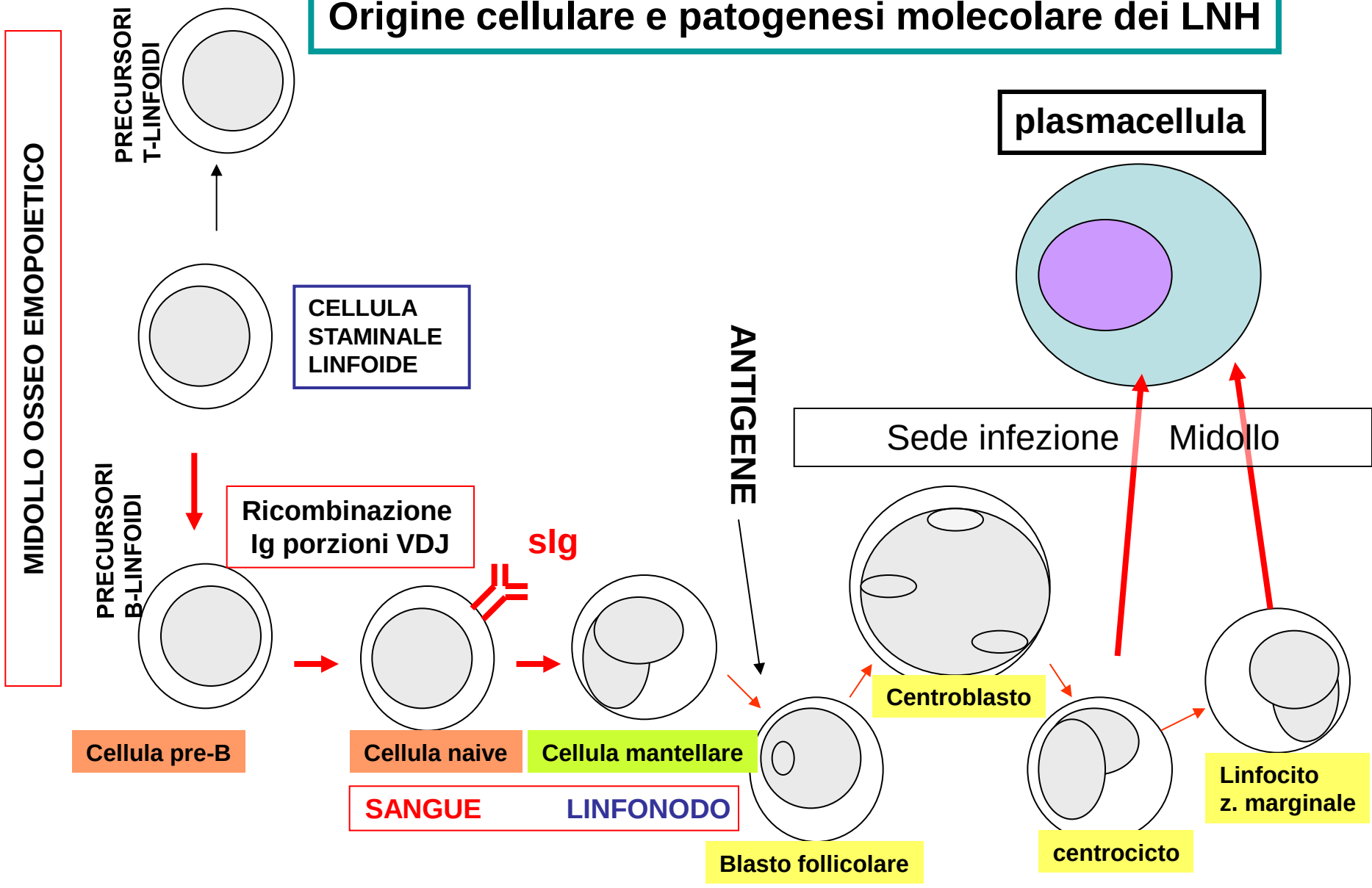
Definizione Linfomi

- Espansione clonale di una cellula linfoide bloccata ad un determinato stadio di maturazione

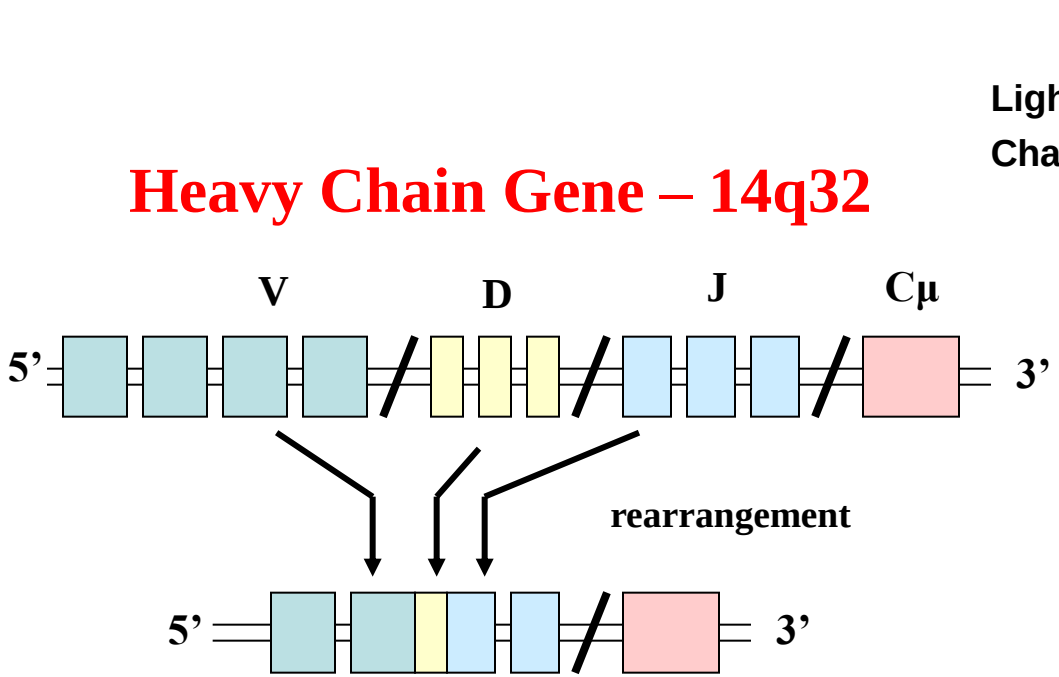
- Localizzazione linfonodale, emato-midollari, extra-linfonodale

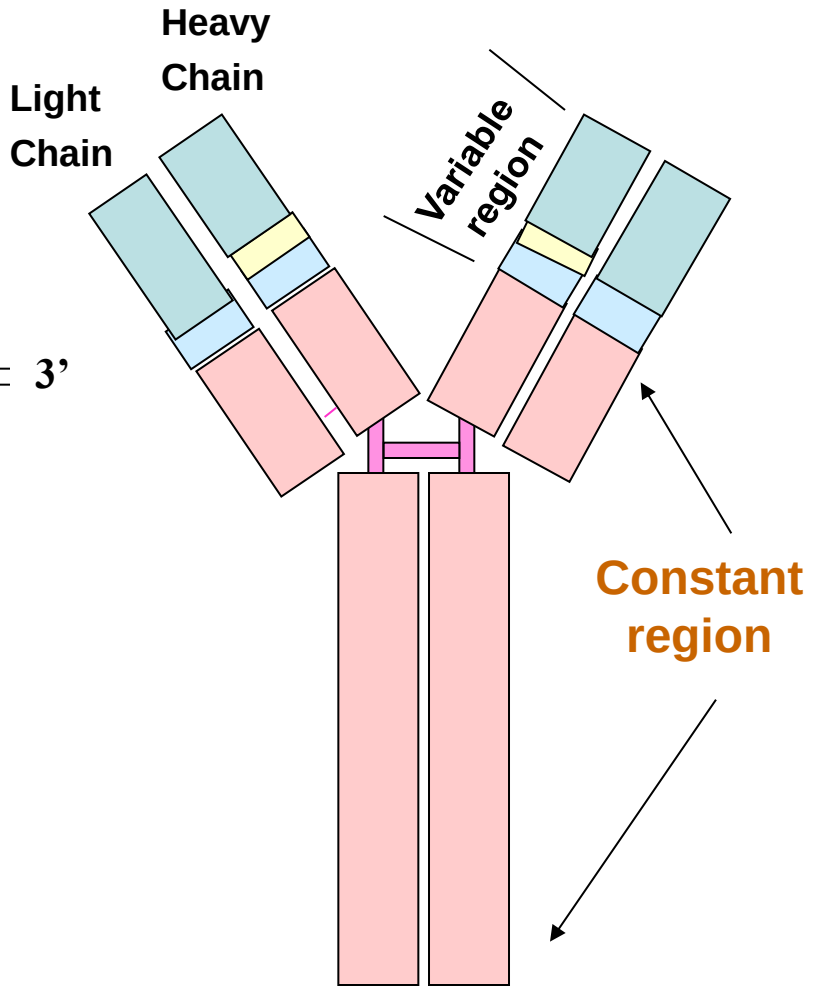
Origine cellulare e patogenesi molecolare dei LNH

