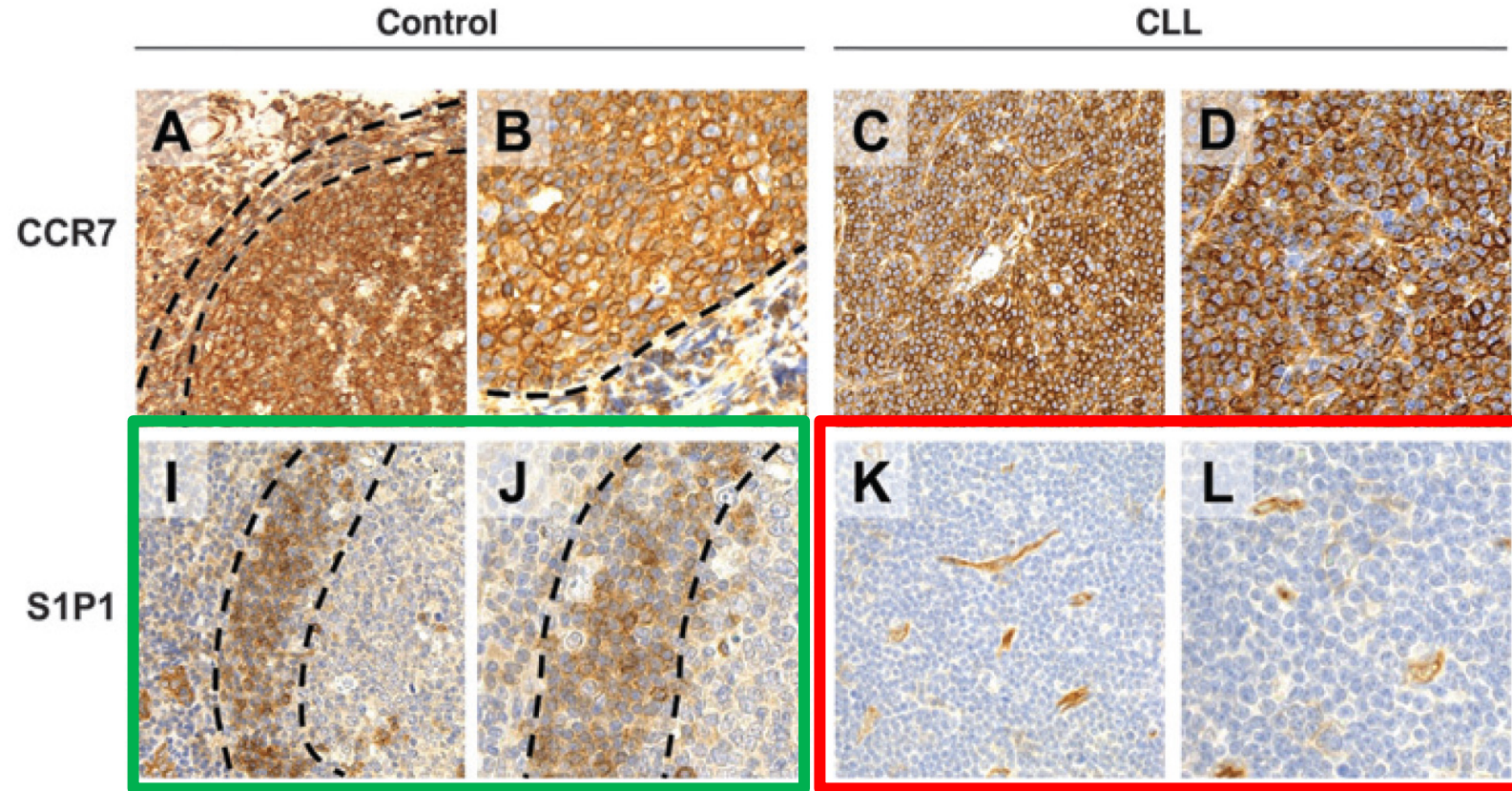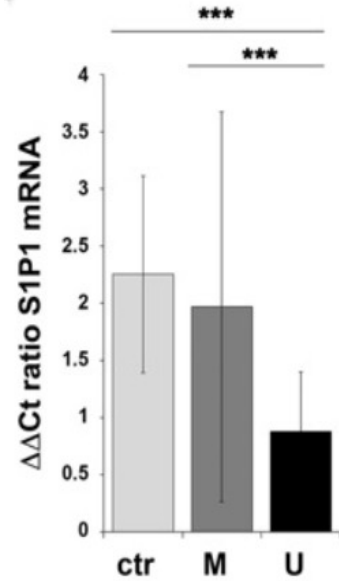
Concomitant upregulation of homing receptors and downregulation of egress receptors in CLL
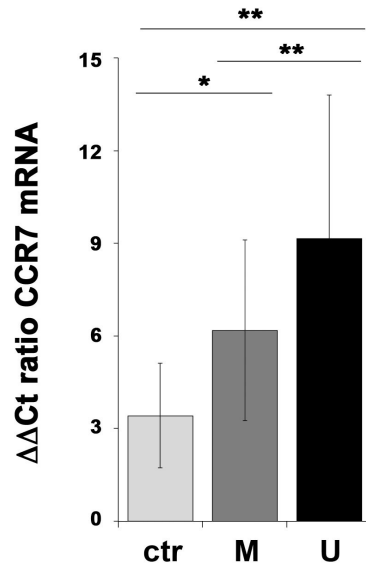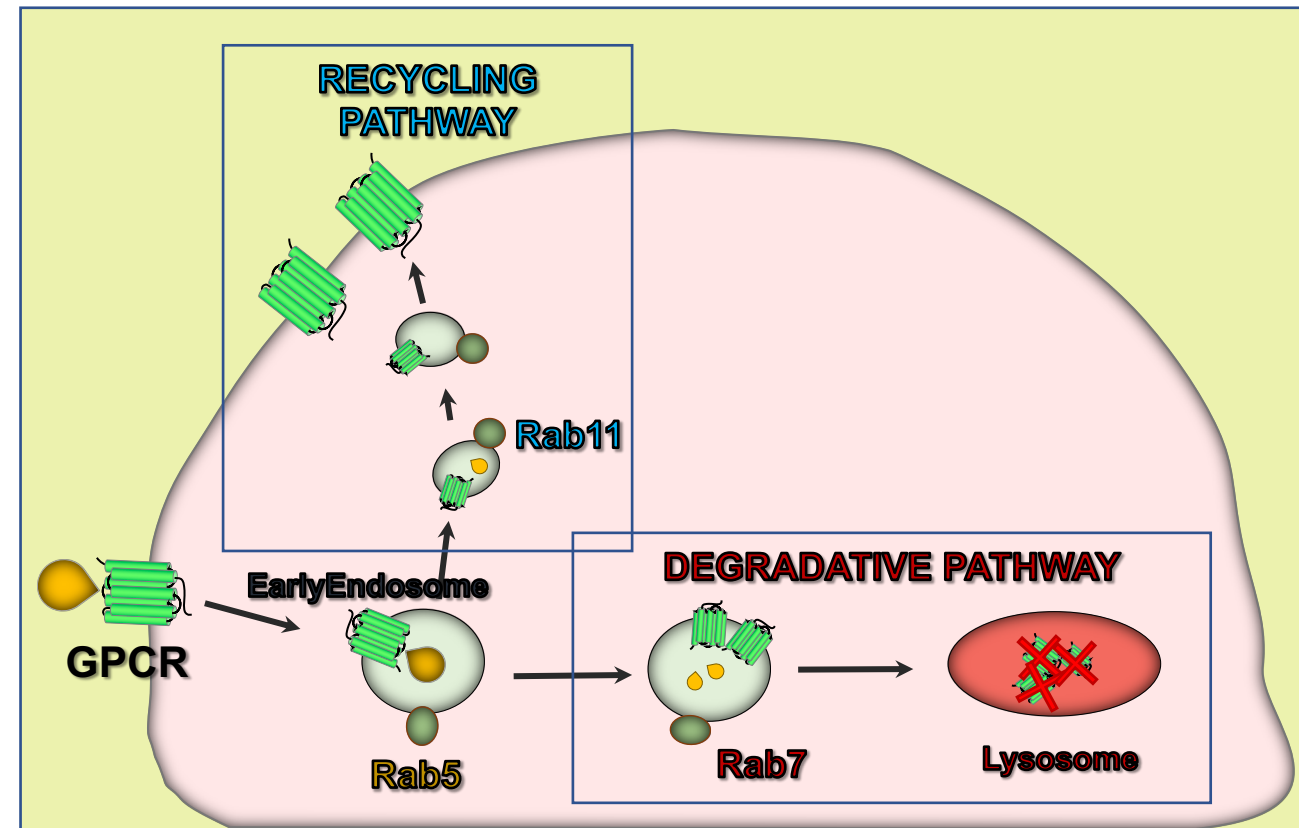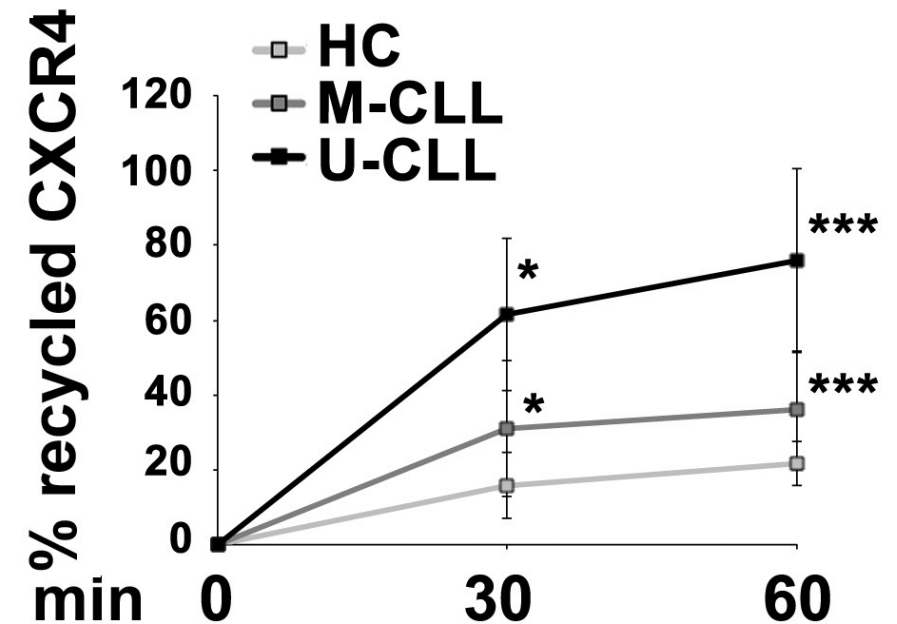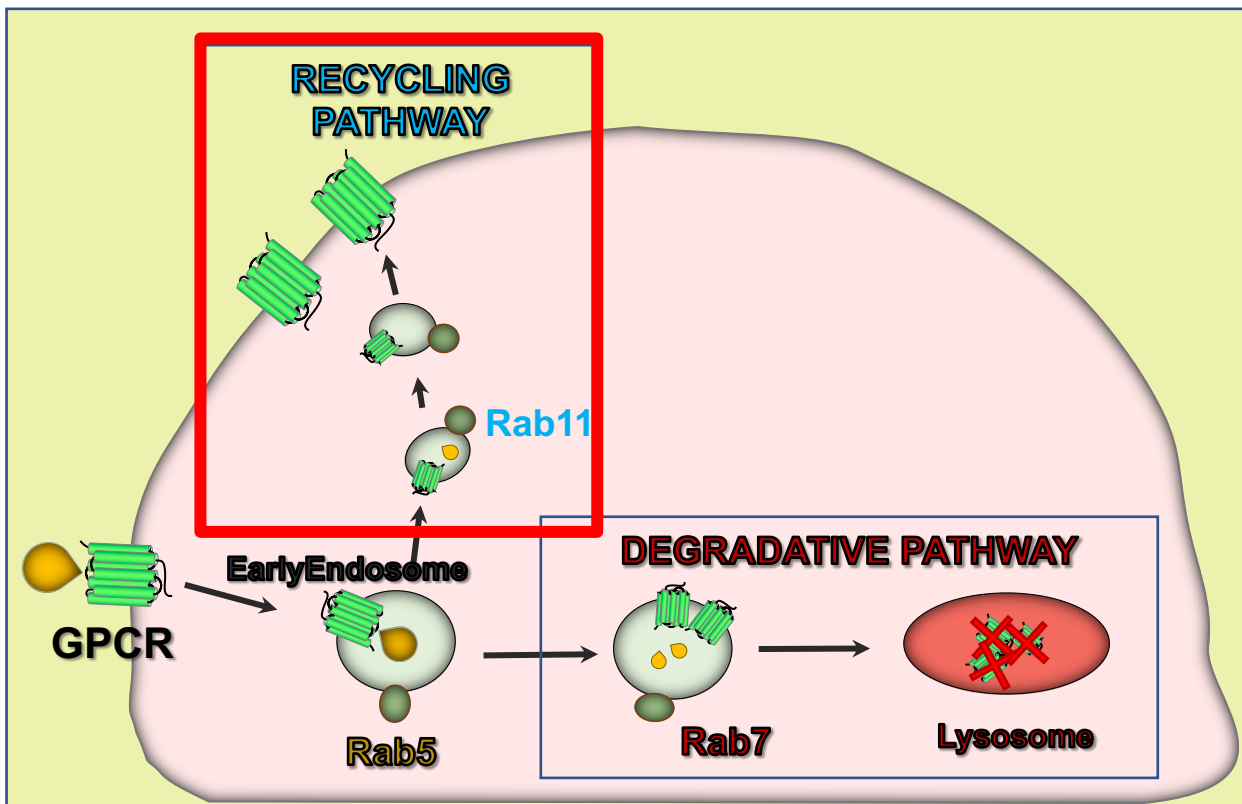