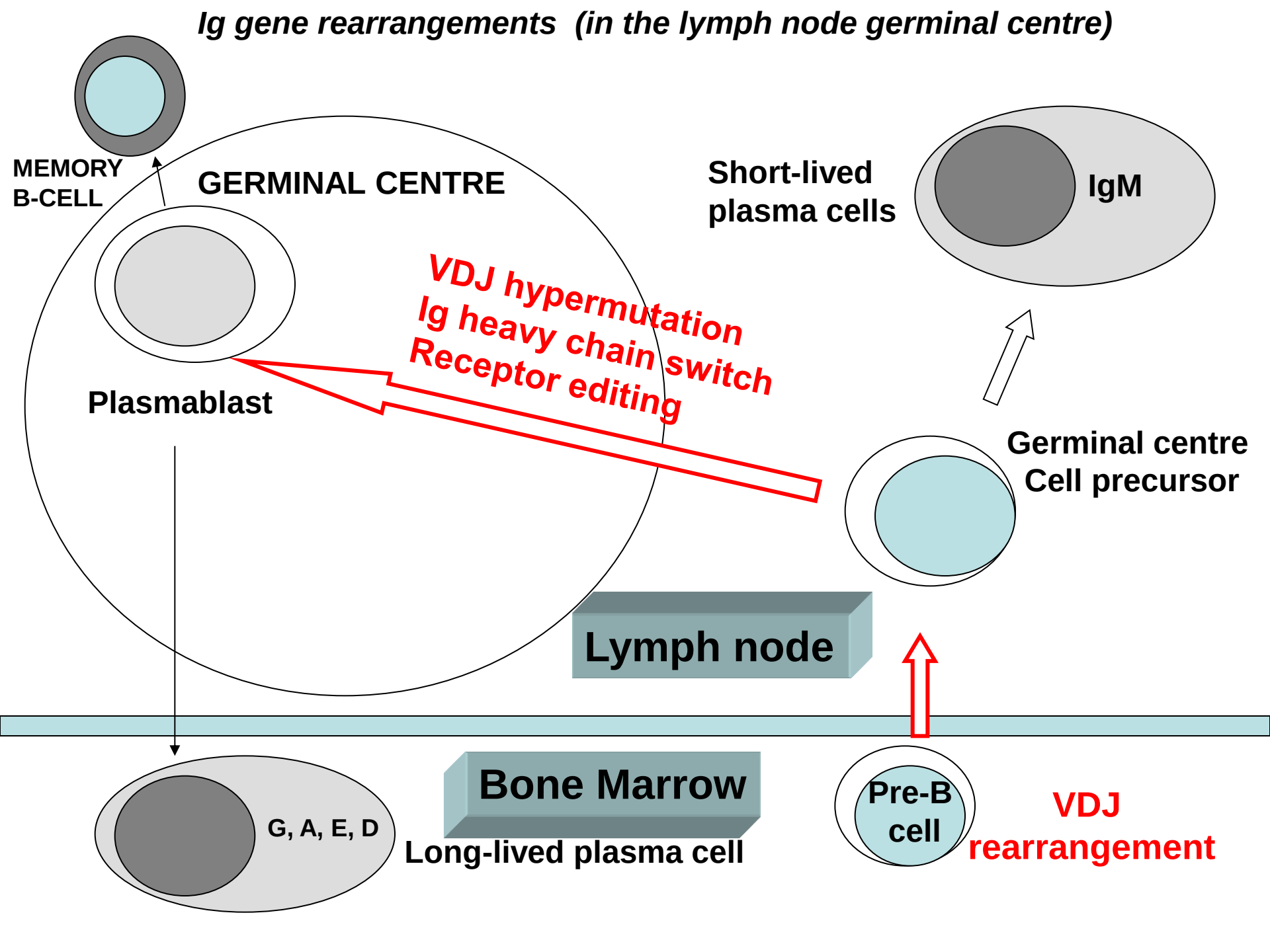


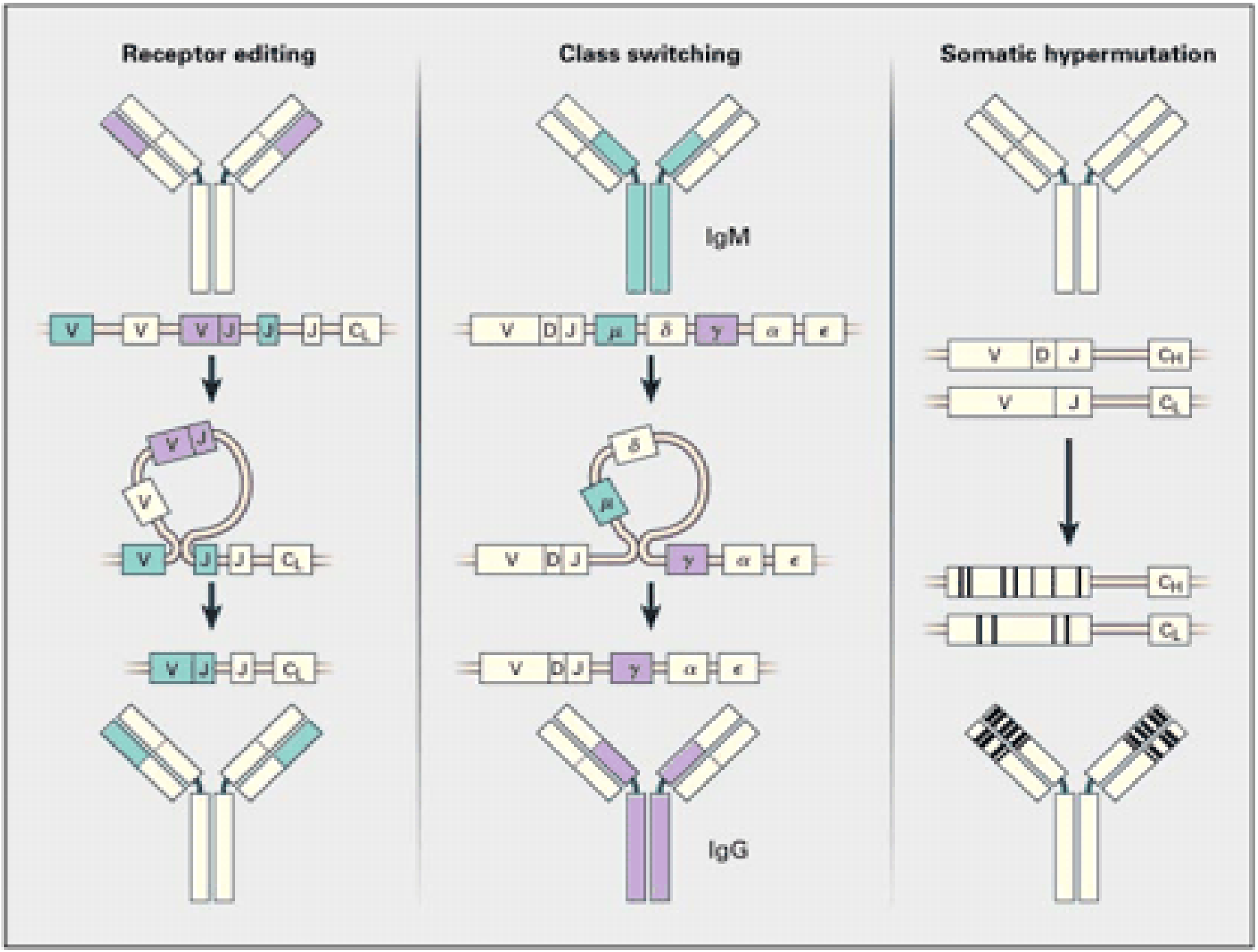
Schema della differenziazione B-linfocitaria

Ig heavy chain nrearrangement (occurs in the bone marrow)

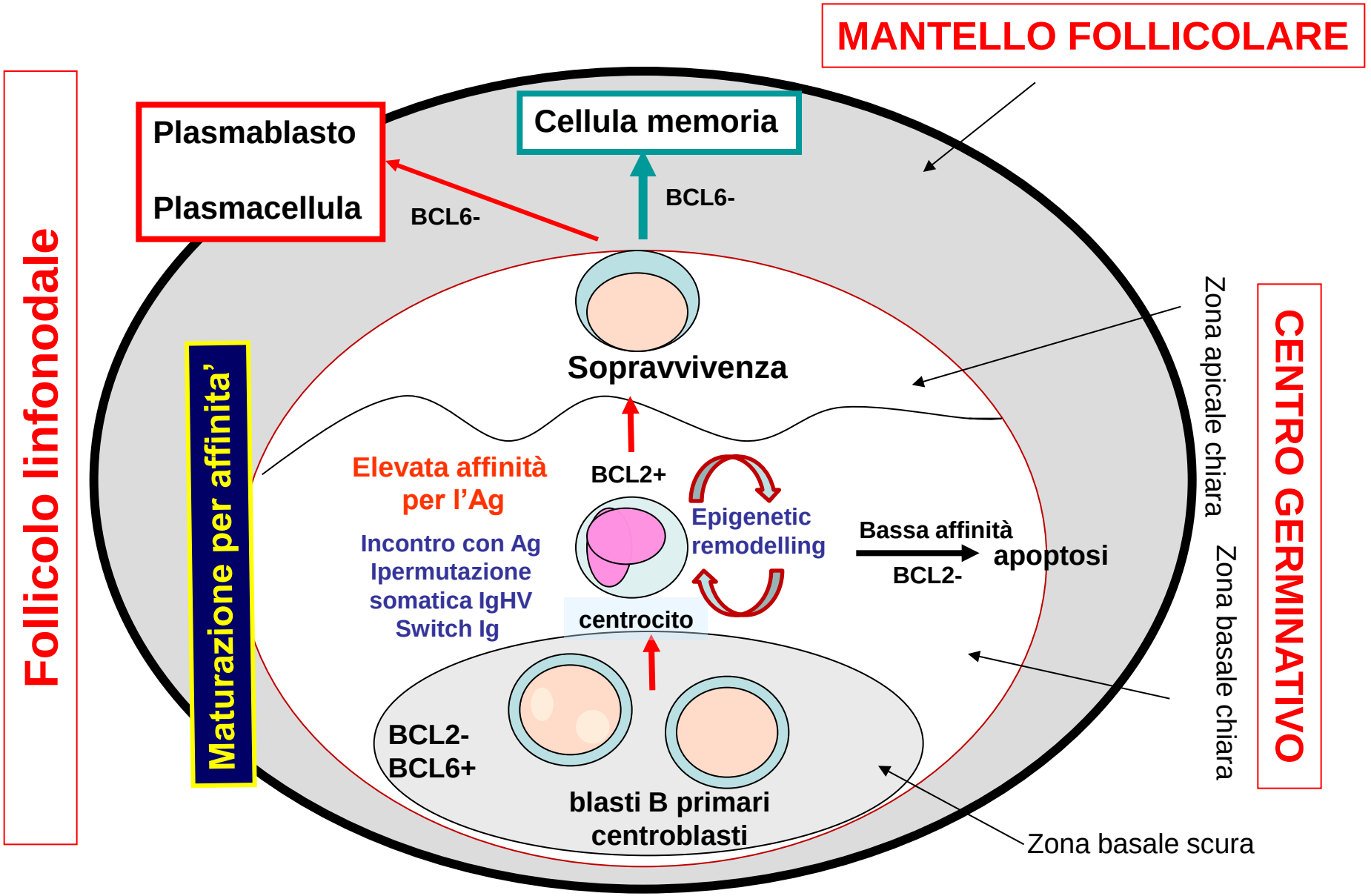




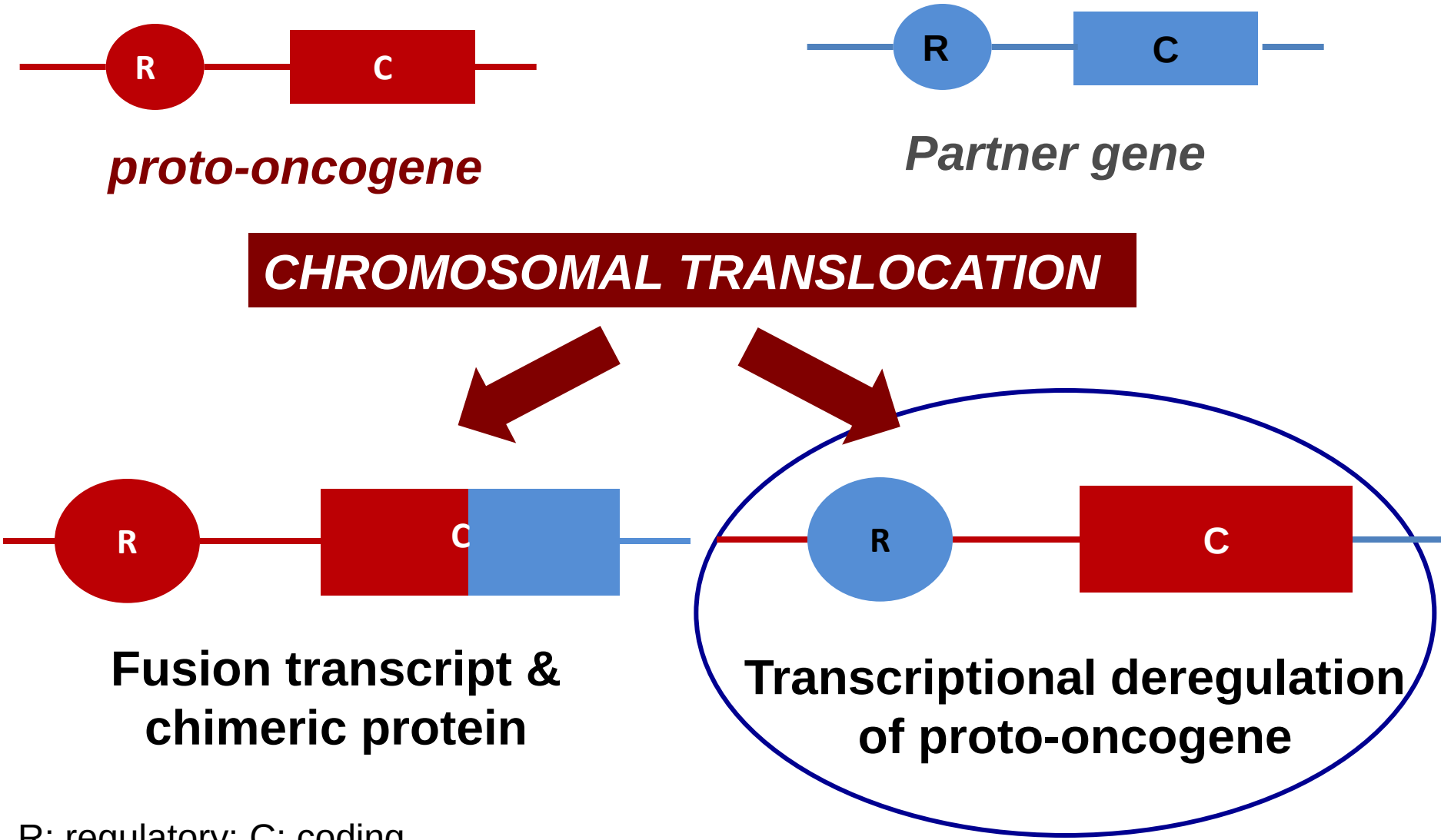

Ig gene rearrangements (in the lymph node germinal centre)
MEMORY B-CELL
GERMINAL CENTRE
Short-lived plasma cells
IgM
VDJ hypermutation
Ig heavy chain switch
Receptor editing
Plasmablast
Germinal centre Cell precursor
Lymph node
Bone Marrow
G, A, E, D
Long-lived plasma cell
Pre-B cell
VDJ rearrangement


Receptor editing
Class switching
Somatic hypermutation
IgM
IgG
V
D
J
μ
δ
γ
α
ε
CH
CL

Formazione del centro germinativo



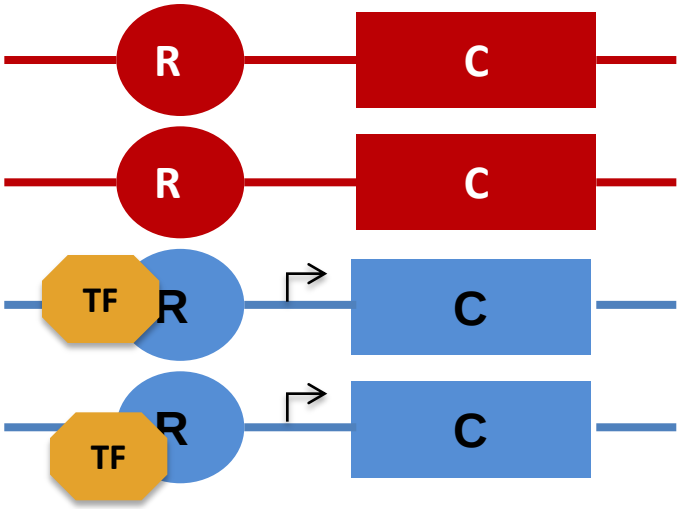
Chromosomal translocations leading to proto-oncogene deregulation



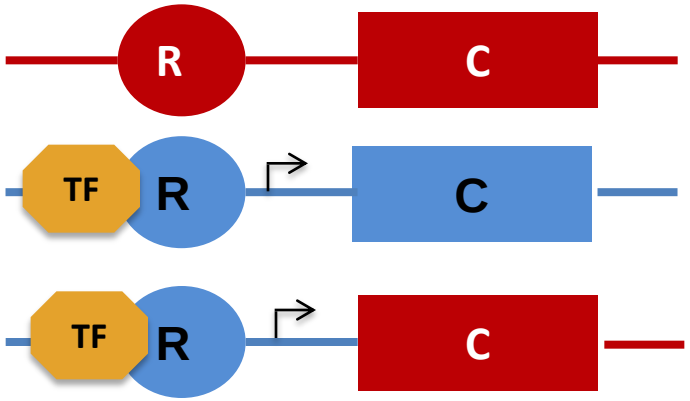
R: regulatory; C: coding

Consequences of chromosomal translocations leading to transcriptional deregulation of proto-oncogenes