CCR7   S1PR1

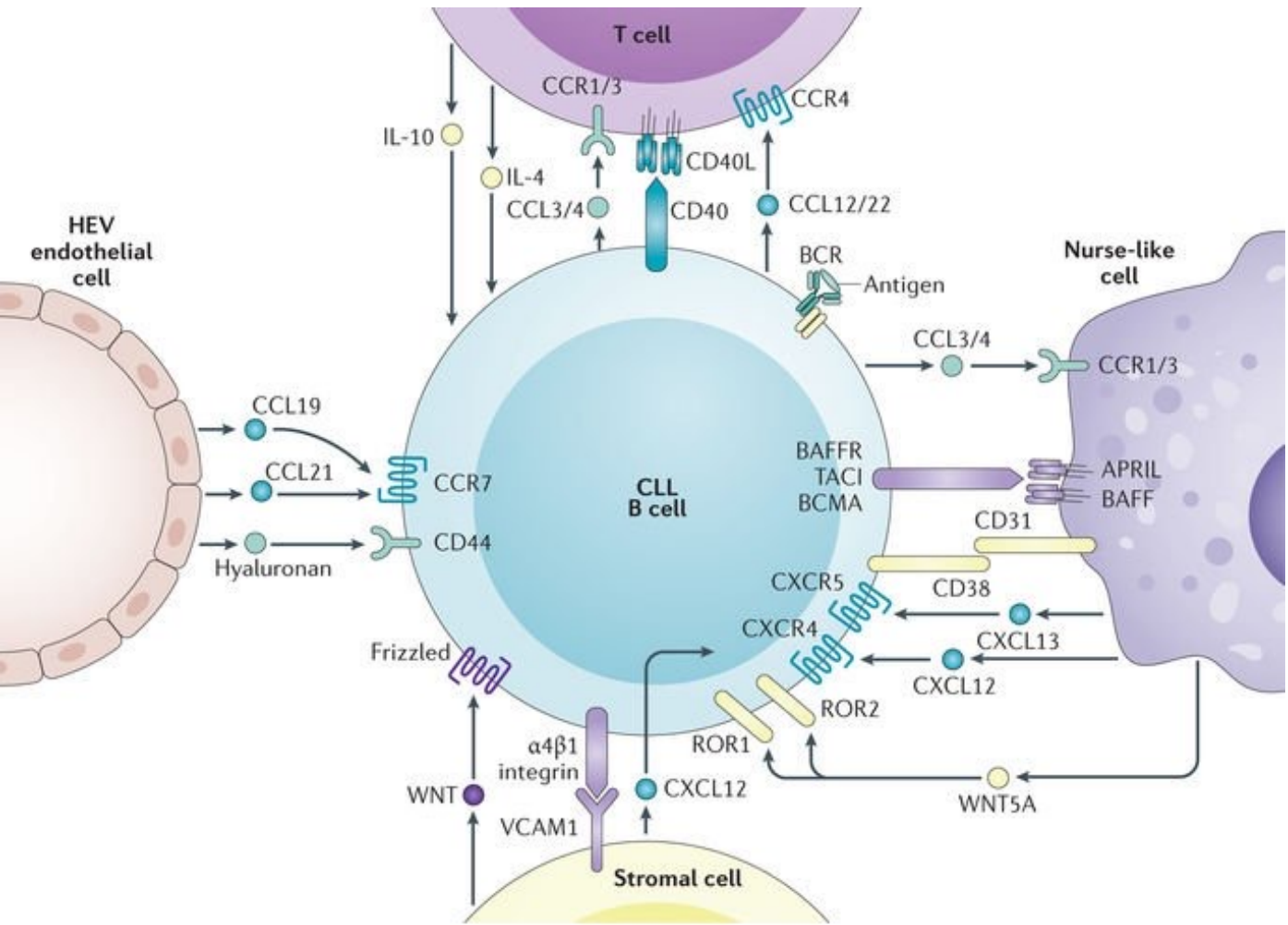# Multiple levels of regulation of surface chemokine receptor expression

➢ Transcription

➢ Post-translational regulation:
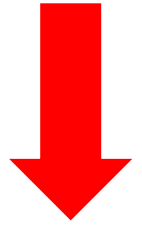
receptor recycling

Abnormalities in homing receptor recycling lead to increased surface levels on CLL cells

The lymphoid stroma is shaped by CLL cells to enhance the production of homing cytokines
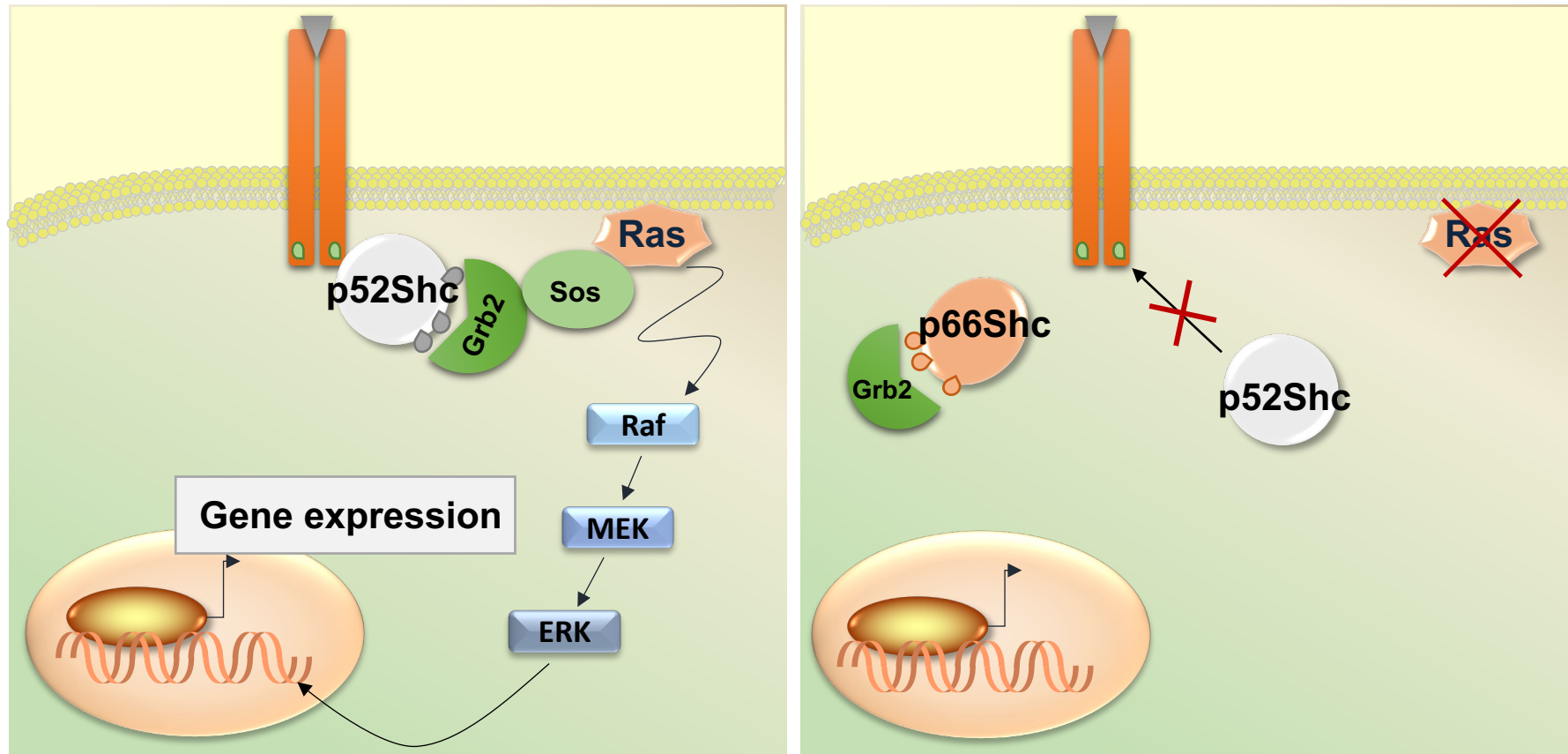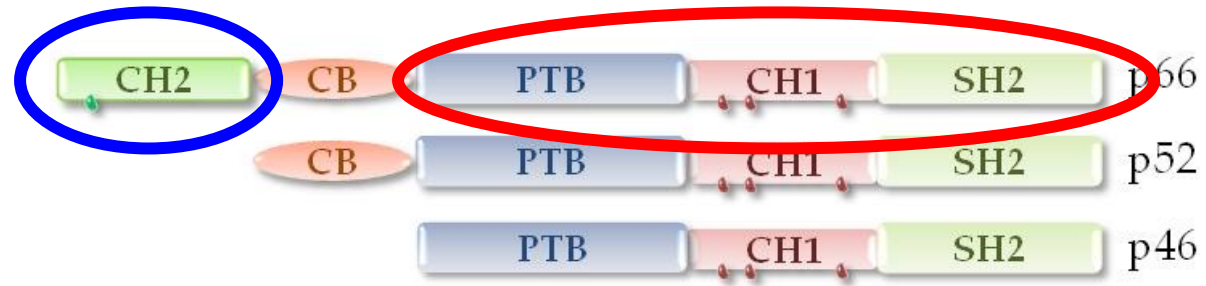

↑ Homing receptor levels on CLL cells

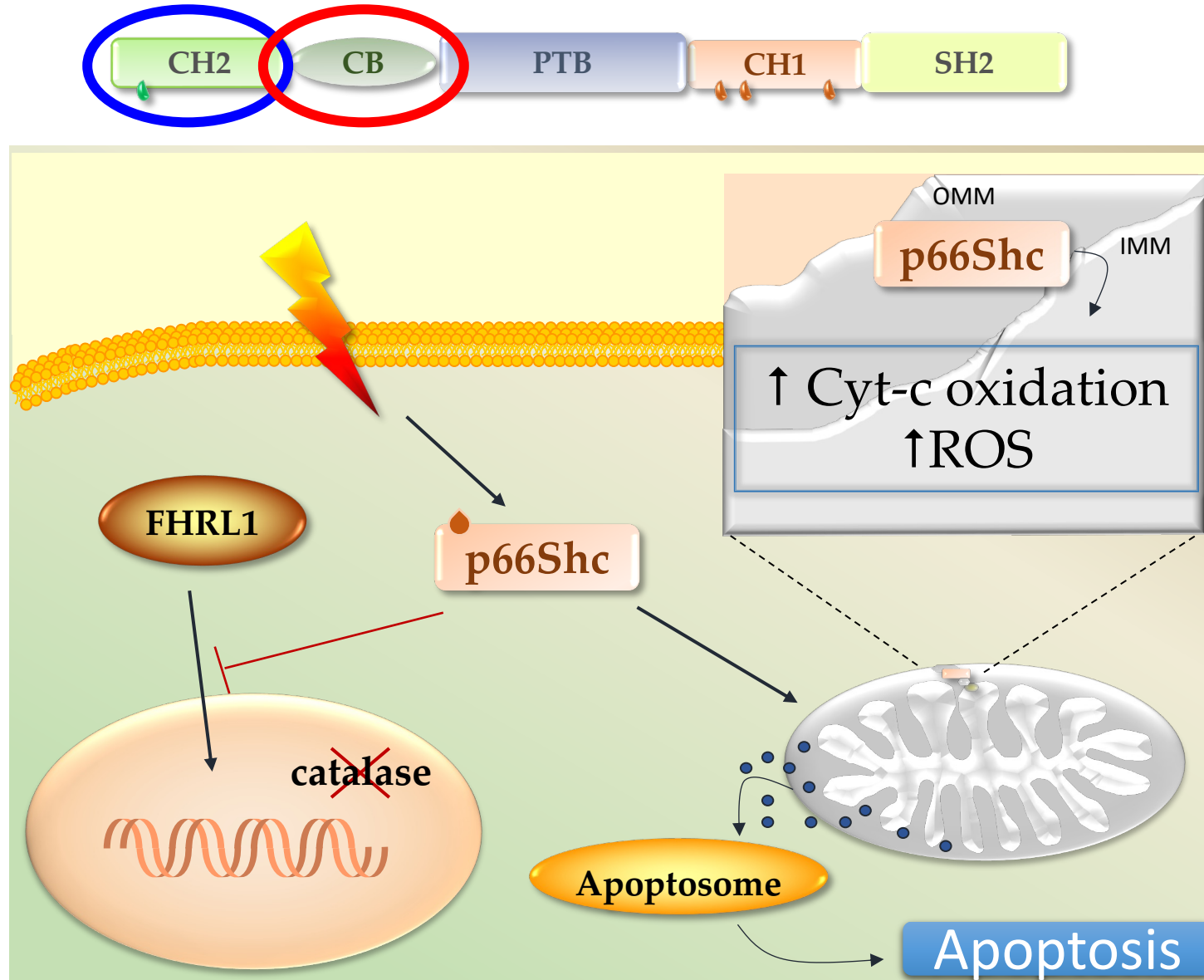↑ Homing receptor signaling in CLL cells

↑ Homing chemokines by stromal cells

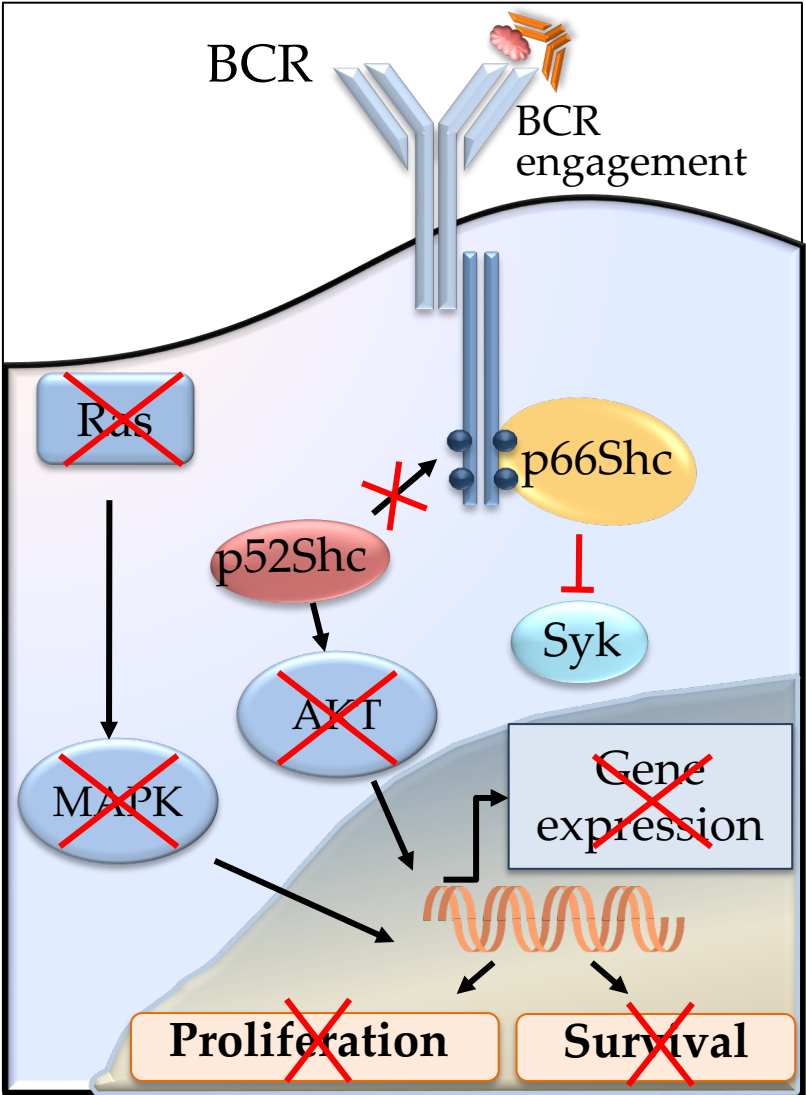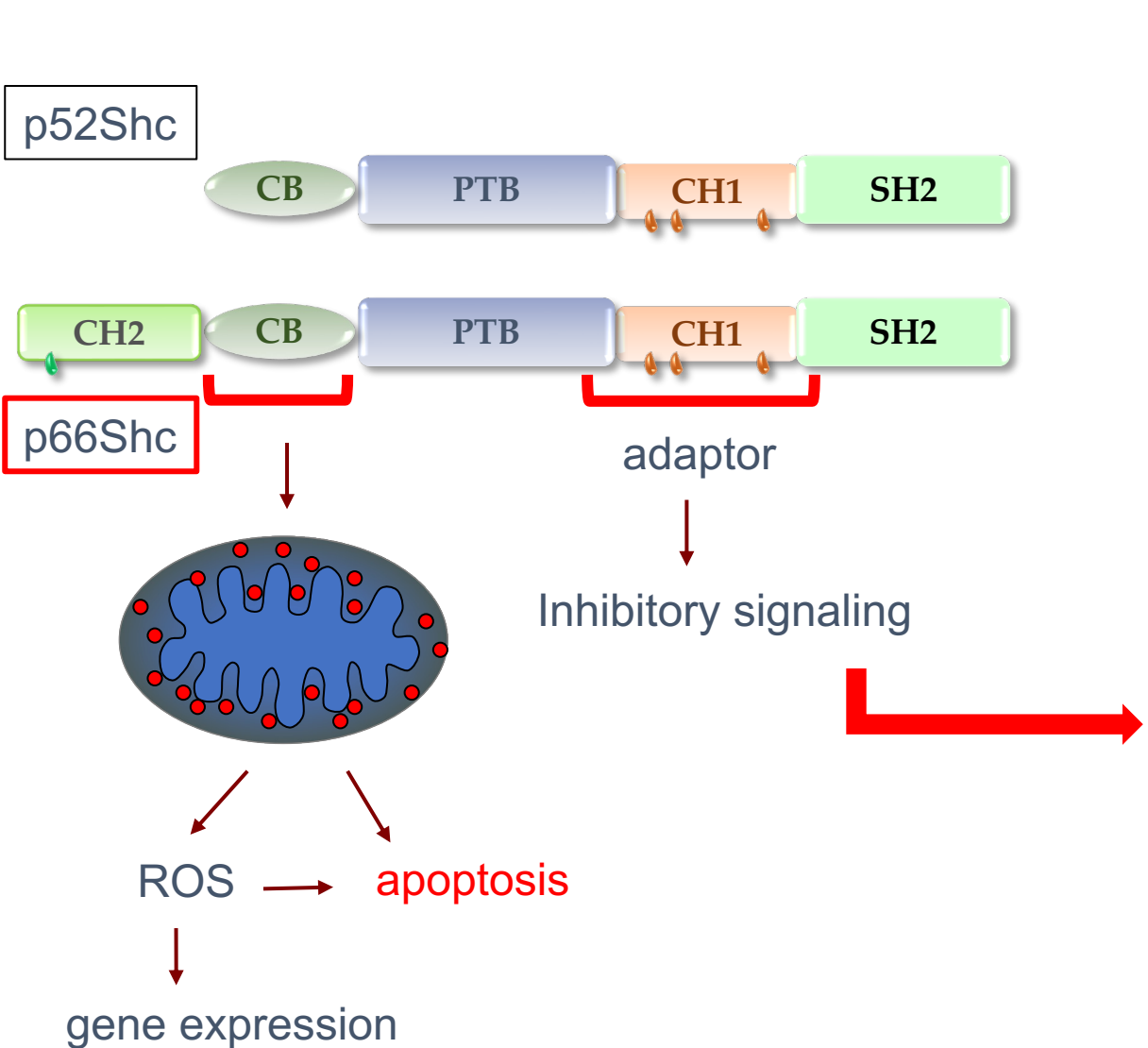Accumulation of long-lived leukemic cells in pro-survival lymphoid niche

Nature Reviews | Disease Primers

p66 Shc: a negative regulator of mitogenic and survival signaling
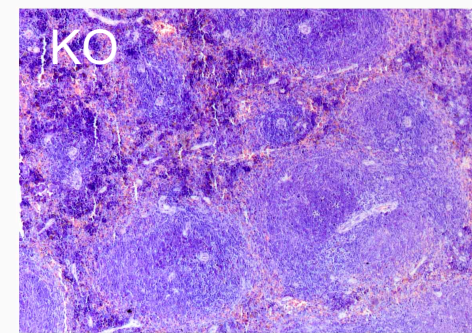
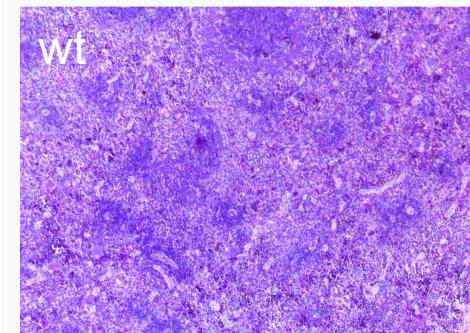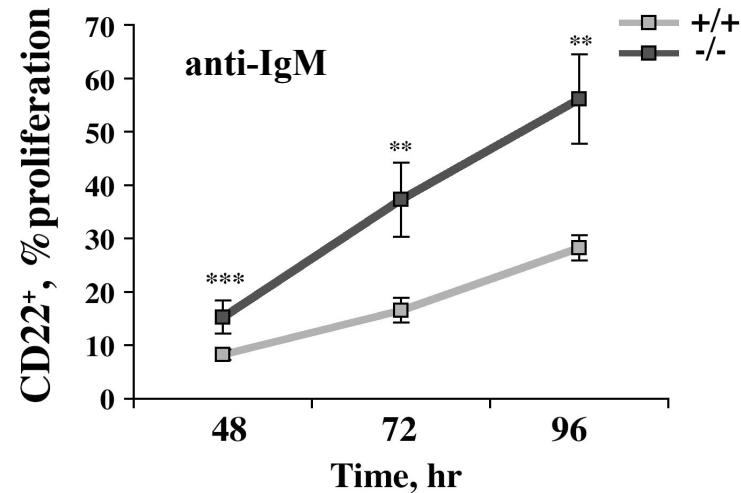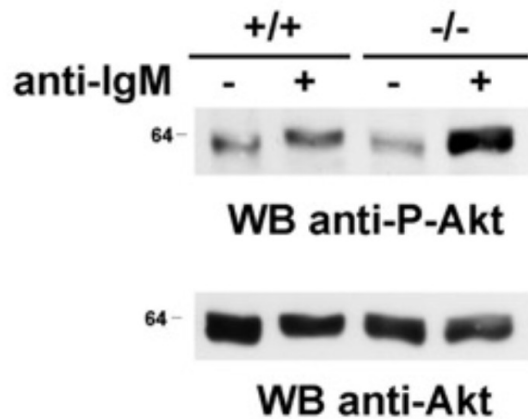# p66Shc and apoptosis: the ROS connection

p66Shc antagonizes mitogenic and survival signaling while promoting apoptosis in B cells

Enhanced T- and B-cell activation in p66Shc$^{-/-}$ mice

➢ Increased resistance of p66Shc$^{-/-}$ cells to apoptotic stimuli
➢ Enhanced TCR and BCR signaling
➢ Enhanced T and B cell proliferation
➢ Enhanced antibody responses to immunization in p66Shc$^{-/-}$ mice
➢ Enhanced delayed type hypersensitivity in p66Shc$^{-/-}$ mice
➢ Spontaneous T and B cell activation

# Spontaneous T- and B-cell activation in p66Shc$^{-/-}$ mice

Impaired lymphocyte apoptosis

Spontaneous lymphocyte activation, TCR and BCR hyper-reactivity
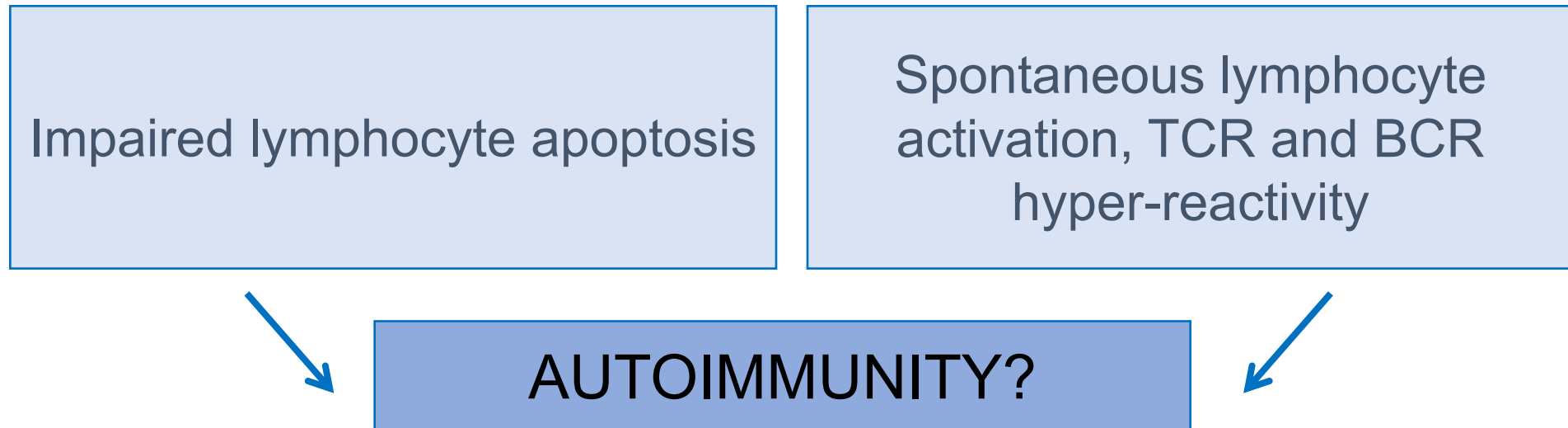
AUTOIMMUNITY?