NORMAL GENOME (DNA)

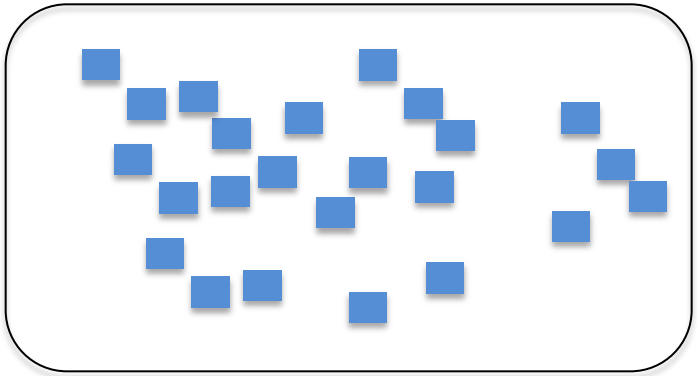


LYMPHOMA GENOME (DNA)

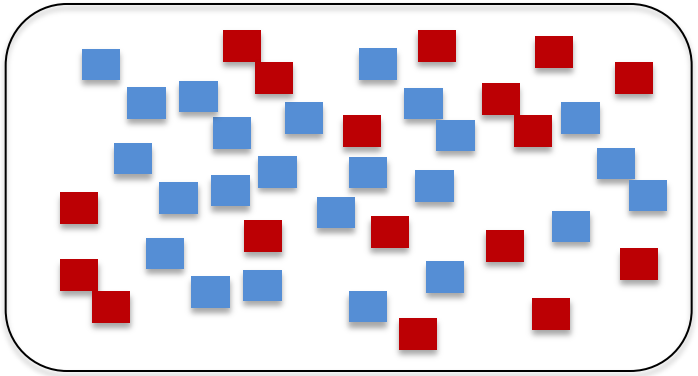


The translocation has caused the jusxtaposition of the regulatory regions of the blue gene in the proximity of the red gene. Expression of the red gene is now directed by the regulatory regions of the blue gene!

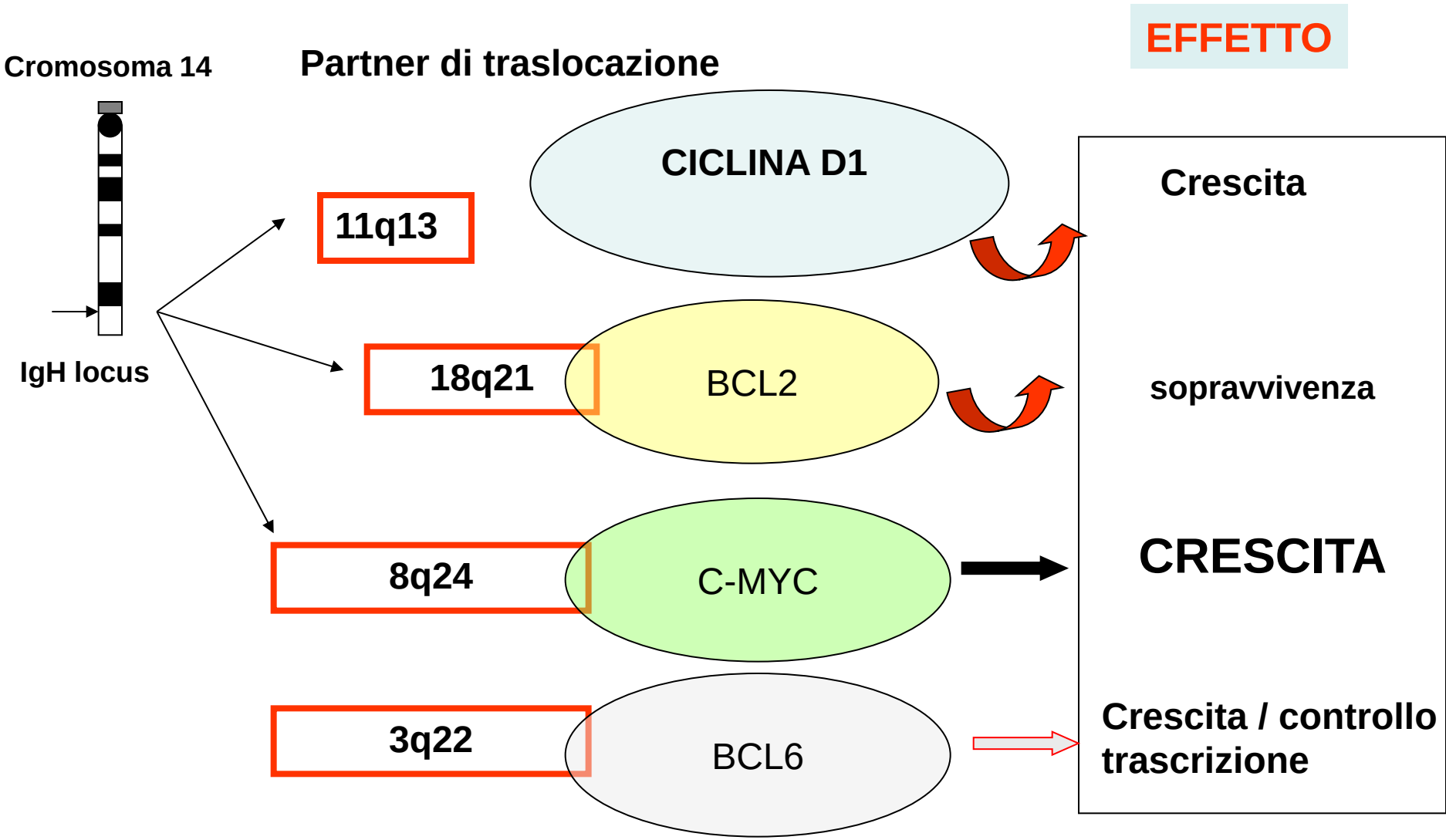
NORMAL TISSUE (mRNA & PROTEIN)

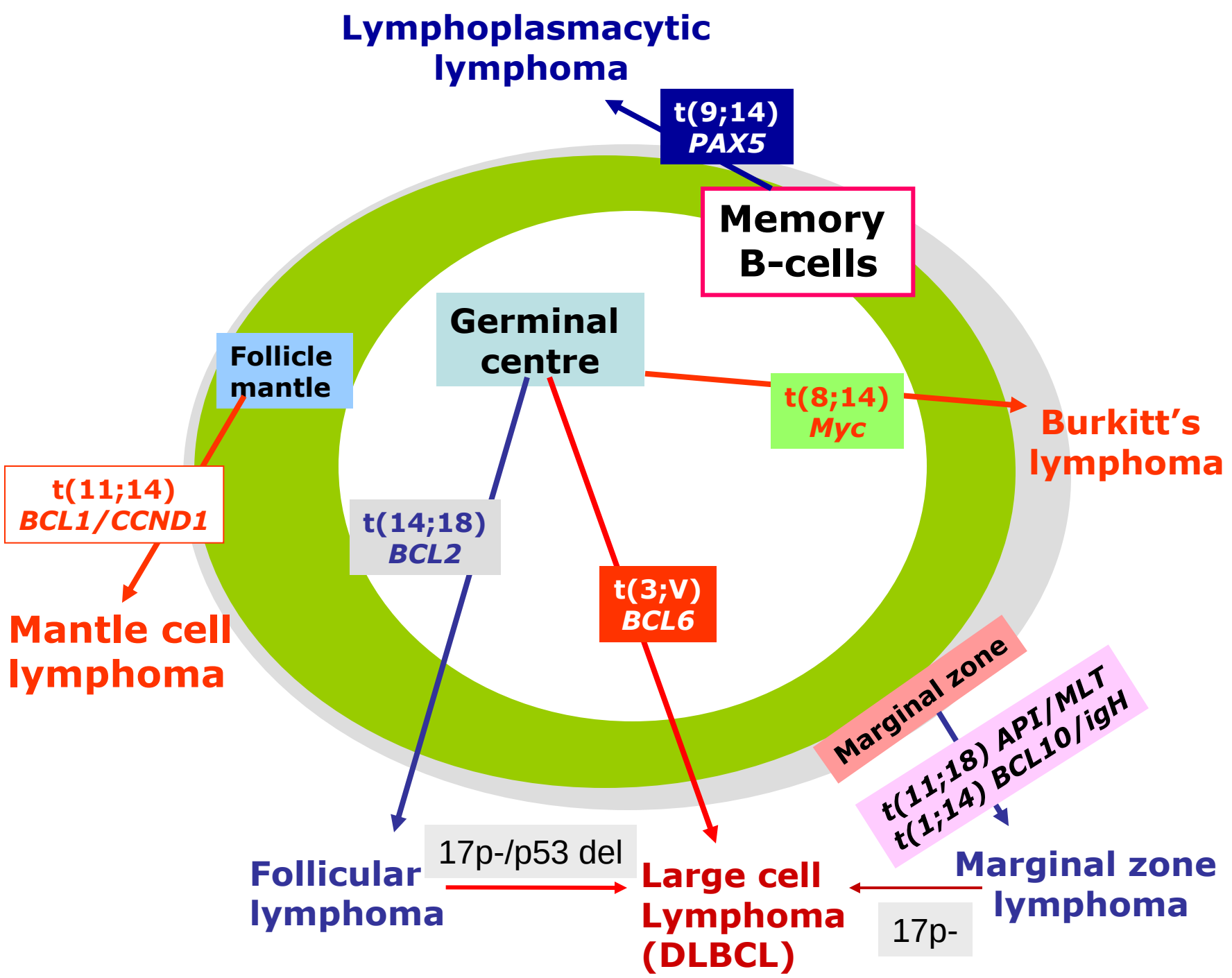


LYMPHOMA TISSUE (mRNA & PROTEIN)

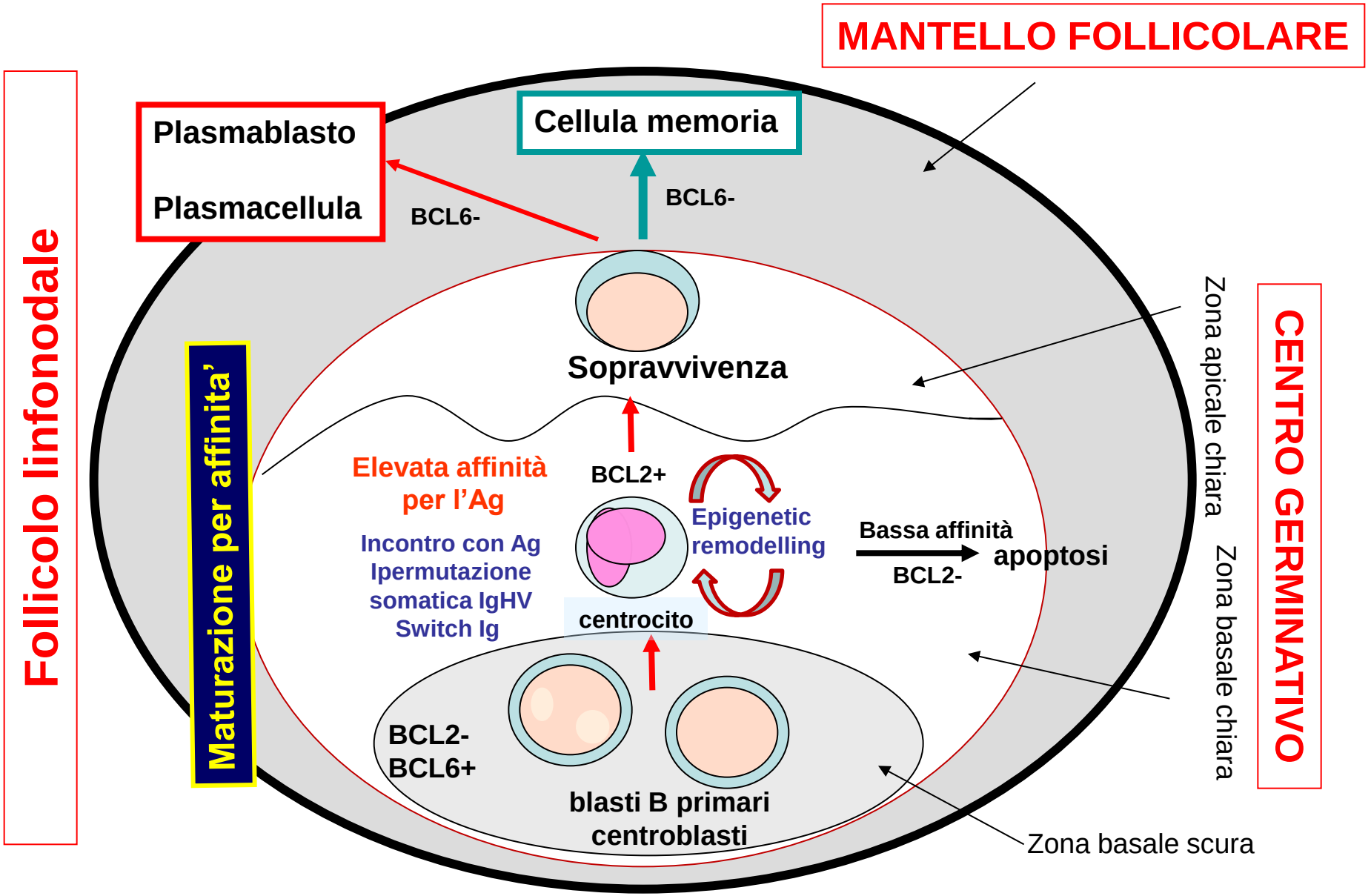


ALCUNE TRASLOCAZIONI PRIMARIE IMPORTANTI NELLA PATOGENESI DEI LINFOMI



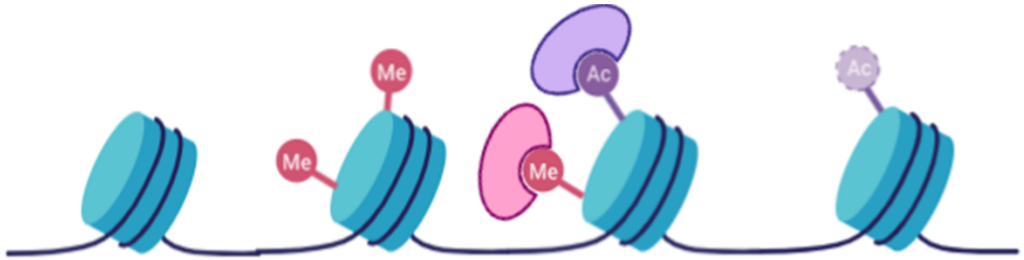

Lymphoplasmacytic lymphoma
t(9;14) PAX5
Memory B-cells
Germinal centre
Follicle mantle
t(8;14) Myc
Burkitt's lymphoma
t(11;14) BCL1/CCND1
t(14;18) BCL2
t(3;V) BCL6
Mantle cell lymphoma
Marginal zone
t(11;18) API/MLT
t(1;14) BCL10/igH
Follicular lymphoma
17p-/p53 del
Large cell Lymphoma (DLBCL)
Marginal zone lymphoma
17p-

Formazione del centro germinativo



Cyclic re-entry

Epigenetic plasticity

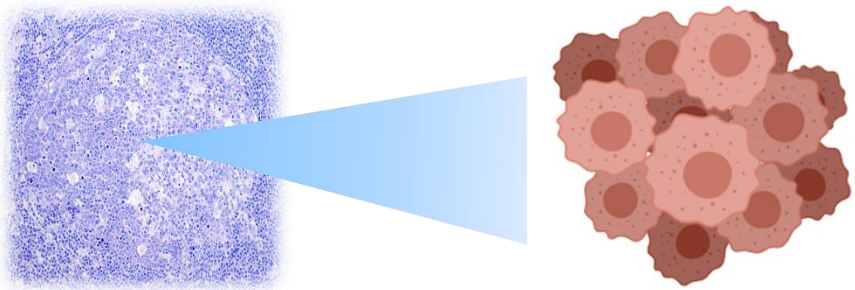


- **methyltransferases (MLL2, EZH2)**
- **acetyltransferases (CREBBP, EP300)**

van Galen, J. C. *et al. Eur. J. Immunol.* 34, 1870–1881 (2004)

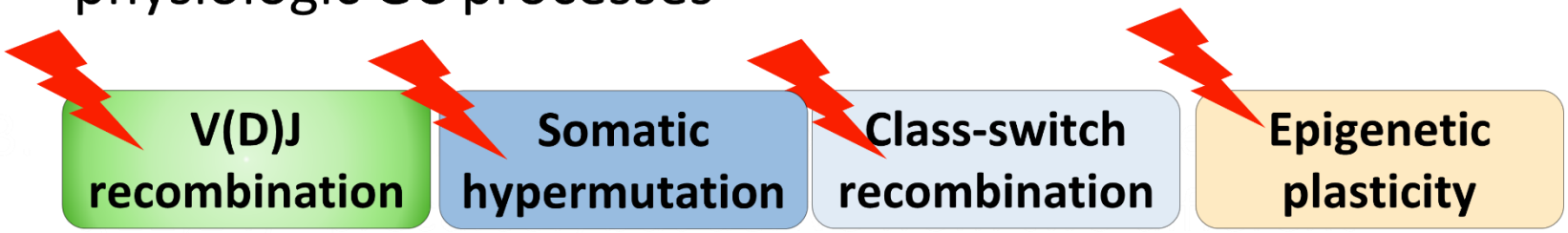
Key Messages

1. FL and DLBCL originate from the clonal expansion of B cells in the GC

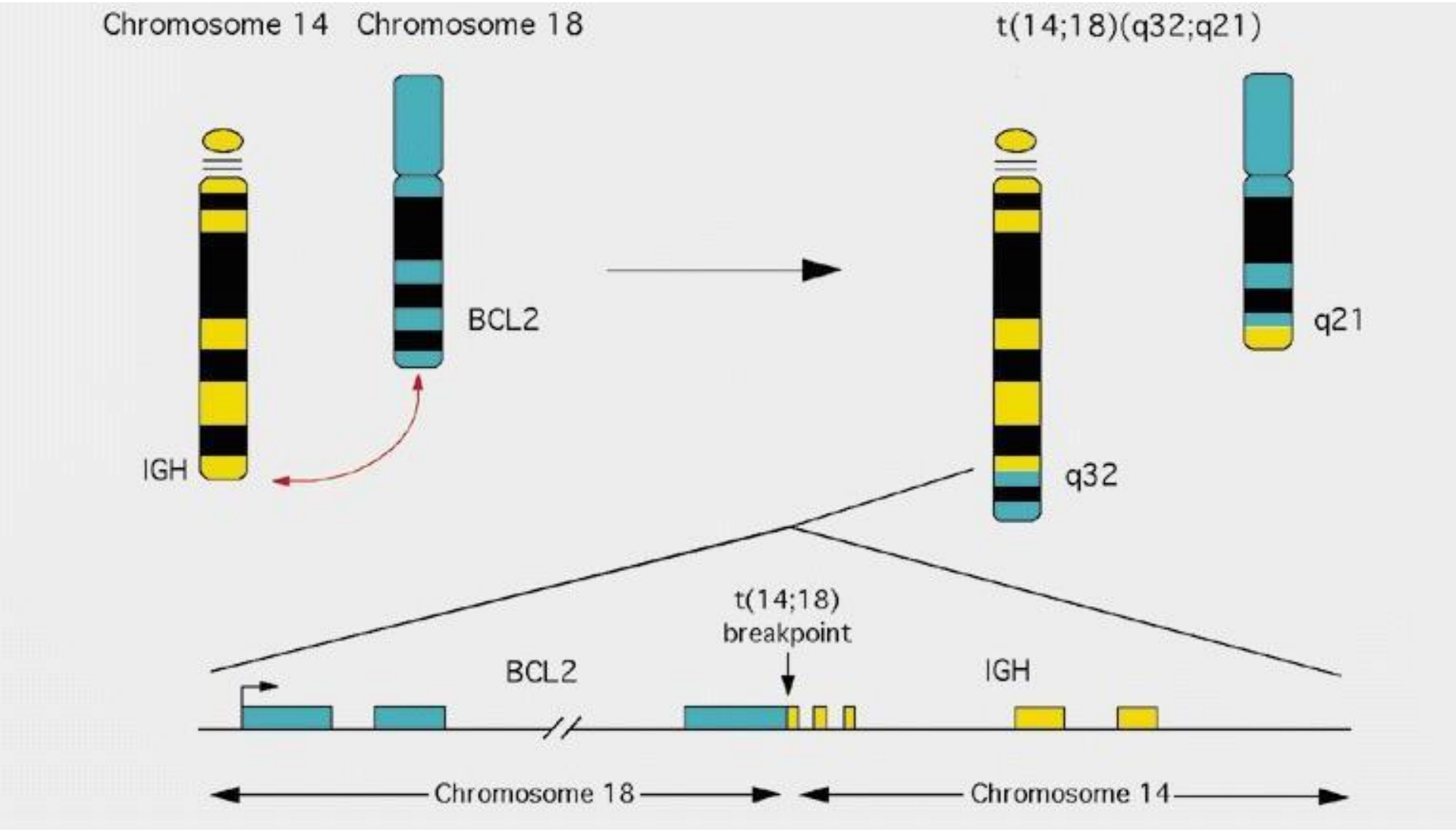


Key Messages

2. The genetic mechanisms involved in FL and DLBCL development are intimately connected to the physiologic GC processes

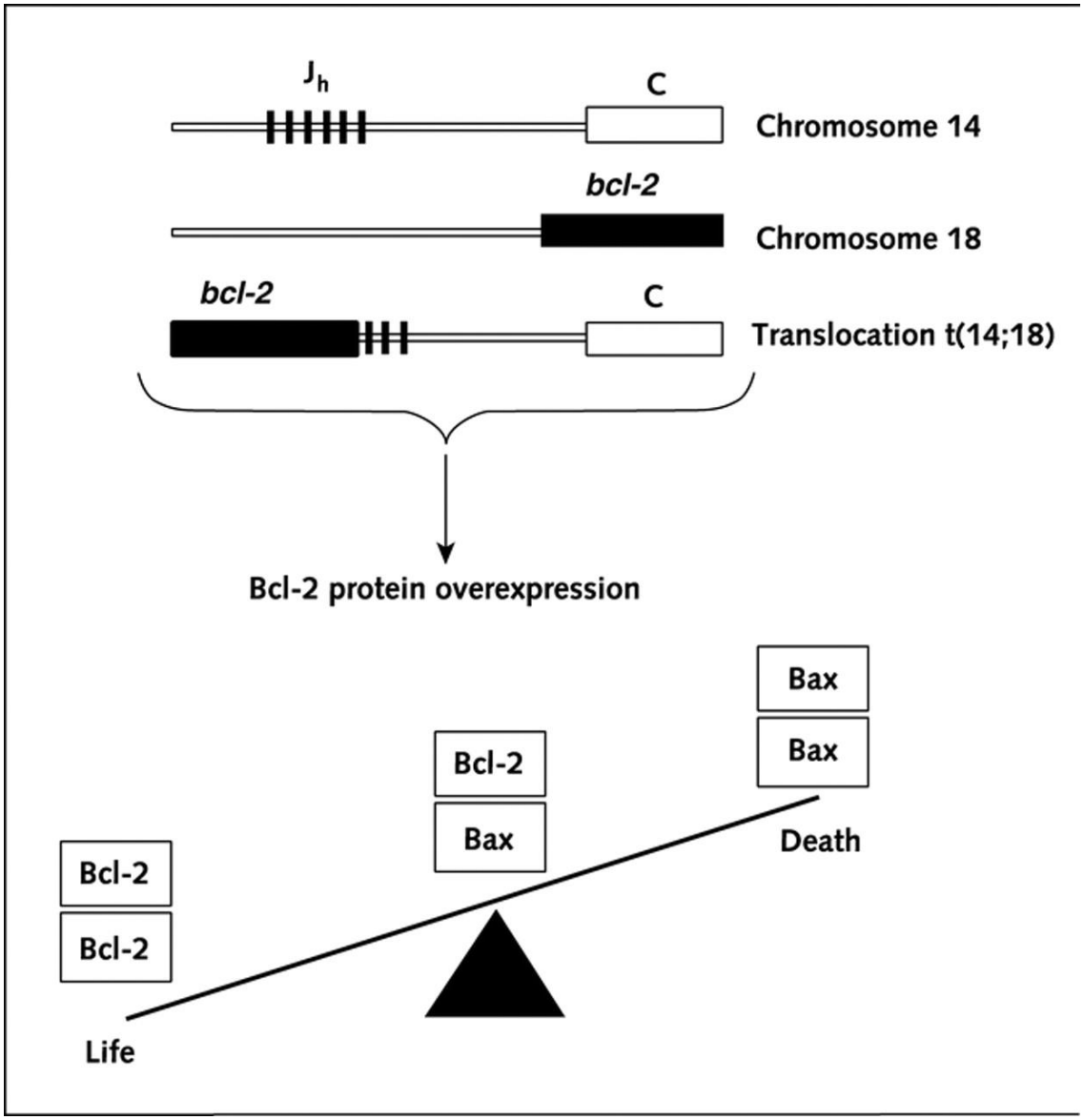


The t(14;18)(q32;q21) translocation of FL involves IGH on chr. 14q32 and BCL2 on chr. 18q21