Ageing p66Shc$^{-/-}$ mice develop lupus-like autoimmunity

- ➢ Circulating anti-DNA antibodies
- ➢ Glomerular deposition of immune complexes
- ➢ Proteinuria
- ➢ Alopecia

+/+

-/-

Finetti 2008 *Blood*
Ulivieri 2011 *J Immunol*
Masi 2014 *J Leuk Biol*
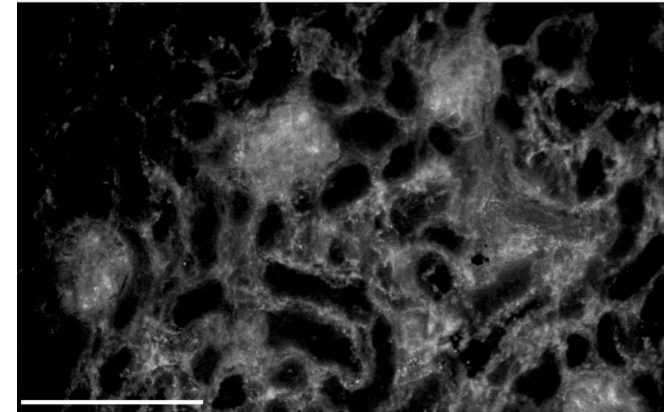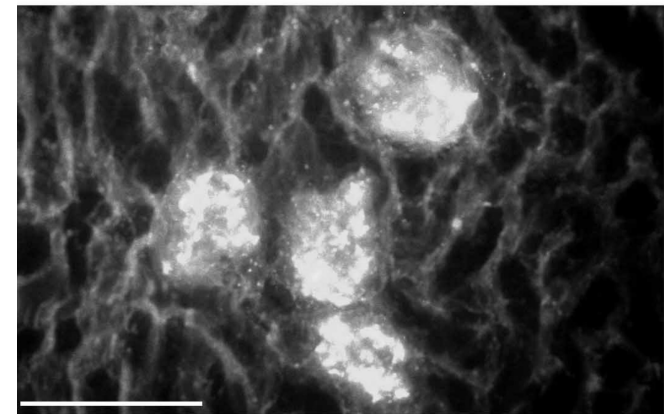
Hypothesis

- p66Shc deficiency is associated with enhanced B cell mitogenic and survival signaling, apoptosis defects and autoimmunity
- CLL B cells are characterized by prolonged survival resulting from apoptosis defects and enhanced survival signaling
- CLL is frequently associated with autoimmune complications

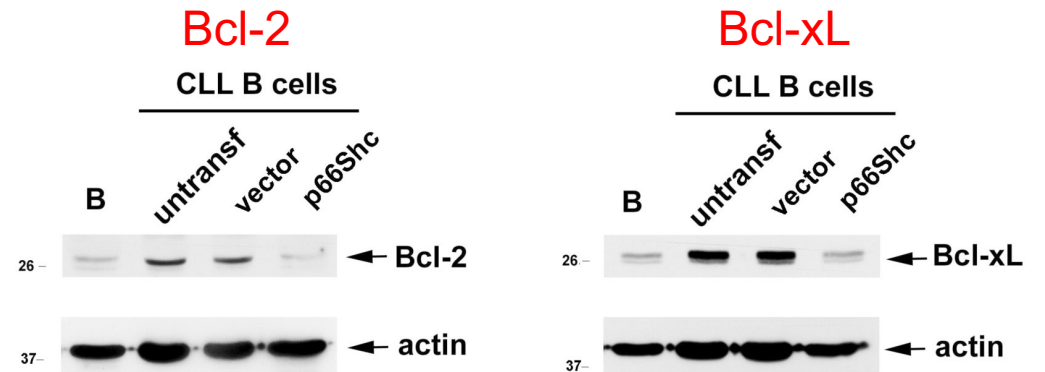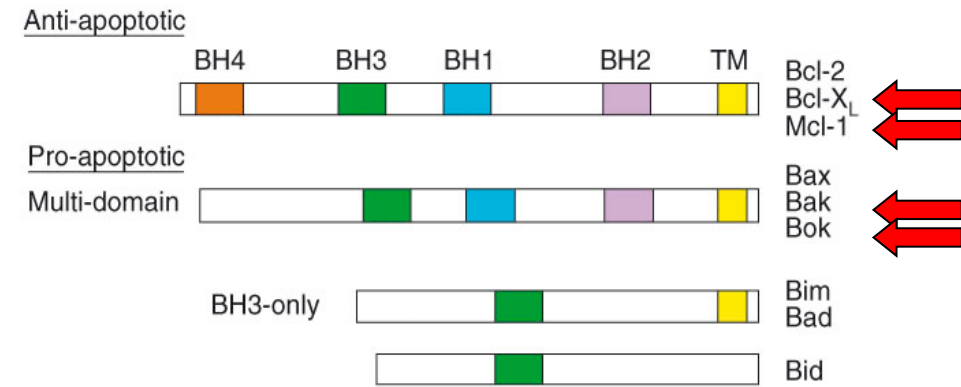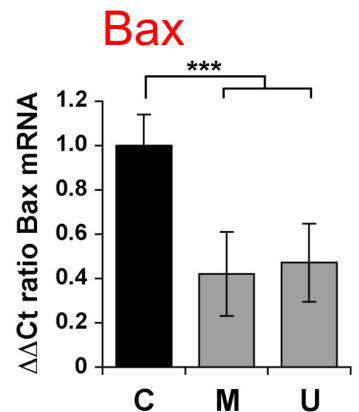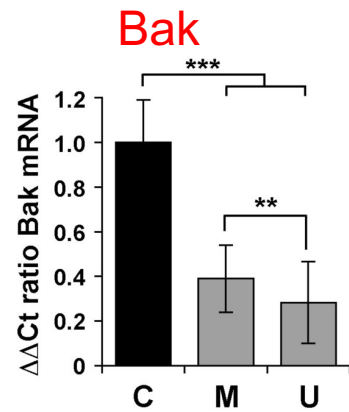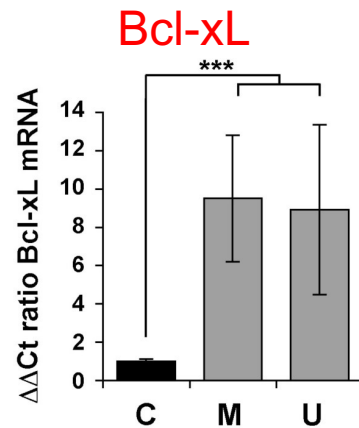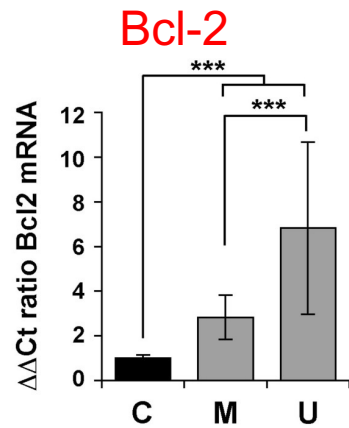Could there be a link between p66Shc and CLL?

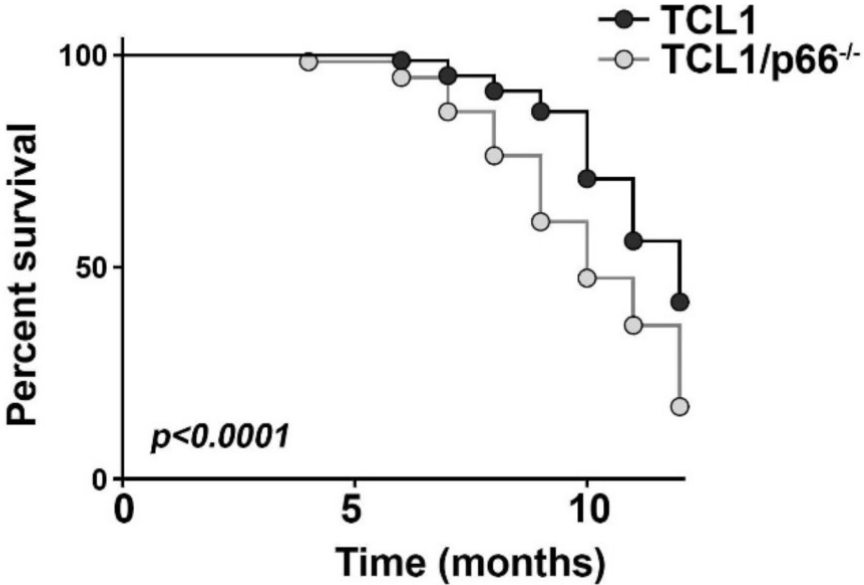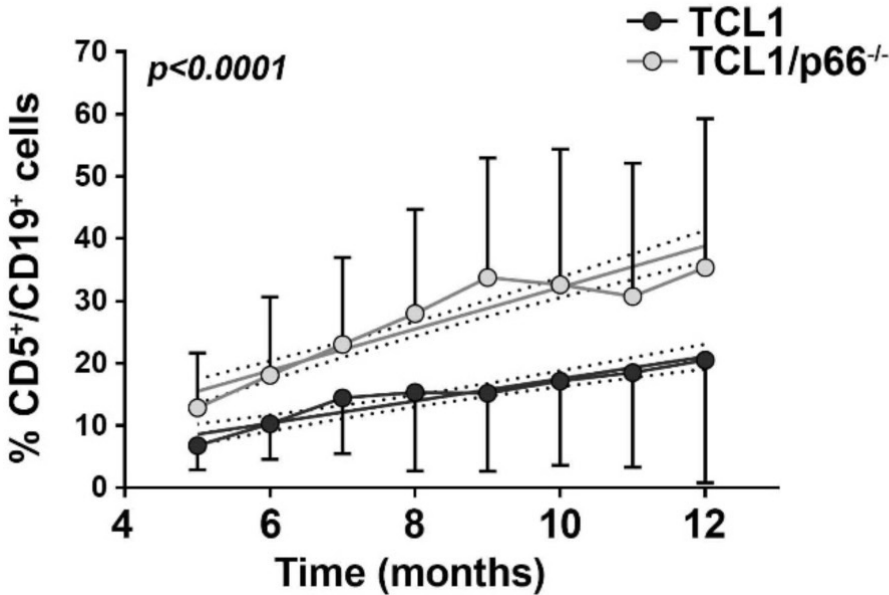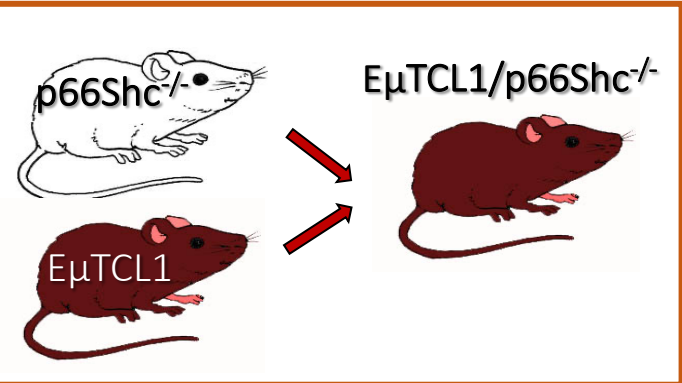# Impairment of p66Shc expression in CLL B cells
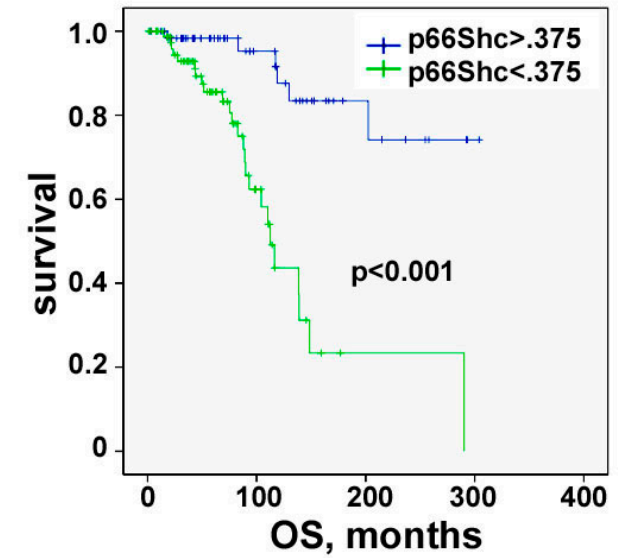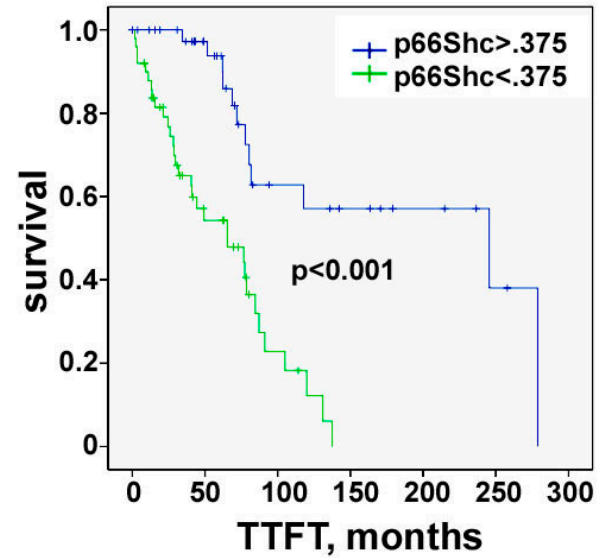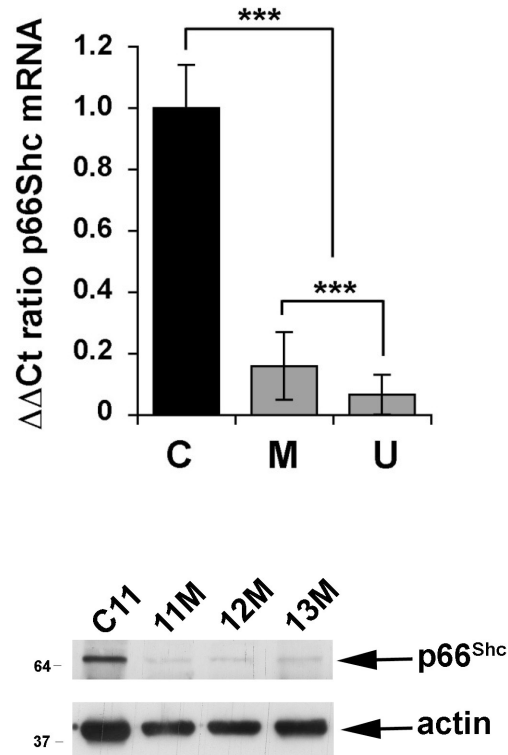
Intrinsic factors underlie the extended lifespan of CLL B cells: p66Shc and apoptosis
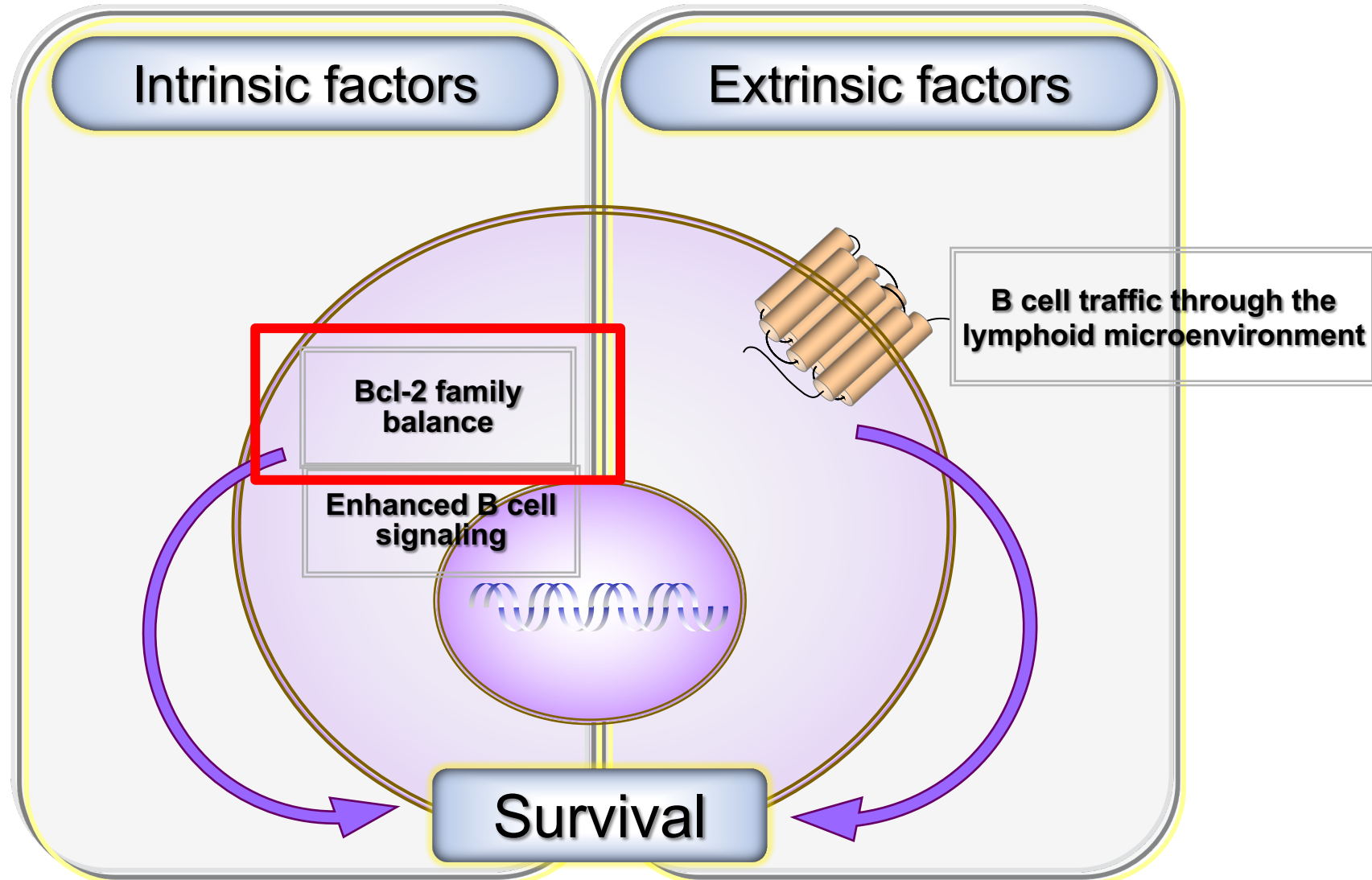
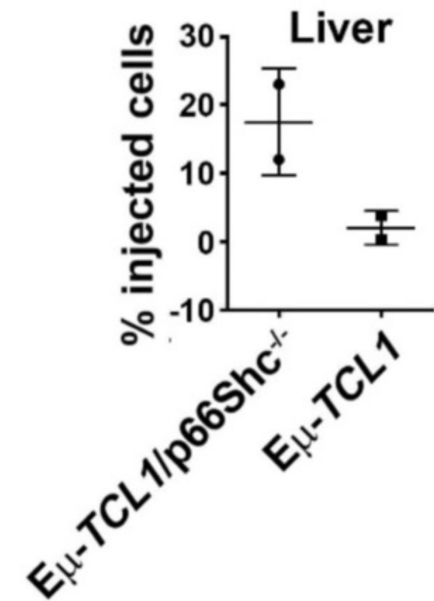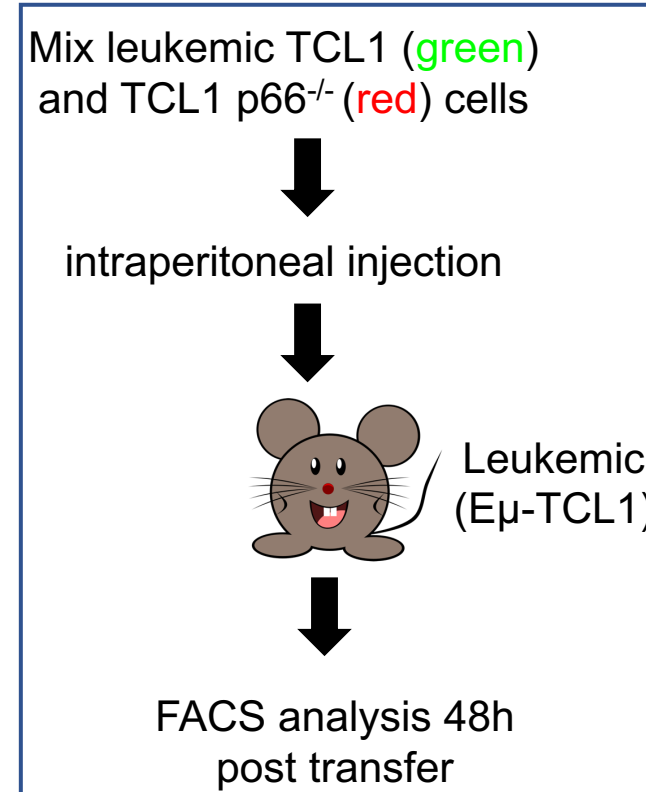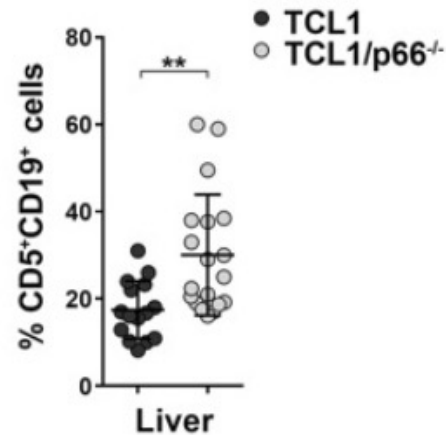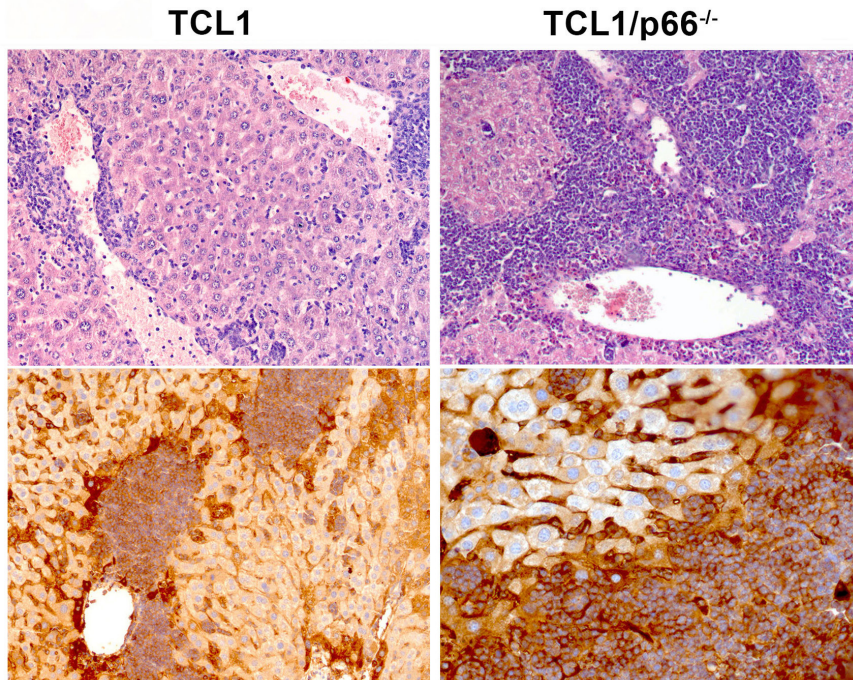# p66Shc deficiency contributes to the apoptosis defects in CLL