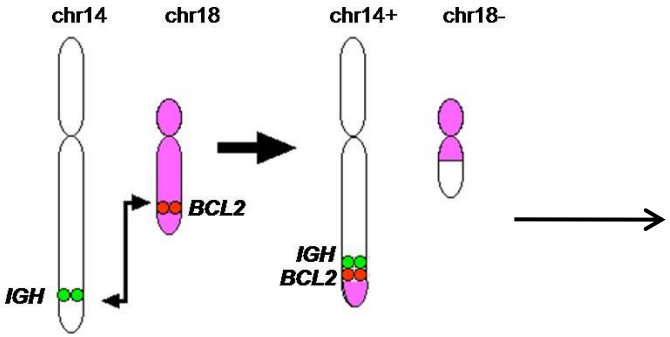


Courtesy of Professor Gianluca gaidano UPO

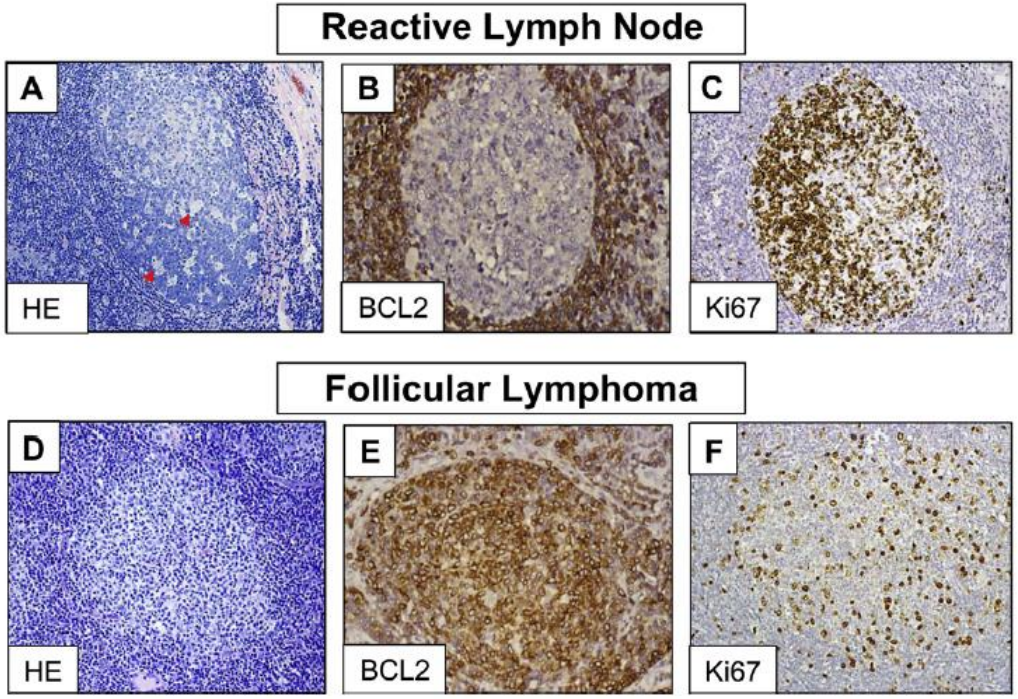
t(14;18) leads to transcriptional deregulation of BCL2, which in turn shifts the apoptosis balance toward survival



t(14;18) is insufficient for the development of FL



90% of FL have the t(14;18)

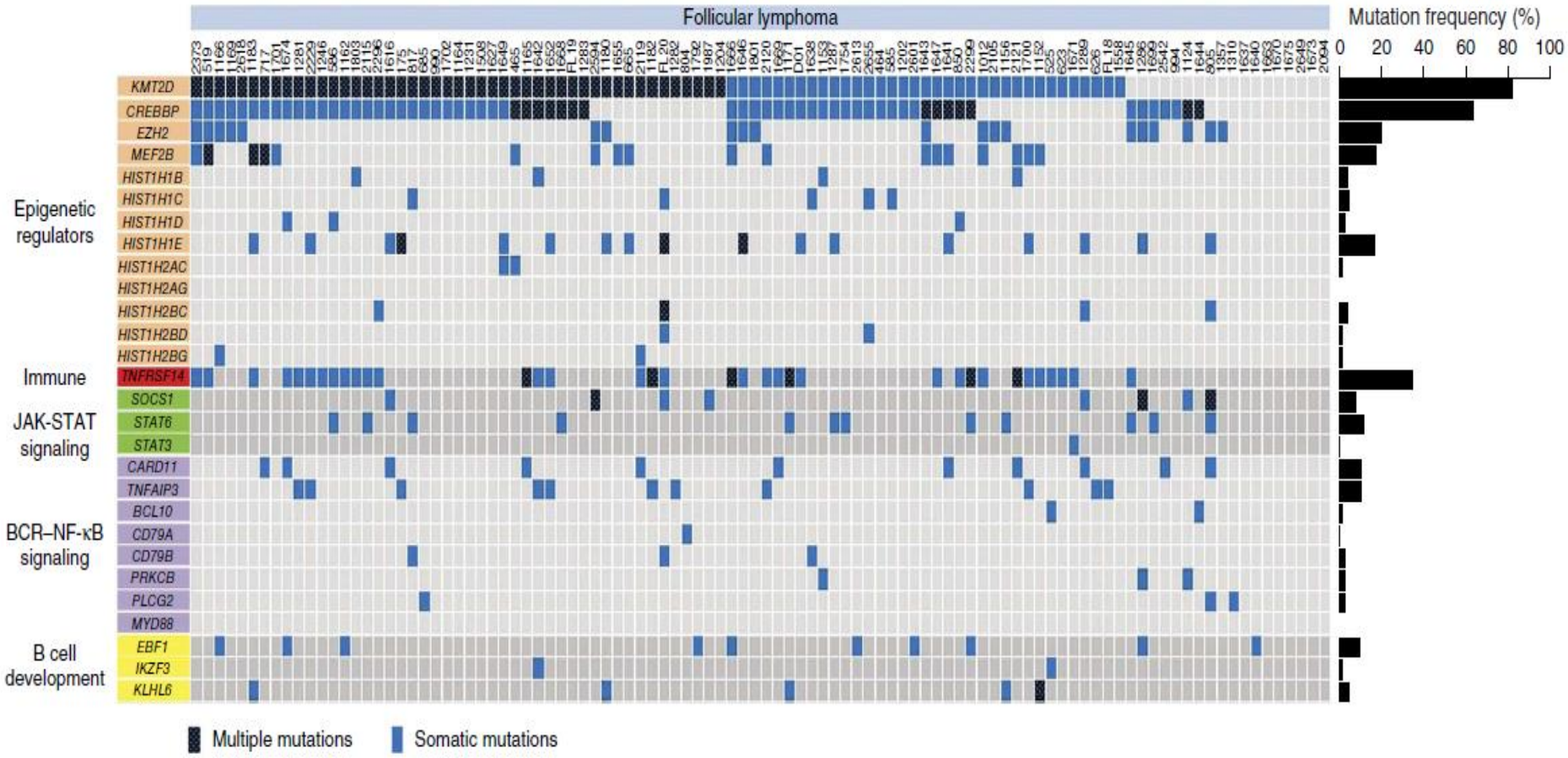


Over-expression of anti-apoptotic BCL2

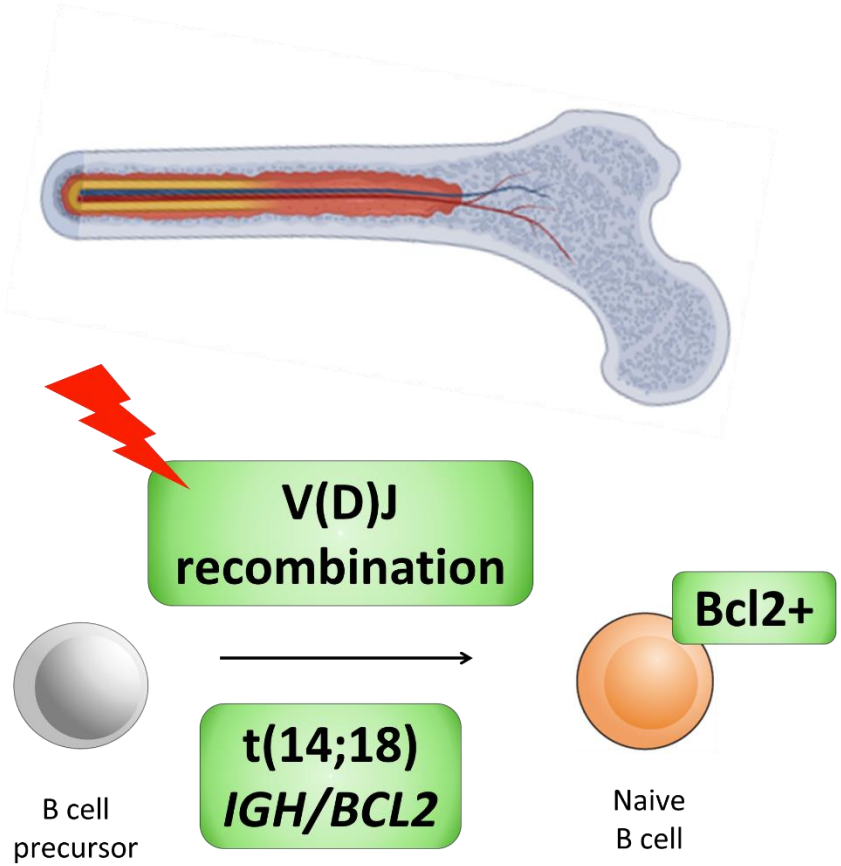
- Transgenic mice do not develop FL *(McDonnell et al., 1989; McDonnell et al., 1991)*
- Healthy individuals carry the translocation *(Limpens et al., 1995, Dolken et al., 1996; Summers et al., 2001; Roulland et al, 2006)*

An epigenetic ‘addiction’ in FL

90% of cases had at least one mutation in an epigenetic regulator



Okosun et al, Nature Genetics 2014



Follicular lymphoma-like B cells in healthy individuals: a novel intermediate step in early lymphomagenesis

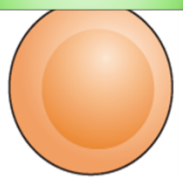
Sandrine Roulland,[1,2,3] Jean-Marc Navarro,[1,2,3] Pierre Grenot,[1,2,3] Michèle Milili,[1,2,3] Julie Agopian,[1,2,3] Bertrand Montpellier,[1,2,3] Pascal Gauduchon,[4] Pierre Lebailly,[4,5] Claudine Schiff,[1,2,3] and Bertrand Nadel[1,2,3]

Victora et al. Blood 120, 2240–2248 (2012)

Trafficking and additional aberrations

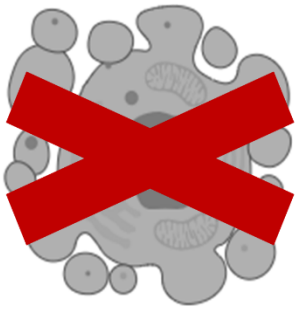
t(14;18)