# p66Shc deficiency accelerates leukemogenesis in Eμ-TCL1 mice

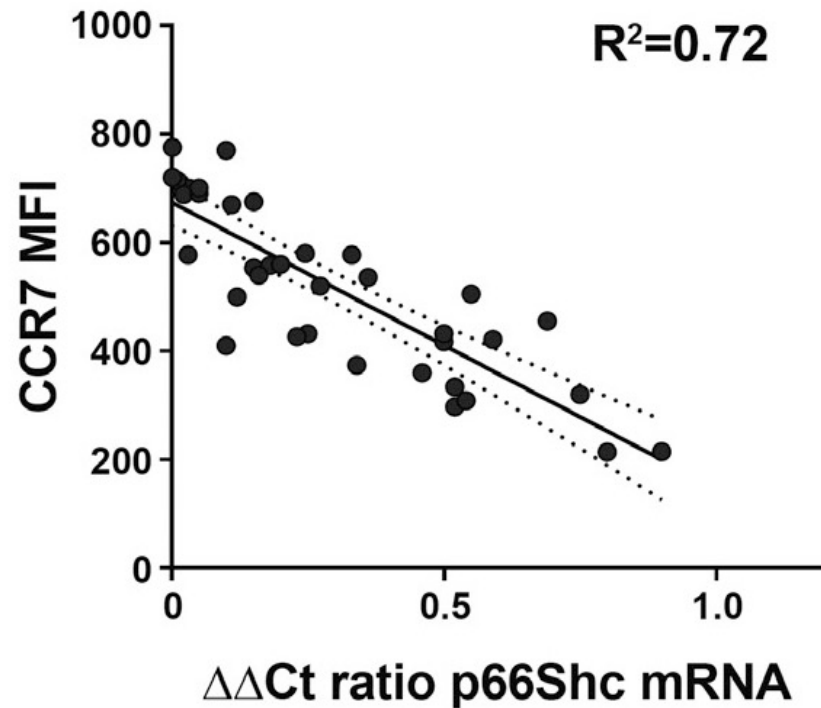➤ p66Shc deficiency enhances the chemoresistance of leukemic cells

p66Shc deficiency in Eμ-TCL1 mice is associated with nodal and extranodal infiltration of leukemic cells
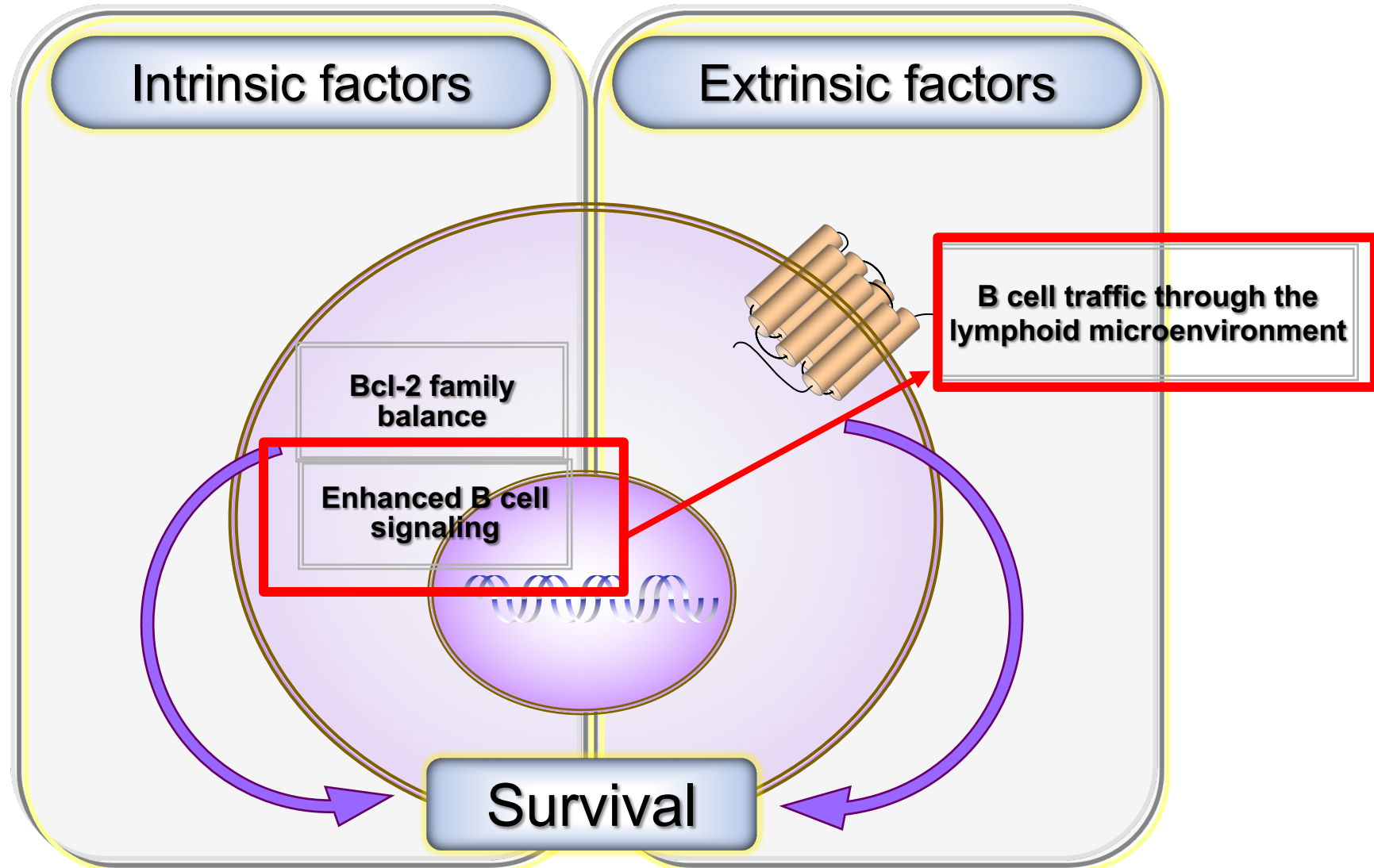

Homing receptor expression on leukemic cells

Anbormalities in homing receptor expression in CLL are related to p66Shc deficiency
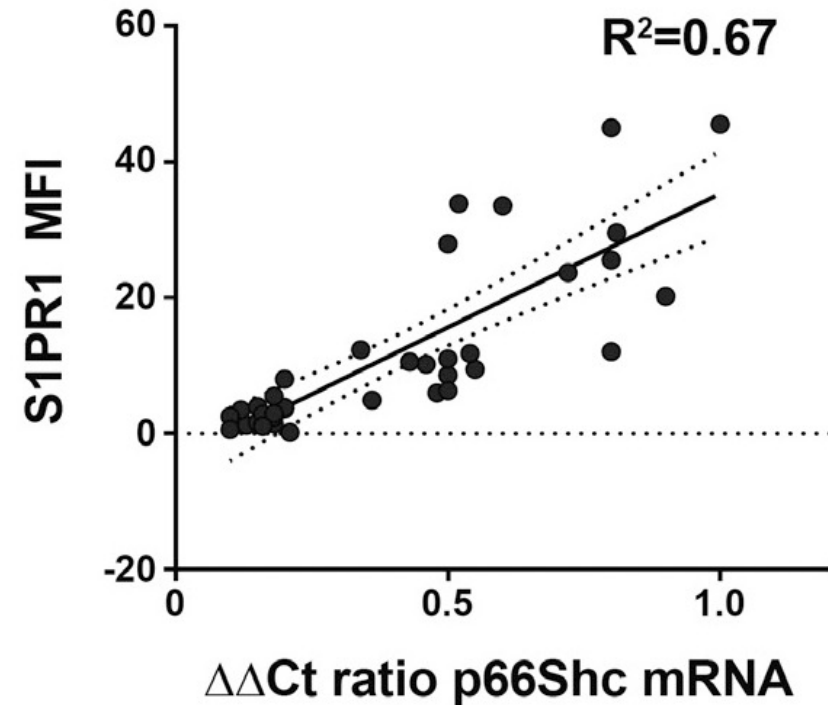
➤ Abnormalities in homing receptor expression in CLL cells can be rescued by forced p66Shc expression

# Intrinsic factors underlie the extended lifespan of CLL B cells: p66Shc and survival signaling by chemokine receptors
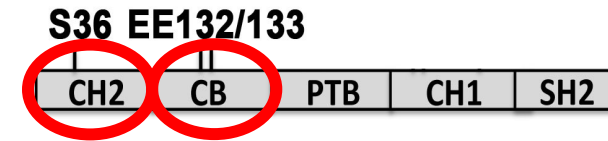
Multiple levels of regulation of surface chemotactic receptor expression

- ➢ Transcription
- ➢ Recycling

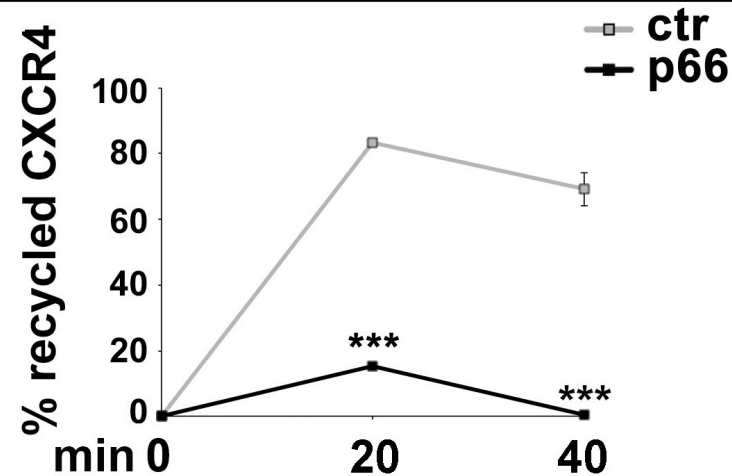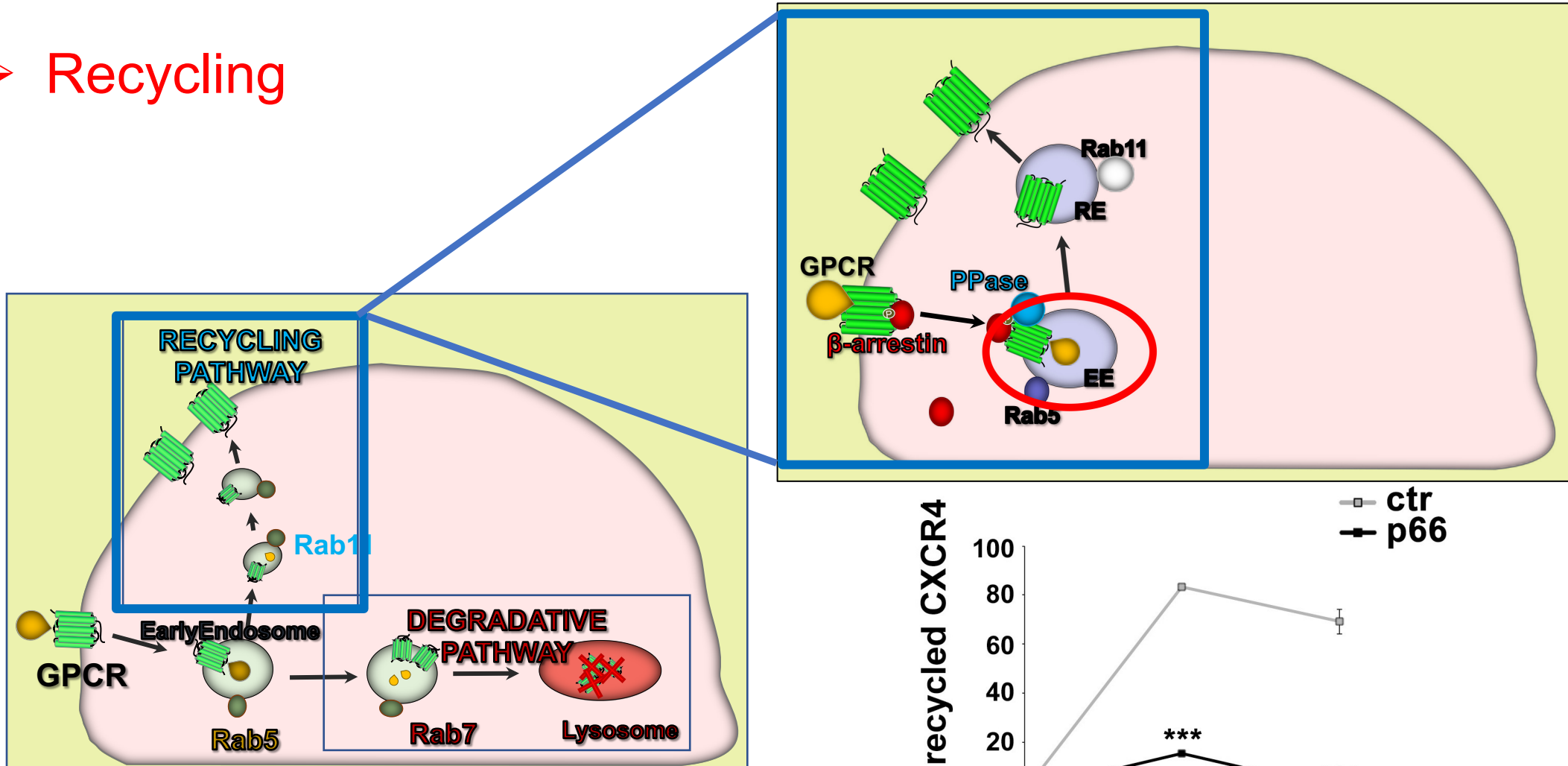**Are there processes influenced by p66Shc?**

p66Shc regulates <u>transcription</u> of homing and egress receptors through its ROS-elevating activity
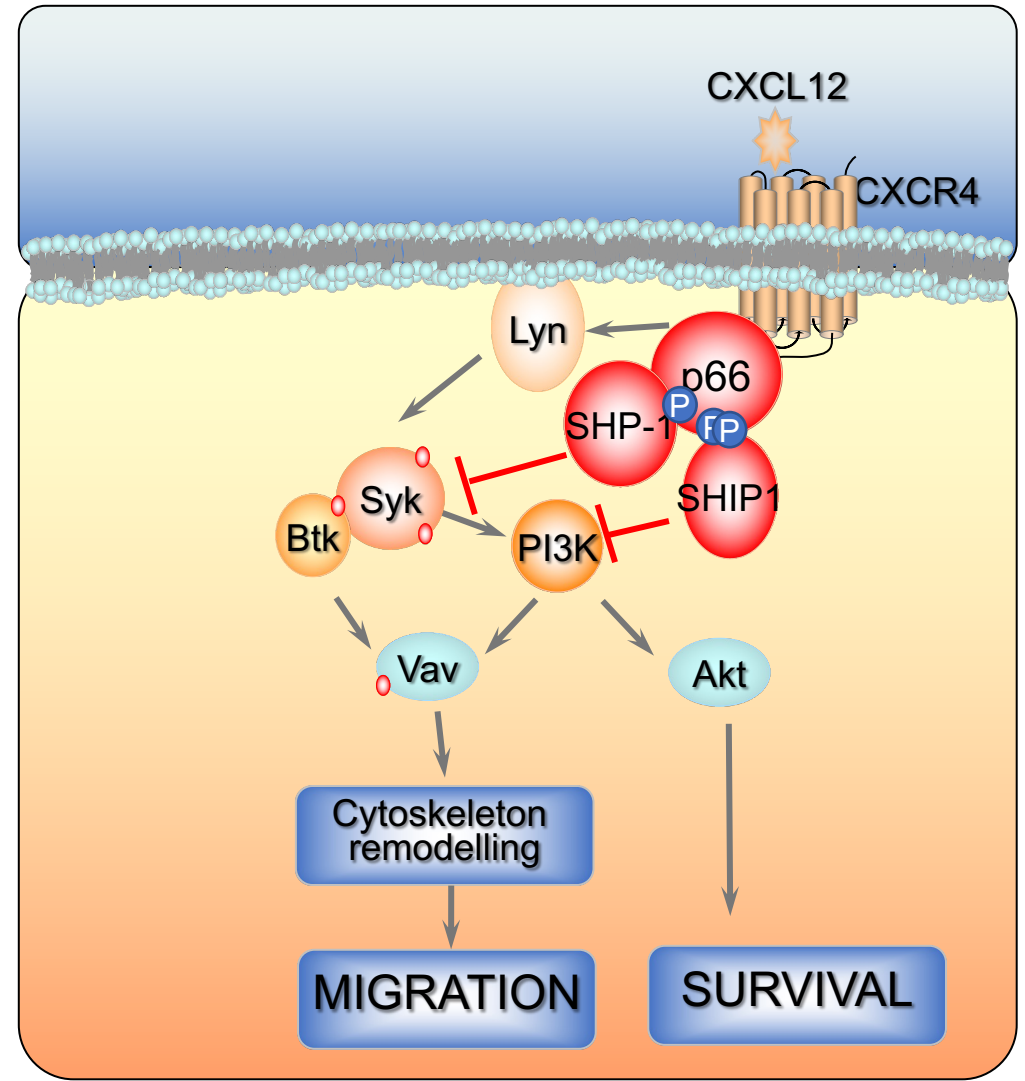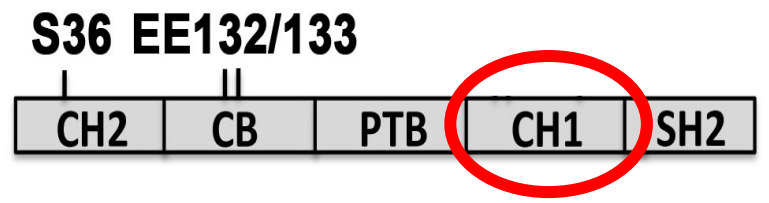
➤ Transcription: ROS-sensitive TF
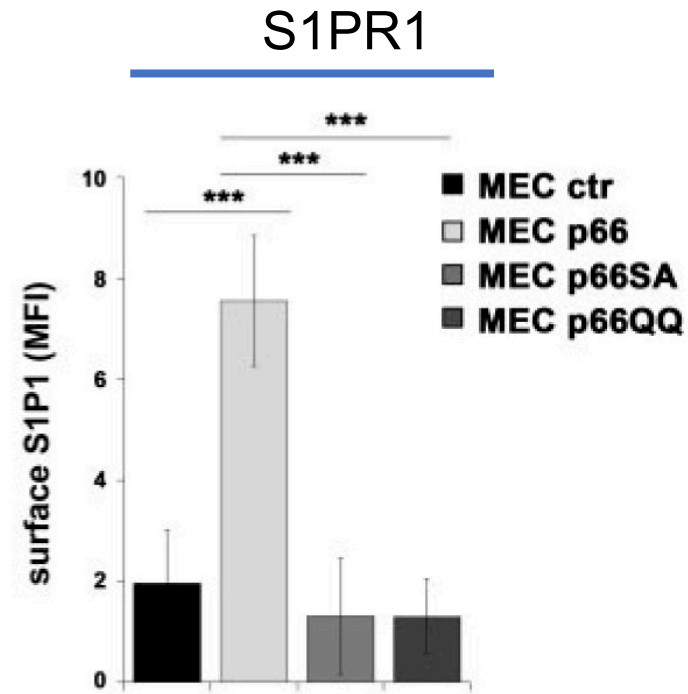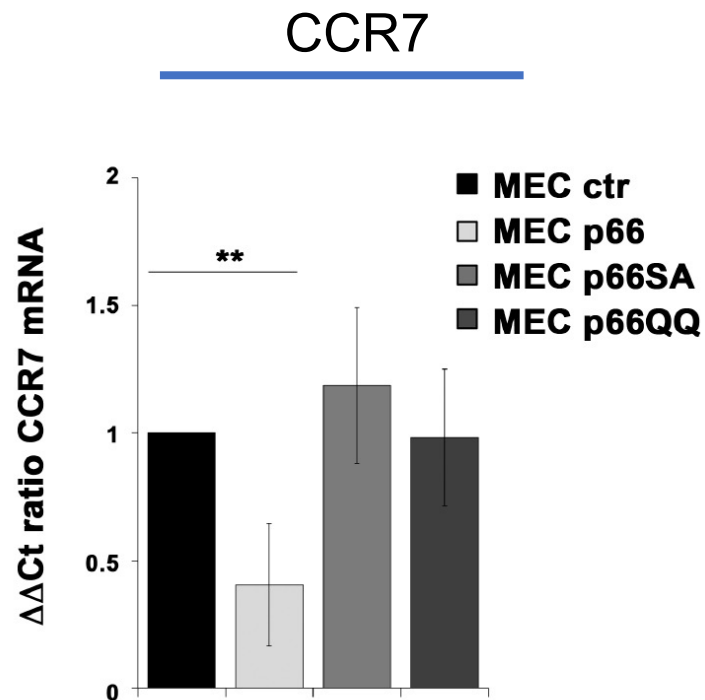
p66Shc regulates <u>recycling</u>-dependent surface expression of homing receptors through its adaptor function