Bcl2+



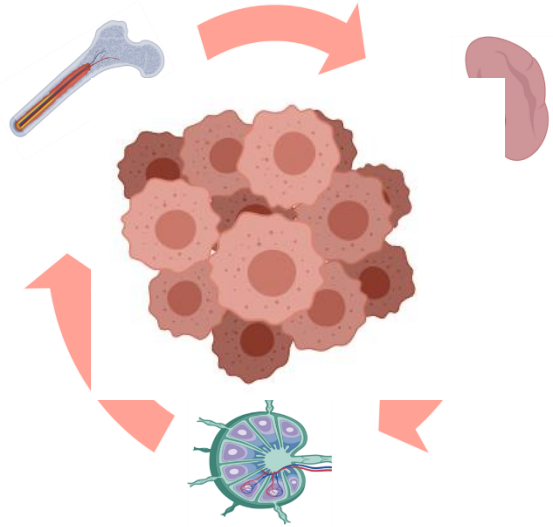
Naive
B cell

Survival advantage

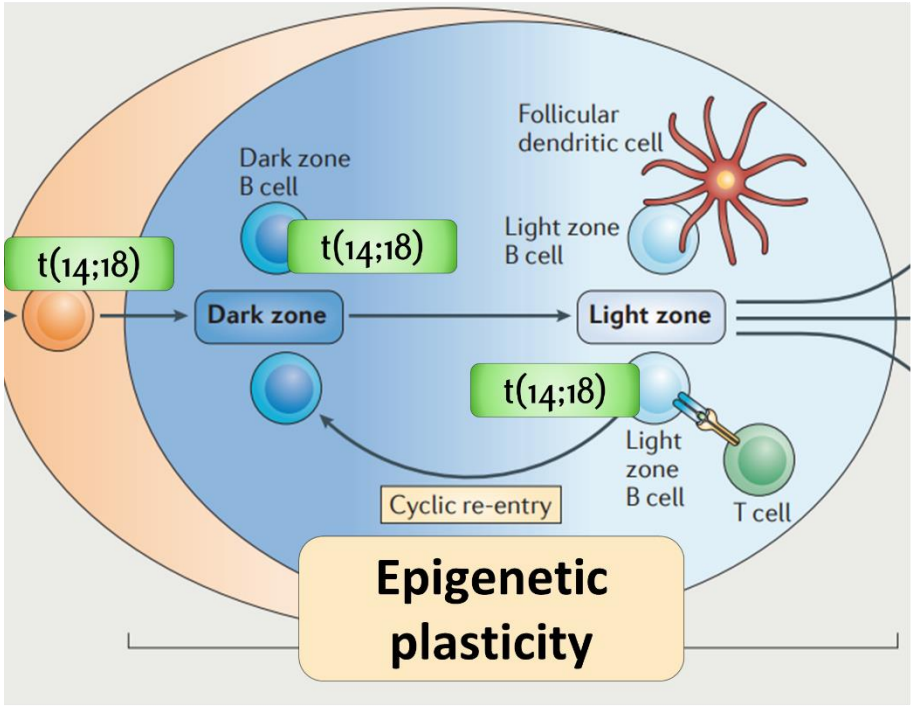


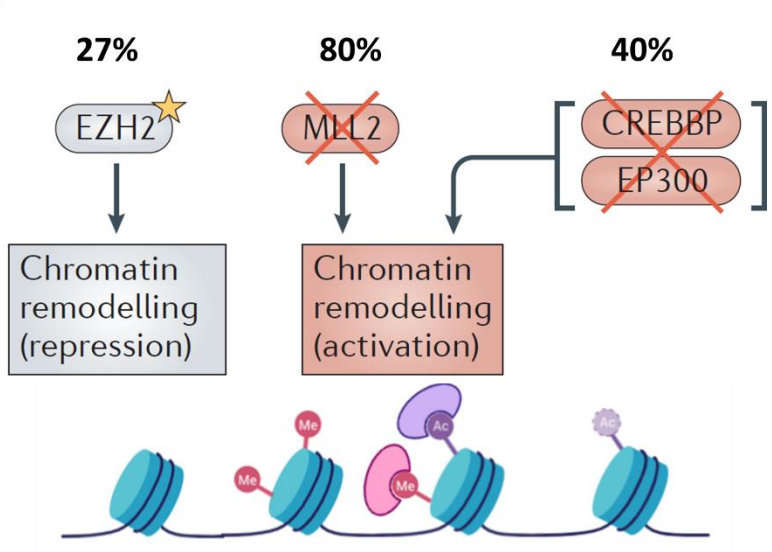
Anti-apoptotic programme

Repeated GC transits



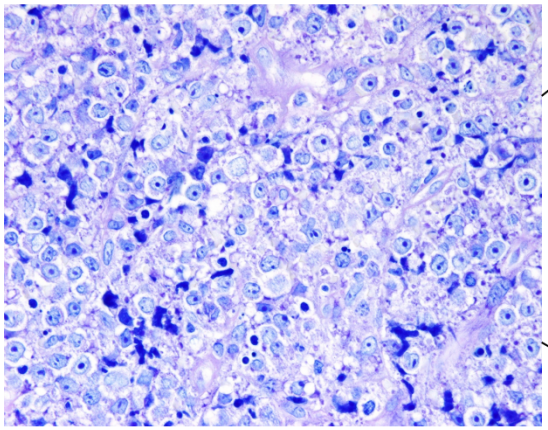
Epigenetic mutations



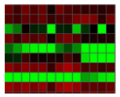


Bodor et al. Blood. 122:3165-3168 (2013)
Morin et al. Nature Genet. 42, 181–185 (2010)
Pasqualucci et al. Nature 471, 189–195 (2011)

2. Diffuse large B-cell lymphoma



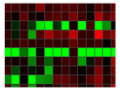
GC B cell-like DLBCL



Light zone

LZ B-cells (centrocytes)

Activated B cell-like DLBCL



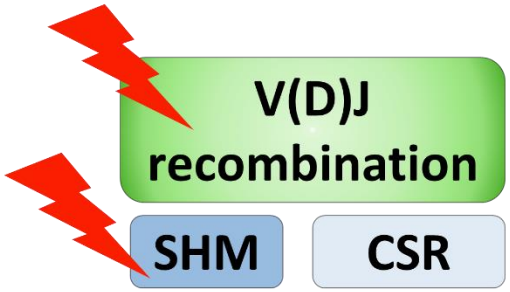
Differentiation

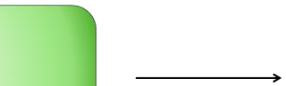
Late GC B cells (plasmablasts)

Alizadeh et al. Nature. 403(6769):503-11.(2000)

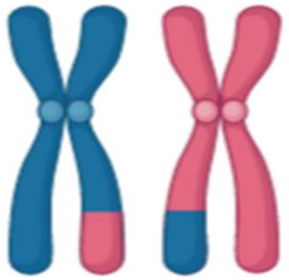
GC: germinal centre

Mechanisms of genetic damage in DLBCL





Chromosomal translocations



IG promoter/proto-oncogenes (*BCL2, BCL6, MYC*)

Aberrant somatic hypermutation

40 genes outside the IG loci (*PIM1, MYC…*)

Kuppers & Dalla-Favera. Oncogene. 20:5580-5594 (2001).
Pasqualucci et al. Nature. 412:341-346 (2001).

SHM: somatic hypermutation; CSR: class switch recombination, Ig: immunoglobulin

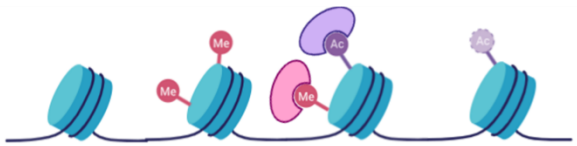
GC B cell-like DLBCL

Light zone

V(D)J recombination → *BCL2* rearrangement

SHM CSA → *MYC* rearrangement

Epigenetic plasticity → EZH2 → Chromatin remodelling (repression)

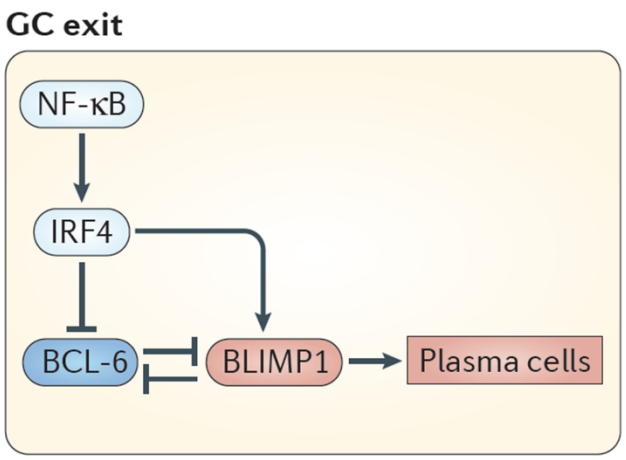


Morin et al. Nature Genet. 42, 181–185 (2010)

Activated B cell-like DLBCL

CD79A/B
MYD88
CARD11
TNFAIP3

→ **NF-kB activation**



BLIMP1

→ **Blockade in terminal differentiation**

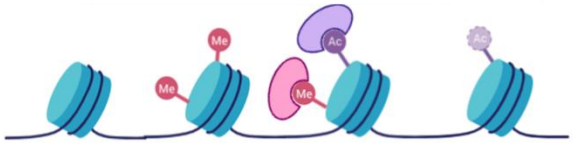
Davis et al. Nature 463, 88–92 (2010).
Lenz et al.Science 319, 1676–1679 (2008).
Ngo et al. Nature 470, 115–119 (2011).
Compagno et al. Nature 459, 717–721 (2009).

GC B cell-like DLBCL

Activated B cell-like DLBCL

BCL6 disregulation

Chromatin modifiers



MLL2

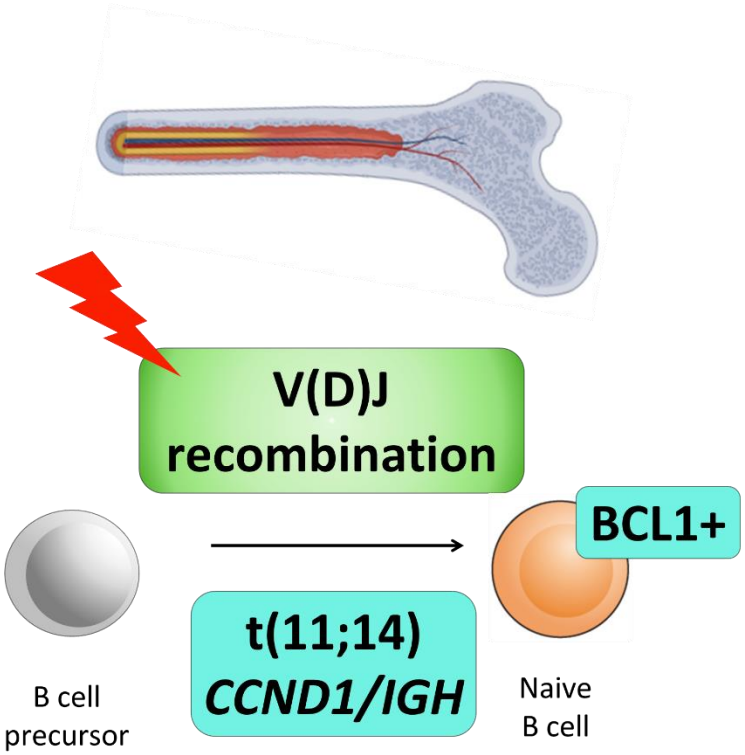
CREBBP

EP300

Chromatin remodelling (activation)

β2M
HLA-I
CD58

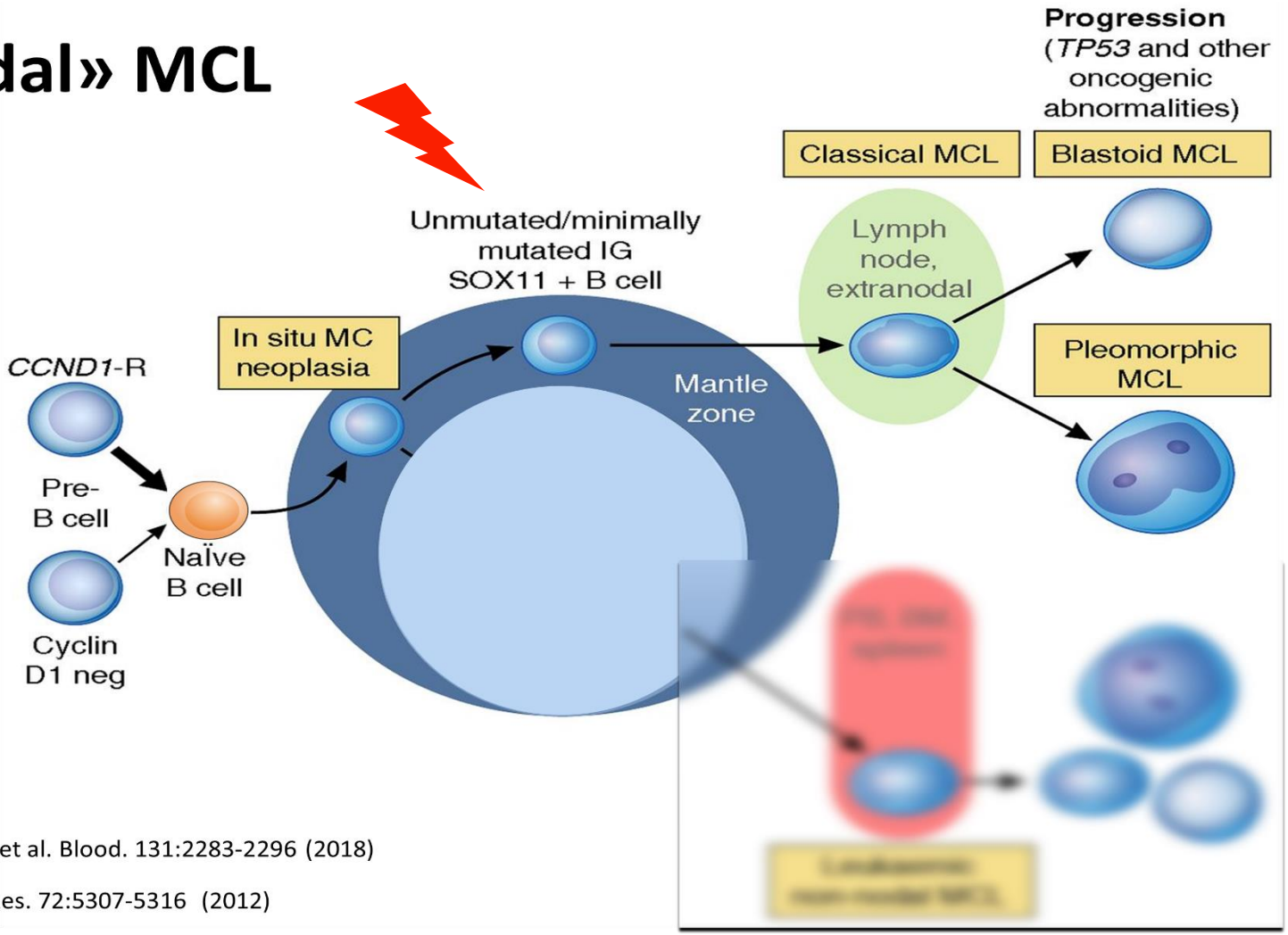
Immune escape



One precursor, two different molecular pathways

Welzel et al. Cancer Res. 61:1629-1636 (2001)