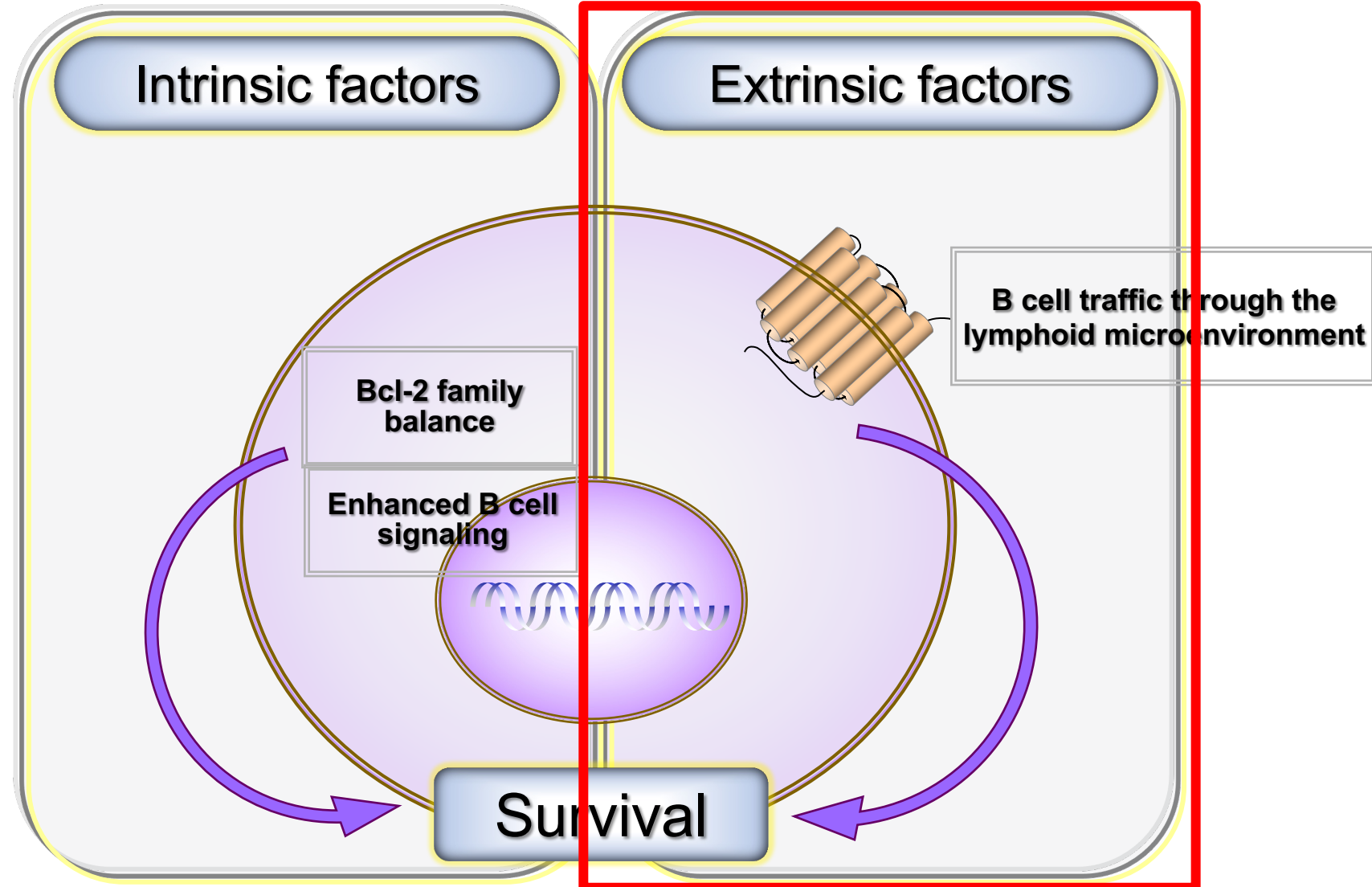➢ Recycling

p66Shc regulates chemotactic signaling by homing receptors through its adaptor function

Patrussi, Capitani. 2014 *Cell Death Dis*

Intrinsic and extrinsic factors underlie the extended lifespan of CLL B cells: role of p66Shc

CLL cells enhance homing to the lymphoid microenvironment through a contact-independent mechanism

Kipps 2017 *Nat Rev Dis Prim*

Patrussi 2021 *Blood*
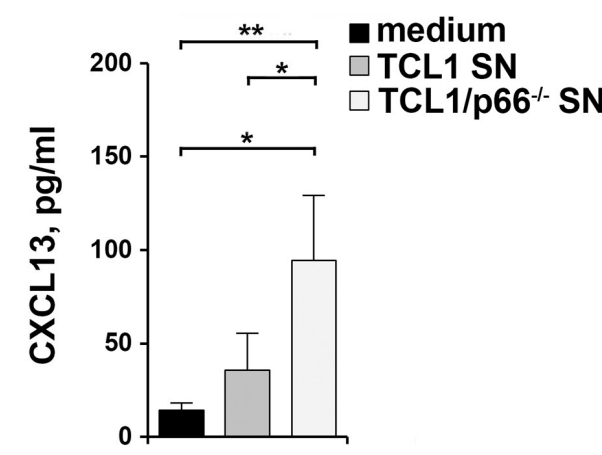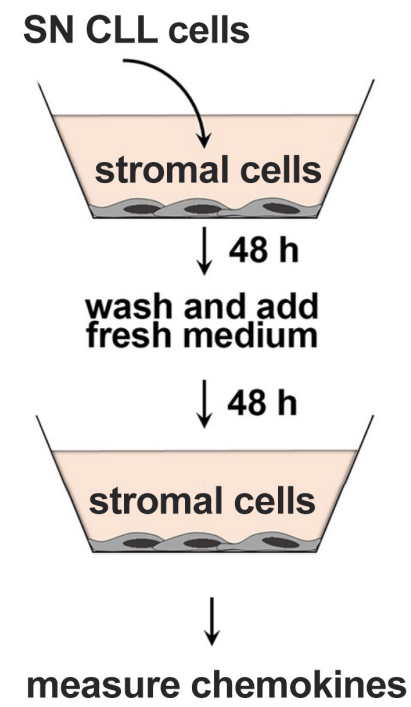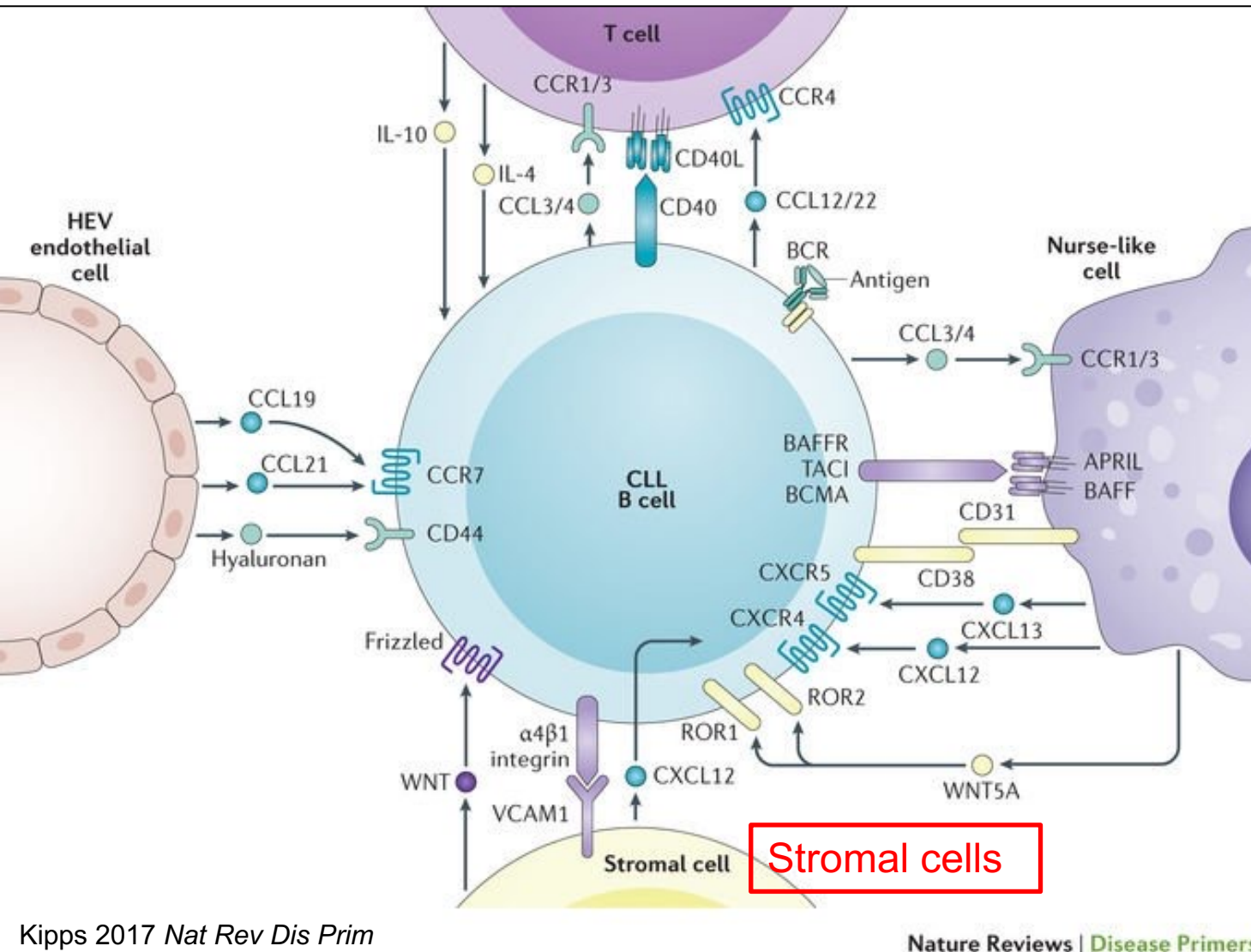
CLL cells modulate stromal chemokine production through IL-9

Hierarchical clustering of Immune system process

IL-9
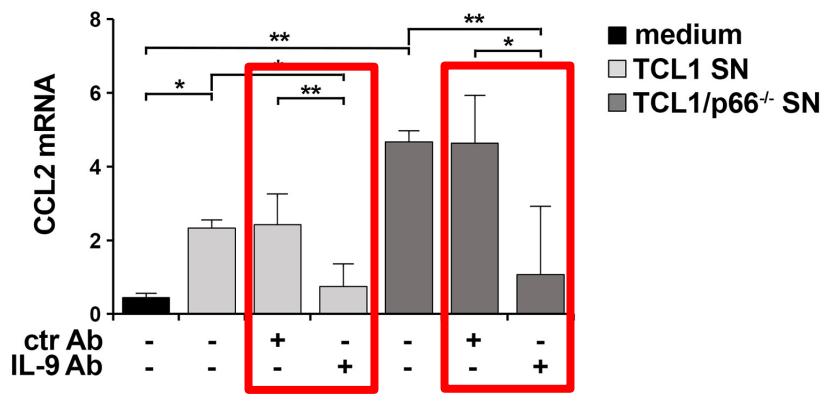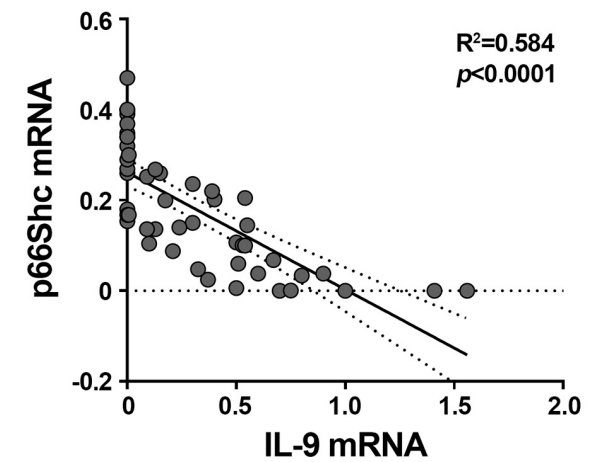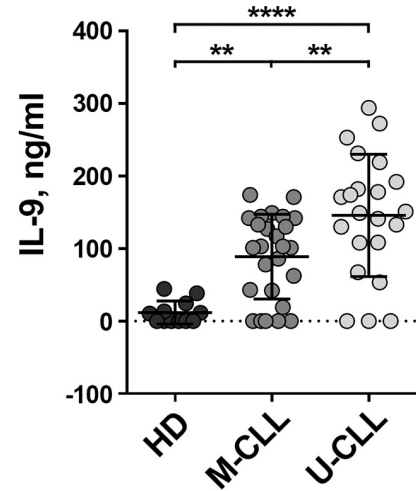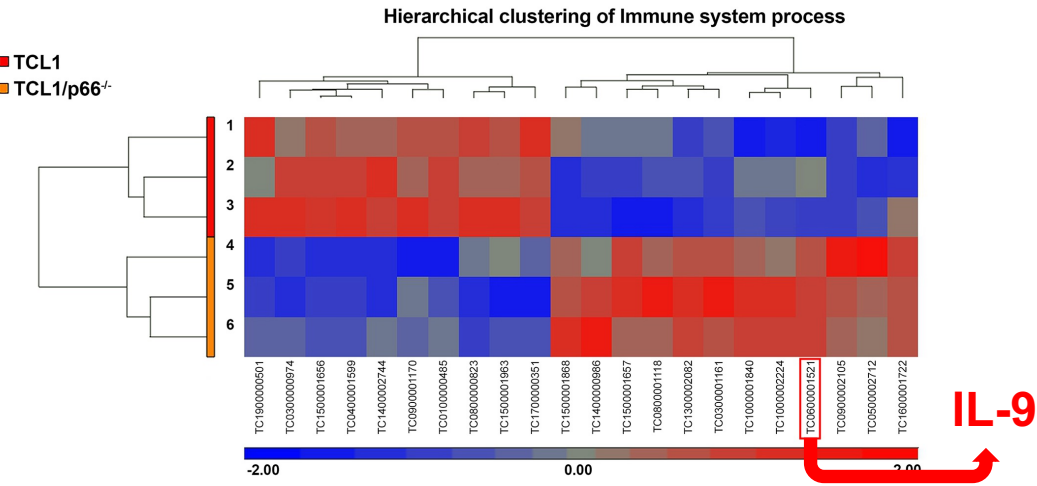
Forced p66Shc expression in CLL cells normalizes IL-9 production and their ability to condition stromal cells

CLL cells enhance the homing potential of the lymphoid microenvironment through IL-9 secretion

Patrussi 2021 *Cancers*
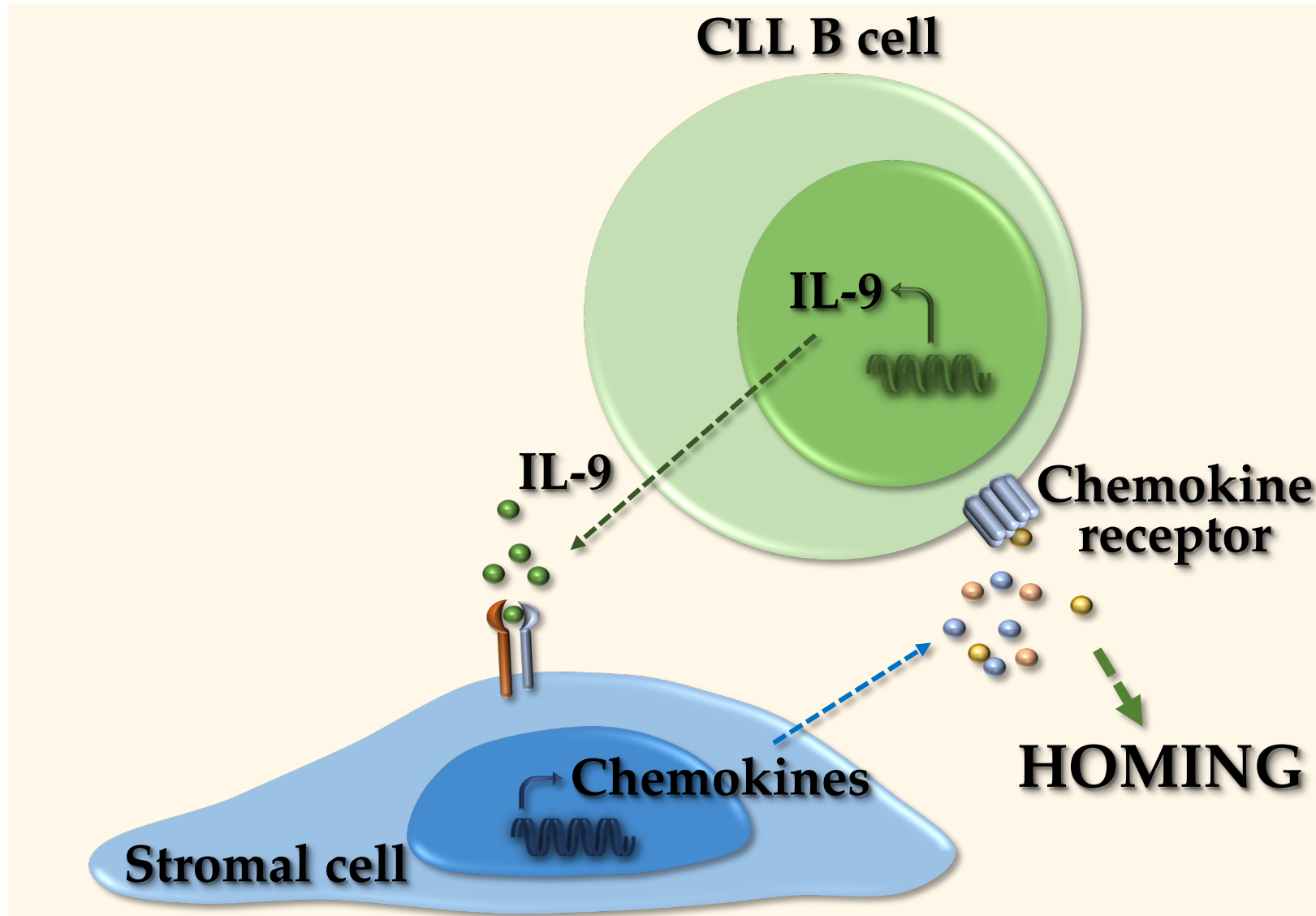
A multipronged strategy for CLL cell survival regulated by p66Shc

The importance of understanding basic principles: personalized therapies in CLL
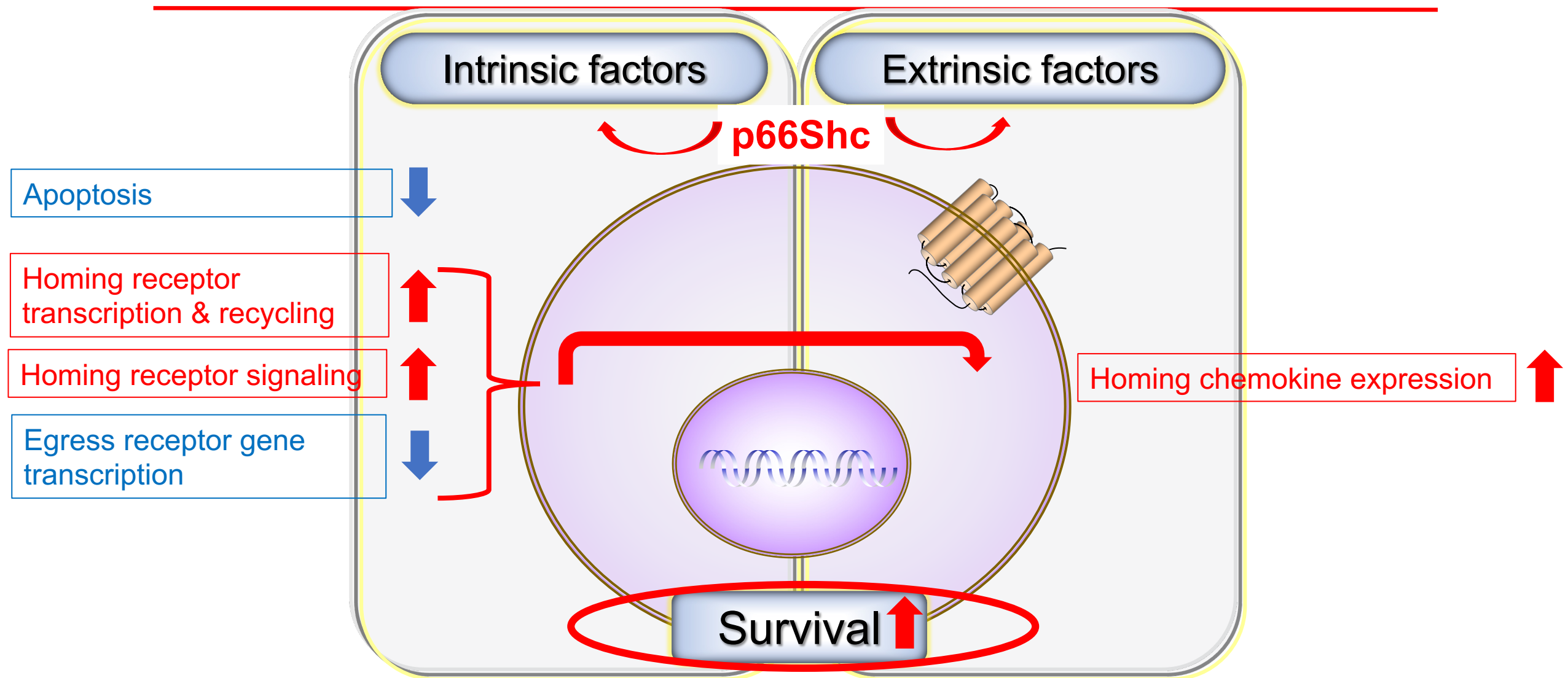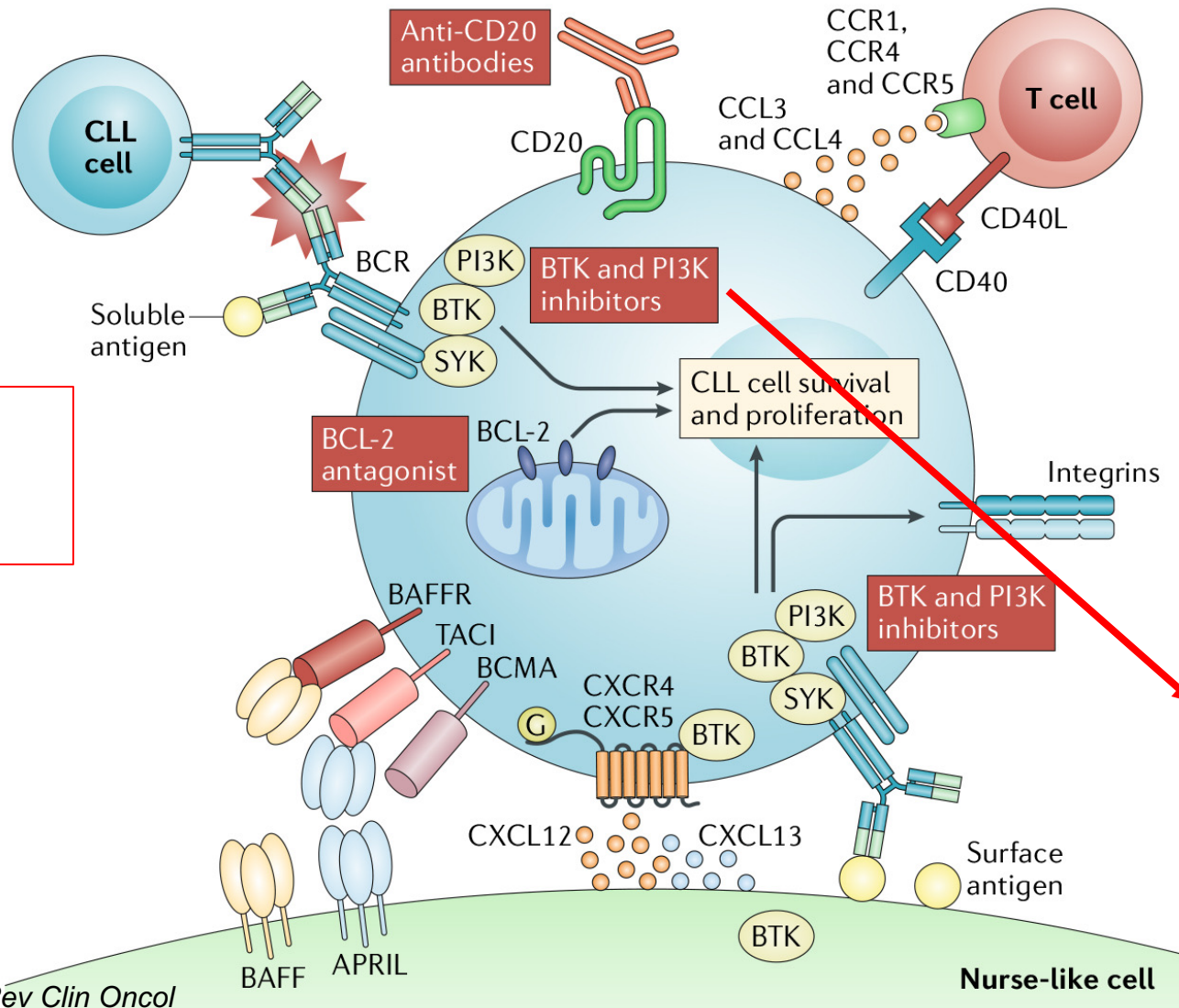

PI3K: idelalisib
Btk: ibrutinib
Bcl-2: venetoclax

Ibrutinib suppresses homing receptor recycling: massive release leukemic cells from SLOs

Burger & O'Brien 2018 *Nat Rev Clin Oncol*
Patrussi 2018 *Oncogene*

Baldari lab, Department of Life Sciences

Laura Patrussi

Nagaja Capitani

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AIRC FIRC