«Nodal» MCL

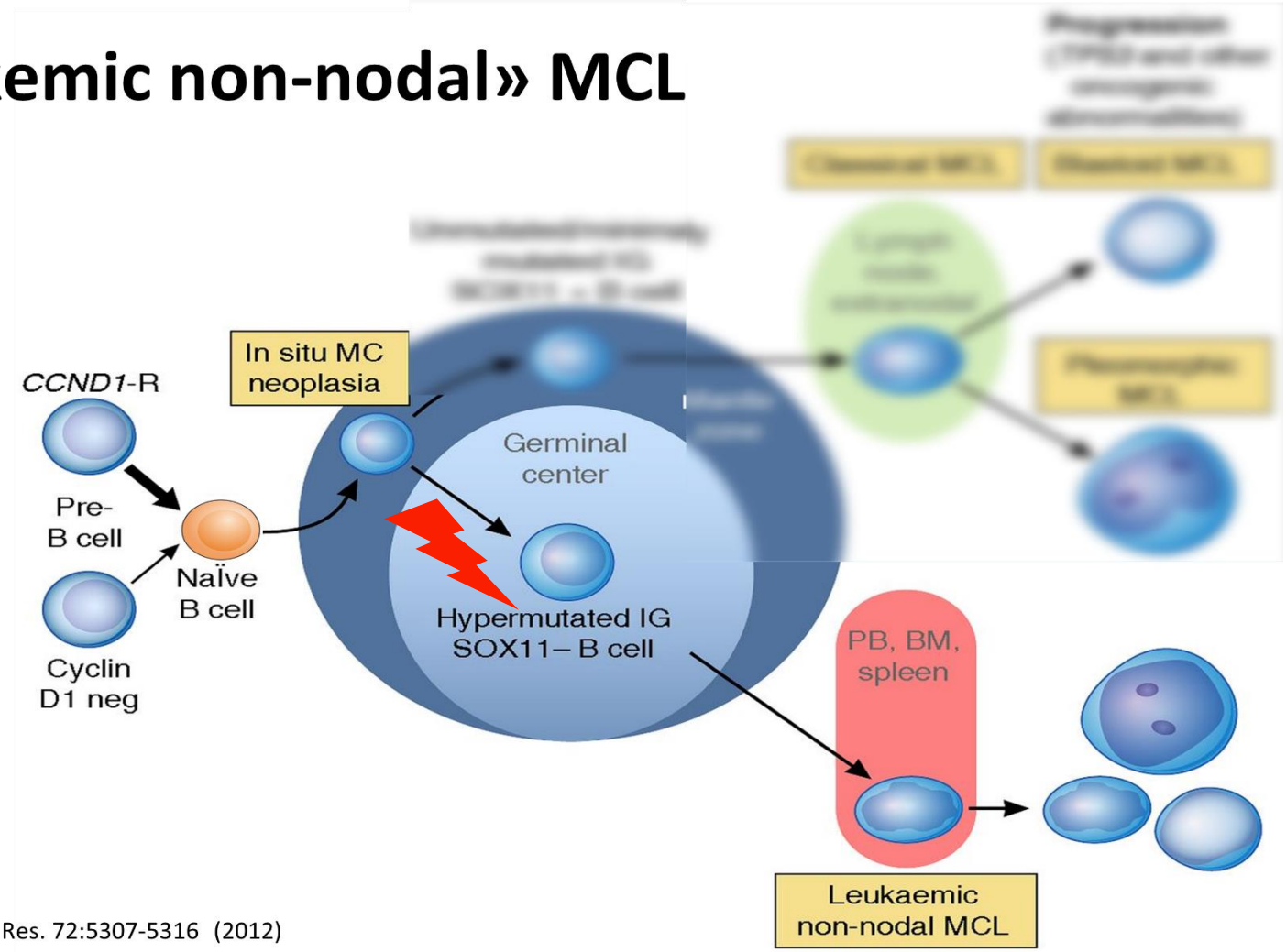


Adapted from Puente et al. Blood. 131:2283-2296 (2018)

Navarro et al. Cancer Res. 72:5307-5316 (2012)

SOX11: promotes tumor angiogenesis and cross-talk between MCL cells and microenvironment
SOX1 silencing in a MCL xenograft
Balsas P et al Blood. 2017;130(4):501-513

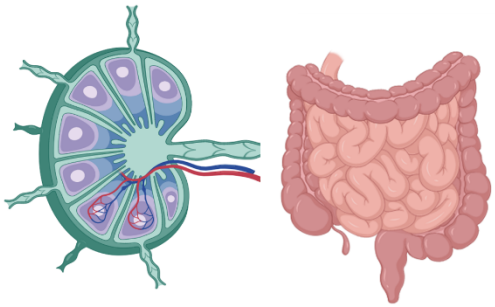
«Leukemic non-nodal» MCL



Navarro et al. Cancer Res. 72:5307-5316 (2012)

«Nodal» MCL

Site



Phenotype

SOX11+
CD5+ (90-100%)
CD200- (90%)

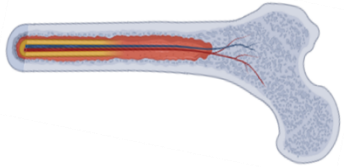
Somatic mutations

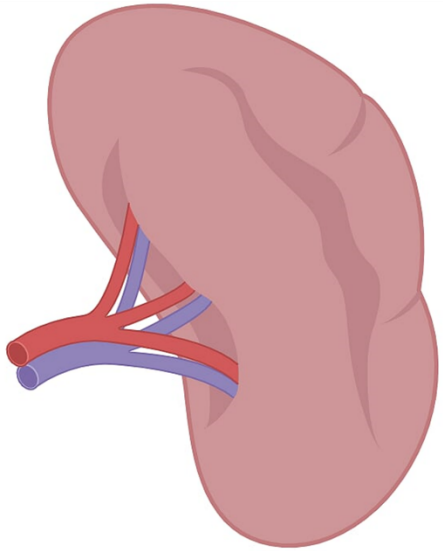
- *DNA repair: ATM (55%), TP53* (25%), CDKN2A (20%)
- *CCND1* (18%)
- Chromatin modifiers: *MLL2* (18%), *NSD2* (15%)
- NF-kB pathway: *BIRC3* (7%)

Clinical behaviour

AGGRESSIVE

«Leukemic non-nodal» MCL

Site	
Phenotype	**SOX11-** **CD5- (25-50%)** **CD200+ (40-90%)**
Somatic mutations	• ***DNA repair: TP53*** **(25%)** • ***CCND1*** **(86%)**
Clinical behaviour	**INDOLENT**



Linfomi MALT

- Eziologia infettiva:

  HP

  C. Jejuni – immunoproliferative small intestinal disease

  B. burgdoferi – MALToma cutaneo

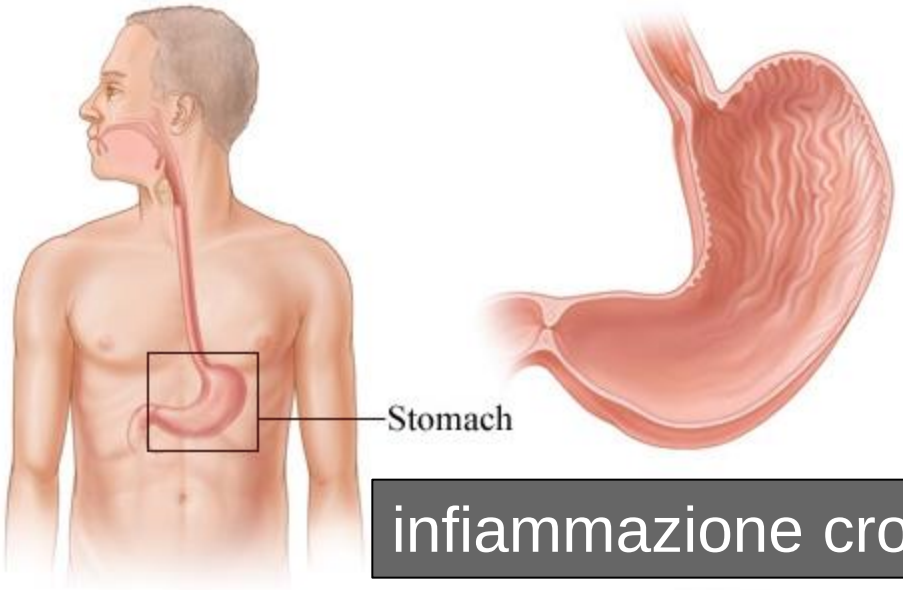
  C. psittaci – linfoma MALT orbitario

  HCV – linfoma della zona marginale splenico

- Eziologia autoimmune:

  Tiroidite di Hashimoto – linfoma marginale tiroideo

  S. Di Sjogren – linfoma marginale delle ghiandole salivari

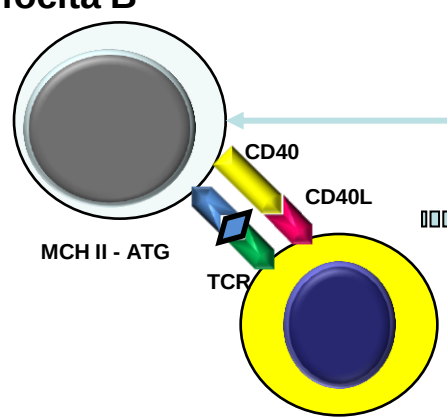


In condizioni fisiologiche lo stomaco NON possiede tessuto linfoide associato alle mucose (MALT)

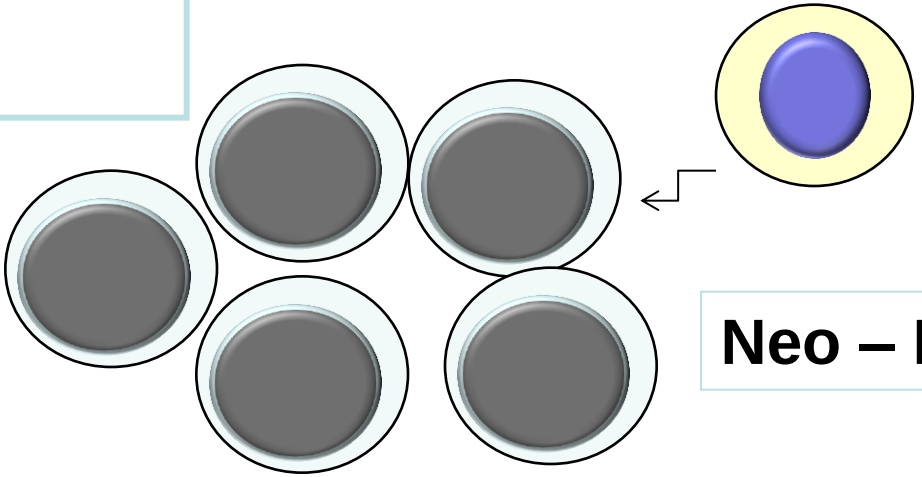
infiammazione cronica da H. pylori

Linfociti CD8: controllo sulla proliferazione B

linfocita B

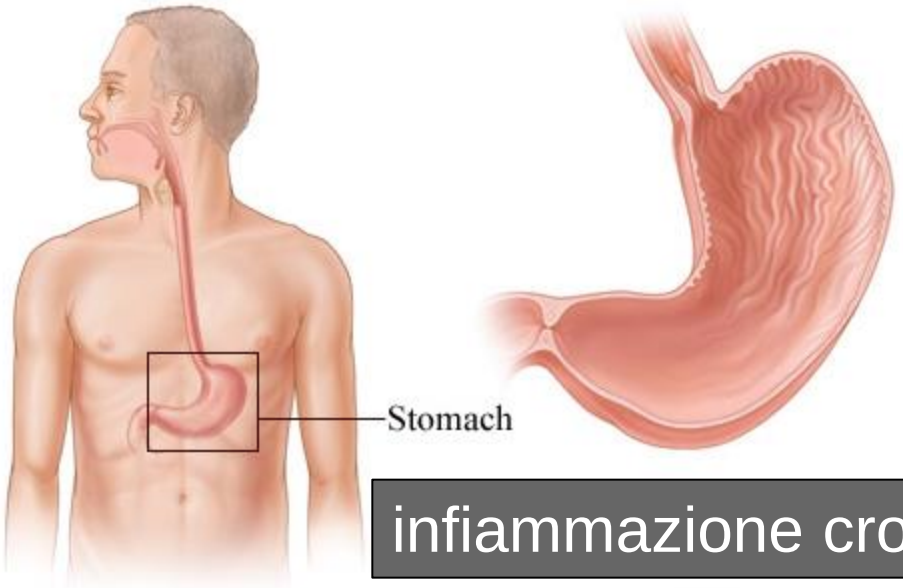


linfocita T_H H. pylori specifico (Ureasi, CagA, VacA, HSP)



Proliferazione ed organizzazione di follicoli linfatici

Neo – MALT

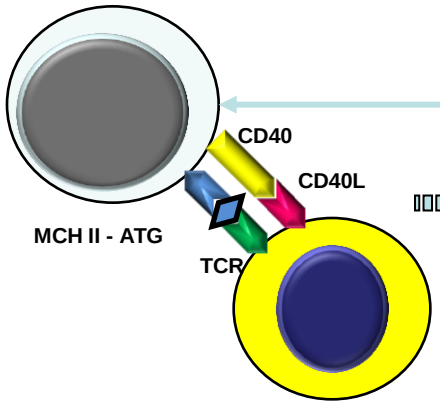


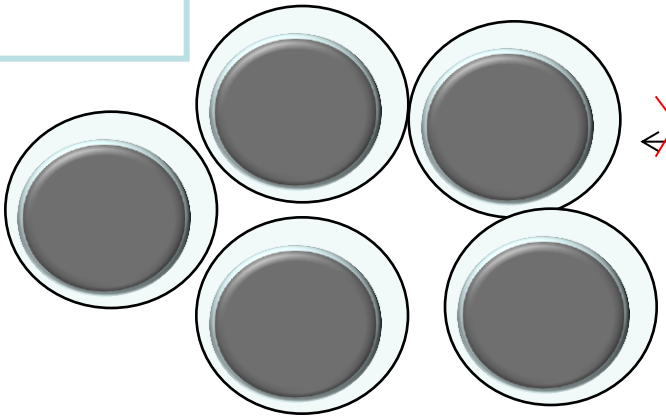
In condizioni fisiologiche lo stomaco NON possiede tessuto linfoide associato alle mucose (MALT)

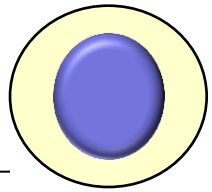
infiammazione cronica da H. pylori

Linfociti CD8
Viene meno
il controllo sulla
proliferazione B

linfocita B







Neo – MALT

Danno
genetico

linfocita T_H H. pylori specifico
(Ureasi, CagA, VacA, HSP)

Proliferazione ed
organizzazione
di follicoli linfatici

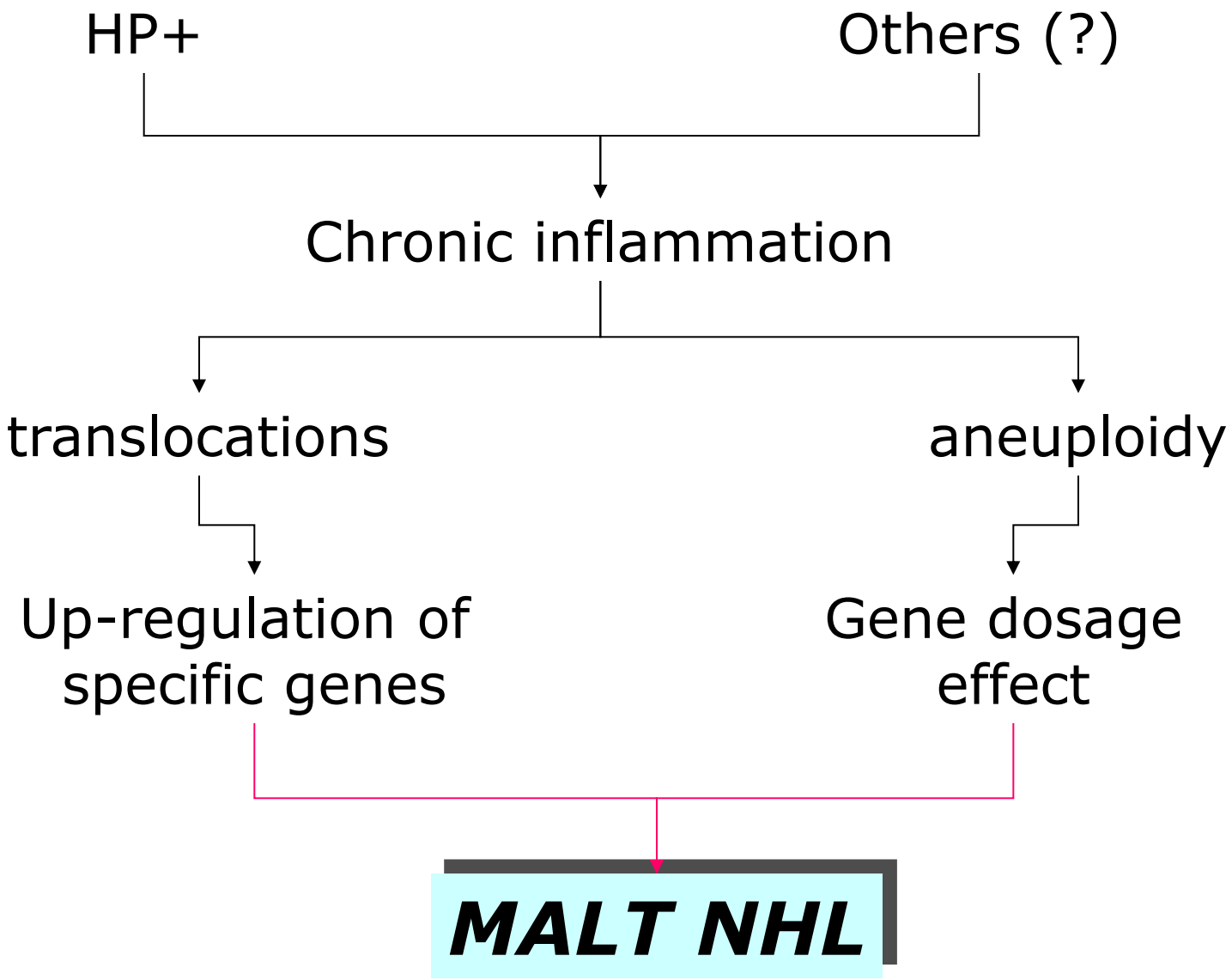
Flogosi
Neutrofili attivati (?)
ROS (?)

Principali alterazioni Citogenetico-molecolari

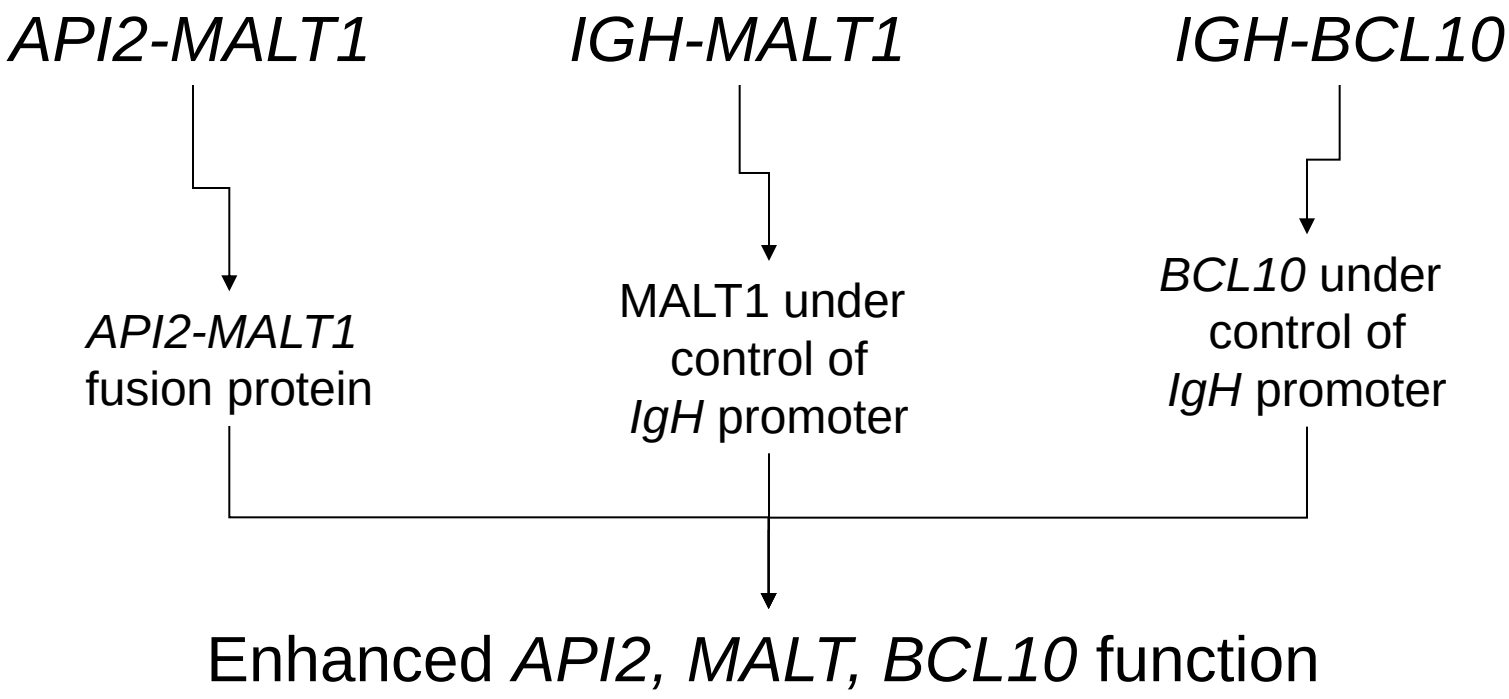
t (11;18)(q21;q21)	API2-MALT1
t (14;18)(q32;q21)	IGH-MALT1
t(1;14)(p22;q32)	IGH-BCL10
t(3;14)(p13;q32)	IGH-FOXP1

Aneuploidie dei cromosomi 3, 7, 12, 18

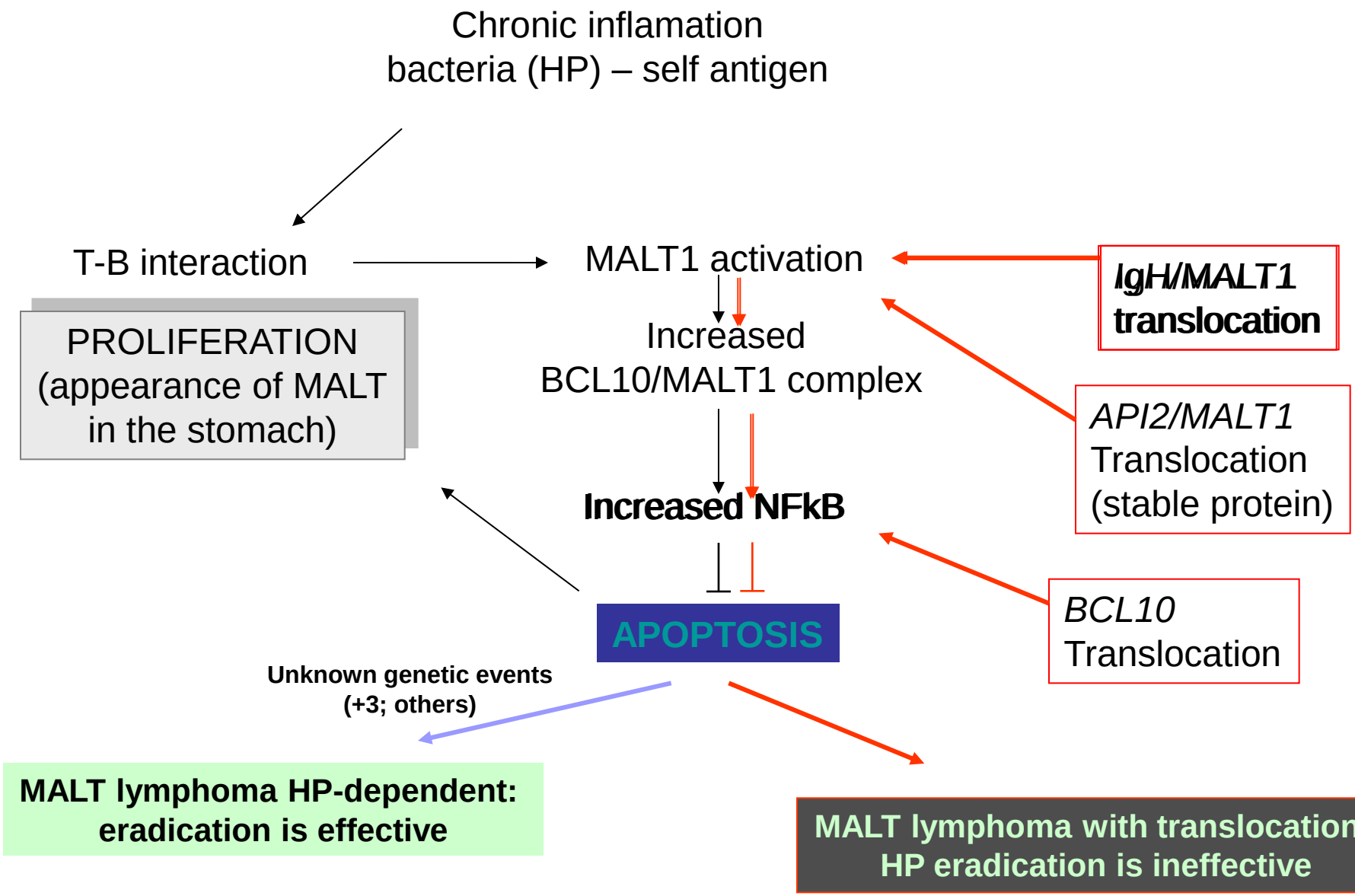
Genetic pathways leading to MALT NHL



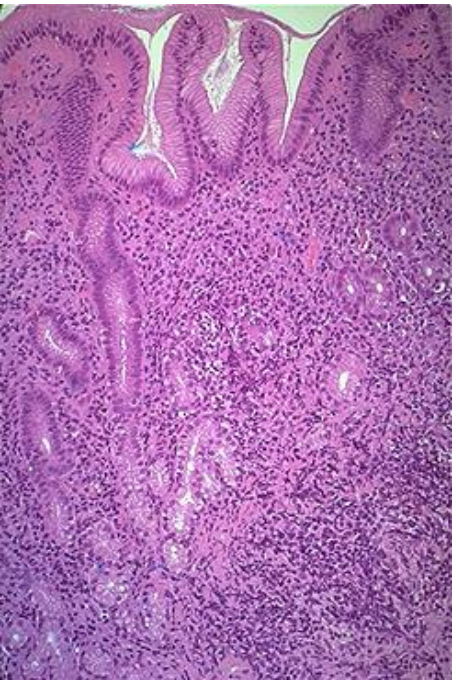
Significance of translocations



Role of chronic inflamation and translocations in the pathogenesis of MALT NHL



Gastric MALT NHL



Low grade gastric MALT NHL is usually caused by HP infection.

It is an indolent disease but may become locally aggressive, spread, or undergo high grade transformation.

Treatment of the infection cures the disease in ~70% of cases.

Resistant or non-localised disease is treated with chemoimmunotherapy (alkylating agents + Anti CD20 Mo Ab Rituximab)